20 November 2014
EMA/76777/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ofev

International non-proprietary name: nintedanib

Procedure No. EMEA/H/C/003821/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BI	Boehringer Ingelheim
bid	bis in die / twice daily
CI	Confidence interval
CTD	Common Technical Document
CTR	Clinical trial report
DL_{CO}	Carbone monoxide diffusion capacity
ECG	Electrocardiogram
ERS	European Respiratory Society
FEV1	Forced expiratory volume in 1 second
FGFR	Fibroblast growth factor receptor
FiO_2	Oxygen fraction in inspired air
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
HR	Hazard ratio
HRCT	High resolution computerised tomography
ICH	International Conference on Harmonisation
IPF	Idiopathic pulmonary fibrosis
LOCF	Last observation carried forward
LoQ	List of Questions (drawn up by CHMP)
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effect model for repeated measures
PaO_2	Arterial oxygen partial pressure
PDGFR	Platelet-derived growth factor receptor
PE	Primary endpoint
P-gp	P-glycoprotein

qd	quaque die / once daily
RS	Randomised set
SE	Standard error
SD	Standard deviation
SGRQ	Saint George's Respiratory Questionnaire
SpO_2	Oxygen saturation on pulse oximetry
SOC	System organ class
SSC	Special search category
TGV	Total gas volume
TLC	Total lung capacity
TS	Treated set
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UIP	Usual interstitial pneumonia
ULN	Upper limit of normal
VEGFR	Vascular-endothelial growth factor receptor
WHO DD	World Health Organization Drug Dictionary

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 5 May 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ofev, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 June 2013. The acceptability of an accelerated review was agreed upon by the EMA/CHMP on the 25 April 2014.

Ofev, was designated as an orphan medicinal product EU/3/13/1123 on 26 April 2013. Ofev was designated as an orphan medicinal product in the following indication: Treatment of idiopathic pulmonary fibrosis.

The applicant applied for the following indication: Ofev is indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF) and to slow disease progression.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Ofev as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that nintedanib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision [P/225/2010] on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant submitted a critical report addressing the possible similarity with authorised orphan medicinal products in a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance nintedanib contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 30 May 2008. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Manufacturers

Manufacturer responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim
GERMANY

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: David Lyons Co-Rapporteur: Robert James Hemmings

- Accelerated Assessment procedure was agreed-upon by CHMP on 25 April 2014.
- The application was received by the EMA on 5 May 2014.
- The procedure started on 28 May 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2014 (Annex 1).
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 August 2014 (Annex 2). In accordance with Article 6(3) of Regulation (EC) No 726/2004.
- During the PRAC meeting on 11 September 2014, the PRAC adopted an RMP Advice and assessment overview.
- During the meeting on 25 September 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 October 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 October 2014 (Annex 5).
- During the PRAC meeting on 6 November 2014, the PRAC adopted an RMP Advice and assessment overview.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 14 November 2014 (Annex 5).
- During the meeting on 20 November 2014, the CHMP, in the light of the overall data submitted and

the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ofev.

- The CHMP adopted a report on similarity of Ofev versus Esbriet on 24 July 2014.

2. Scientific discussion

2.1. Introduction

Problem statement

Idiopathic pulmonary fibrosis (IPF) is a rare disease of unknown aetiology that is characterized by progressive fibrosis of the interstitium of the lung, leading to decreasing lung volume and progressive pulmonary insufficiency. The prevalence of IPF is estimated at not more than 3 in 10,000 in the Community, and is most prevalent in middle aged and elderly patients, and usually presents between the ages of 40 and 70 years (ATS/ERS 2000).

Pathophysiology

The pathophysiology of IPF i.e. the underlying fibroproliferative process remains incompletely understood. IPF is assumed to be caused by an unknown insult to the lung that leads to alveolar epithelial cell injury and subsequent dysregulated repair, characterised by excessive deposition of extracellular matrix (ECM) and loss of normal parenchymal architecture and lung function. Fibroblasts, which produce ECM proteins in fibrosing diseases such as IPF, exhibit unregulated proliferation and differentiate into myofibroblasts. The latter is considered the hallmark cell in the development and establishment of lung fibrosis.

Patients with IPF may have sub-clinical or overt co-morbid conditions including pulmonary hypertension, gastroesophageal reflux, obstructive sleep apnoea, obesity, diabetes mellitus and emphysema. Most patients die of respiratory failure. Median survival, as described across a range of studies, is only 2 to 5 years after diagnosis.

Many patients experience long periods of relative stability but acute episodes of rapid respiratory deterioration may result in death.

Diagnosis

The histopathological feature of IPF is usual interstitial pneumonia (UIP). The major diagnostic criterion is a heterogeneous appearance at low magnification in which areas of fibrosis with scarring and honeycomb change alternate with areas of less affected or normal parenchyma. These histopathologic changes often affect the subpleural and paraseptal parenchyma most severely. Inflammation is usually mild and consists of a patchy interstitial infiltrate of lymphocytes and plasma cells associated with hyperplasia of type 2 pneumocytes and bronchiolar epithelium. The fibrotic zones are composed mainly of dense collagen, although scattered convex subepithelial foci of proliferating fibroblasts and myofibroblasts (so-called fibroblast foci) are a consistent finding. Areas of honeycomb change are composed of cystic fibrotic airspaces that are frequently lined by bronchiolar epithelium and filled with mucus and inflammatory cells. Smooth muscle metaplasia in the interstitium is commonly seen in areas of fibrosis and honeycomb change.

On high resolution computed tomography (HRCT) UIP is characterized by the presence of reticular opacities, often associated with traction bronchiectasis. Honeycombing is common, and is critical for making a definite diagnosis. Honeycombing is manifested on HRCT as clustered cystic airspaces, typically

of comparable diameters on the order of 3–10 mm but occasionally as large as 2.5 cm. It is usually subpleural and is characterized by well-defined walls. Ground glass opacities are common, but usually less extensive than the reticulation.

Classification

IPF is a well-recognised and distinct interstitial lung disease with unique histopathologic, clinical and prognostic characteristics (American Thoracic Society/European Respiratory Society (ATS/ERS), 2000; ATS/ERS, 2002). The natural history of the disease and the factors influencing prognosis are incompletely understood. Due to the limited knowledge of the variability in the natural history of IPF there are currently no data to support staging approaches i.e. the definition of subpopulations (mild/moderate/severe, early/advanced/end-stage, and stabile/progressive). Proposed stages are commonly based on resting pulmonary function test measurements and/or extent of radiologic abnormalities. However, it is unknown if these staging approaches are relevant to clinical decision making [P11-07084].

Existing methods of treatment of IPF

Conventional IPF treatments such as corticosteroids, cyclophosphamide, cyclosporine and azathioprine are not approved treatments for IPF, and their efficacy is questionable. Pirfenidone recently became the first product to receive EU approval under the tradename Esbriet as a treatment for mild to moderate IPF. Pirfenidone has antifibrotic and anti-inflammatory activity and a demonstrated efficacy and marketing authorisation for the treatment of IPF in adults but the treatment effect is modest.

Lung transplant (LTx) is the only intervention that has been shown to positively impact survival in patients with IPF. Median survival after LTx in IPF patients is approximately 4-5 years, and 5-year survival is estimated at 39-50% [R11-5086; R12-2785; R12-3474]. The number of patients transplanted due to IPF has increased steadily over the last years, particularly in the US, where IPF has become the most common indication for transplantation since the introduction of the Lung Allocation Score [R12-3676; R12-3680; R12-3474]. However, broader application of this approach is limited given the scarce availability of donor organs. In addition, comorbidities and advanced age preclude many patients from referral to lung transplant given a mean age of IPF patients at presentation of 66 years [R10-2843].

About the product

Nintedanib is a small molecule receptor tyrosine kinase inhibitor (TKI) blocking vascular endothelial growth factor receptors (VEGFR 1-3), fibroblast growth factor receptors (FGFR 1-3) and platelet-derived growth factor receptors (PDGFR) α and β kinase activity in the low nanomolar range.

Nintedanib binds competitively to the ATP binding pocket of these receptors and blocks the intracellular signalling which is crucial for the proliferation, migration and fibroblast to myofibroblast transformation of lung fibroblasts. In addition Flt-3, Lck and Src kinases are inhibited by nintedanib.

The inhibition of signalling pathways of several tyrosine kinases; vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) involved in lung fibrosis is expected to reduce progressive fibrosis and fibroblast foci with interspersed areas of lung sparing and minimal excess inflammatory infiltrate in IPF.

Type of Application and aspects on development

Legal basis

This application concerns a centralised procedure and has been submitted as complete and independent application according to Article 8.3 of Directive 2001/83/EC meaning that it includes complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature supporting certain tests or studies.

Nintedanib was designated as an orphan medicinal product in the following indication: the treatment of idiopathic pulmonary fibrosis (IPF).

With regard to the paediatric development, a product specific waiver for all subsets of the paediatric population has been granted on the grounds that the disease or condition, Idiopathic Pulmonary Fibrosis, for which the specific medicinal product as intended, occurs only in the adult population.

Protocol Assistance/Scientific advice

The applicant requested CHMP scientific advice (EMEA/CHMP/SAWP/209064/2007) on aspects of non-clinical (need for reproductive toxicity studies) and clinical development for the oncology indication (interim analysis of the PFS endpoint). The CHMP recommended to include exploratory analyses directed at increasing the knowledge about the mechanism of action of nintedanib and to identify possible biomarkers.

There are no specific CHMP guidelines that are pertinent to the condition of idiopathic pulmonary fibrosis. In the design of the Phase III pivotal trials to compare nintedanib with placebo, account was taken of the EMA paper "EU Standard of Medicinal Product Registration: Clinical Evaluation of Risk/Benefit – the role of Comparator Studies" (EMEA/119319/04). At the time CHMP advice was obtained on the absence of an active comparator arm in the pivotal trials, there was no authorised medicinal product available in the EU for the treatment of idiopathic pulmonary fibrosis. This approach was therefore acceptable.

For the development of nintedanib a further Protocol Assistance was received from the CHMP pertaining to non-clinical and clinical aspects of the dossier in IPF. CHMP Protocol assistance was provided on 20th January 2011 (EMA/CHMP/SAWP/18782/2011) and was followed broadly with respect to the planned pivotal Phase III trials. As recommended by CHMP, diagnostic criteria for inclusion of patients with IPF were broadly in line with American Thoracic Society / European Respiratory Society (2011) Guidelines that rested in essence on diagnostic features on high resolution computed tomography (HRCT) and / or histopathological features on surgical lung biopsy (obtained via thoracotomy or thoracoscopy but not by transbronchial biopsy). The recent guidelines therefore obviate the necessity for surgical lung biopsy in the presence of characteristic features of IPF on HCRT; surgical biopsy becomes necessary when diagnostic features are not present on HCRT but the patient otherwise has symptoms of IPF. The recommendation of CHMP was that HCRT should be conducted no more than 3 months prior to study entry; however, the study enrolled patients who had had a diagnostic HCRT performed up to one year previously. Given that the disease is irreversible, this is not considered to be a major deviation from the advice. Furthermore, the HCRT evidence for all enrolled patients was evaluated centrally by a recognised expert in the field. The efficacy endpoints proposed by the Company were broadly endorsed by CHMP although it was commented that FVC (the selected primary efficacy variable) is an indirect measure of disease progression whereas diffusing capacity may be a more direct measure.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as soft capsules containing 100 mg and 150 mg nintedanib (as esilate) as active substance.

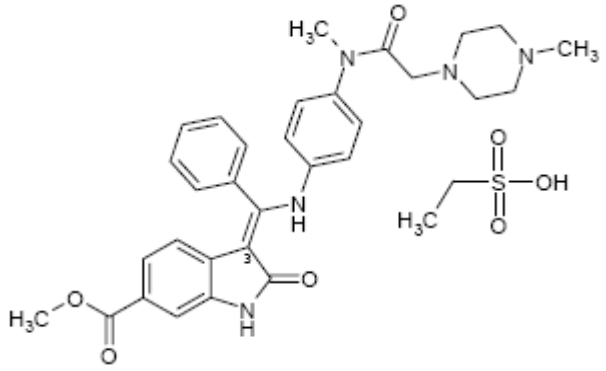
Other ingredients are medium-chain triglycerides, hard fat, lecithin, gelatin, glycerol (85 %), titanium dioxide, iron oxide red, iron oxide yellow and black ink. The black ink of the capsule has the following composition: shellac glaze, iron oxide black and propylene glycol.

The product is available in Alu/Alu blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of the active substance is ethanesulfonic acid - methyl (3Z)-3-{[(4-{methyl-[(4-methylpiperazin-1-yl)acetyl]amino}phenyl)amino]-(phenyl)methylidene}-2-oxo-2,3-dihydro-1H-indole-6-carboxylate (1:1) and has the following chemical structure:



Nintedanib esilate is a bright yellow powder soluble in water. The solubility increases at lower pH and decrease at higher pH due to the non-protonated free base which has a low solubility in water.
At room temperature, the active substance exists only in one single crystalline form. The active substance contains no chiral centres. The double bond at C-3 of the indole moiety allows for *E/Z* isomerism, but the active substance is the Z-isomer.

The chemical structure elucidation has been performed by infrared spectroscopy, ^{1}H NMR and ^{13}C NMR spectroscopy, ESI-CID mass spectroscopy, ultraviolet absorption (UV), X-ray powder diffraction and x-ray diffraction. The molecular formula is confirmed by elemental analysis.

Manufacture, characterisation and process controls

The active substance is synthesised in six steps using well defined starting materials. The final active substance is purified by crystallisation. According to the synthetic process described the active substance is consistently obtained as the Z-isomer.

The designation of the starting materials for the synthesis of the active substance has been justified with respect to their impurity profiles, their potential for carry-over into the final active substance, their structural complexity and with respect to their proximity to the final intermediate and the active substance, respectively.

The information provided adequately describes the manufacturing including reactions conditions, quantities of raw materials and yields.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origins and adequately characterised. The carry-over of impurities, reagents, solvents and catalysts from the starting material into the final active substance has been discussed. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediates, starting materials and reagents have been presented.

The active substance is packed in double low density polypropylene plastic bags (clear) and packed inside a fibre drum. The materials in contact with the active substance comply with the EC directive 2002/72/EC and EC 10/2011.

Specification

The active substance specification includes tests for appearance, identification (IR and TLC), chromatographic purity (HPLC), heavy metals (Ph Eur), residual solvents (GC), water (KF), sulphated ash (Ph Eur), assay (HPLC) and particle size (laser diffraction).

The control tests were carried out according to Ph. Eur. or the relevant in-house procedure. A detailed description and full method validation data were provided for the in-house analytical methods in accordance with the relevant ICH Guidelines. The analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable from a quality and safety point of view. Batch analysis data of the active substance are provided for a range of product scale batches which were manufactured according to the proposed synthetic route. The batch analysis data show that the active ingredient can be manufactured reproducibly. All results are within the specifications and consistent from batch to batch.

Stability

Three production scale batches of the active substance packed in the intended commercial packaging from the proposed manufacturer were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up to 60 months and accelerated conditions (40°C/75%RH) for up to 6 months. The active substance used in the primary stability studies was manufactured according to the commercial process.

The following parameters were tested: integrity of the packaging material, appearance, chromatographic purity (HPLC), water (KF), assay (HPLC), particle size distribution (laser diffraction), alkyl ethanesulfonates, crystalline modification and microbiological purity (HPLC). The analytical methods used in the stability studies, which were not included in the specifications, have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Forced degradation studies were conducted by exposing the active substance to high temperatures, high humidity, light, different pH values and oxidative conditions. Photostability testing following ICH guidelines Q1B was performed on one batch of the active substance. The results showed that there are no significant changes for any of the evaluated parameters established for the stability studies. Nevertheless, the active substance is sensitive to extreme oxidative conditions and high temperatures.

All stability studies results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of the drug development was to develop an immediate release solid oral dosage form, containing 100 mg and 150 mg of nintedanib as ethanesulfonate salt, considering the physicochemical properties of the active substance.

The selection of the soft capsule formulation was based on the relative high drug load, the properties of the active substance and excipient compatibility results. Due to the technology and process available the manufacturing process of this pharmaceutical form minimise the exposure of manufacturing personnel to the active substance, which is a highly potent compound.

Due to poor solubility of nintedanib esilate at neutral conditions, the active substance cannot be formulated as solution and is therefore suspended in a lipophilic fill mix. Selection of the lipophilic excipients mix was generally based on technical and functional formulation requirements and active substance stability.

All excipients are well known pharmaceutical ingredients and are commonly used for soft gelatin formulations. Their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. Relevant warnings are included in section 2 and 4.4 of the SmPC regarding the content of soya lecithin.

Milled active substance is used to prevent generation of active substance agglomerates in the fill mix. The composition of the 2 dosage strengths is proportional.

Quality by Design principles were used during development and an acceptable quality target product profile was established and the critical quality attributes were defined. A suitable control strategy was applied based on risk assessments. The development was used to establish the targets for critical process parameters and critical material attributes used for further process validation and the proposed commercial manufacturing. It is important to emphasise that no design space is proposed. The formulation development has been acceptably described and the choice of excipients has been justified.

The composition of the capsule fill has remained practically unchanged during phases 1 to 3 of clinical development, and is identical with the final formulation for the commercial product. The composition of the capsules shell has changed only with respect to the amount of the used colorants, which was adjusted to manufacture the desired colors of the capsule shell. The composition of Ofev capsules 100 mg and 150 mg used in the pivotal phase 3 clinical trials is identical with the composition of the proposed commercial product.

The discriminatory power of the dissolution method has been demonstrated. Bioequivalence study was performed showing bioequivalence between two batches, represented maximum batch-to-batch variability seen in the dissolution rate.

A standard process, utilizing well-established manufacturing technology, is selected for manufacturing of OFEV (100 mg and 150 mg) soft capsules.

The primary packaging is described as stated in the SmPC. The material complies with Ph Eur and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of eight main steps: fill mix preparation, gelatin mass preparation, encapsulation, drying, size sorting, washing, printing and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this type of dosage form: appearance, identification (HPLC and UV), Uniformity of dosage Units (Ph Eur), assay (HPLC), impurities (HPLC) and microbiological quality (Ph Eur).

Batch analysis data of 63 commercial batches of the 100 mg strengths and 46 commercial batches of the 150 mg strength are provided. The results confirm the consistency of the process and its ability to manufacture a product complying with the product specification.

Stability of the product

Stability data of three production scale batches of finished product stored under long term conditions for 36 months at 25 ºC / 60% RH, for up to 12 months under at 30ºC / 75% RH and for up to six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The parameters tested are appearance, dissolution, impurities (HPLC), assay (HPLC) and microbiological quality (Ph Eur). The analytical methods used during the stability studies are the same as used for release testing of the finished product.

One batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. In addition stress stability studies were performed on one fully representative batch under various extreme conditions of humidity and high temperatures. The finished product exposed to high humidity showed a decrease in dissolution, changes in the appearance, and an increase in water content of the capsule shell with a corresponding decrease in capsule hardness. The temperature stress results in decrease in dissolution and decrease in capsule hardness. No changes attributed to light stress were seen. The results obtained for temperature and humidity stress underscore the need for a moisture protective packaging material and the restriction in storage temperature.

Based on the all available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

Gelatine obtained from swine sources is used in the product. It was confirmed that the swine sources are from healthy animals fit for human consumption.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The main goal of the drug development was to develop an immediate release solid oral dosage form, containing 100 mg and 150 mg of nintedanib as ethanesulfonate salt, considering the physicochemical properties of the active substance. The development of the medicinal product includes elements of Quality by Design (QbD), but no design space has been established or claimed. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process is adequately validated at full scale at the proposed manufacturing site and a validation protocol has been presented.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

2.3.1. Introduction

The primary and secondary pharmacodynamics of nintedanib were investigated in a number of *in vitro* and *in vivo* studies. Pivotal toxicology studies and most of the safety pharmacology studies were carried-out in compliance with GLP.

Scientific advice (EMEA/CHMP/SAWP/209064/2007) has been sought on non-clinical aspects (need for reproductive toxicity studies).

2.3.2. Pharmacology

Primary pharmacodynamic studies

BIBF1120 was tested for its ability to interfere with essential fibrotic processes in a variety of *in vitro* assays and *in vivo* studies. Potency and selectivity were determined in enzymatic assays using human recombinant protein kinase domains. The inhibitory activity of BIBF1120 was confirmed at the cellular level in human lung fibroblasts from patients with IPF and from control donors. The *in vivo* efficacy of BIBF 1120 was explored in three animal models of pulmonary fibrosis, bleomycin-induced lung fibrosis in mice and rats and silica-induced lung fibrosis in mice. The *in vitro* findings are summarised in Table 1 and 2 and the *in vivo* findings in Table 3, respectively.

***In vitro* pharmacological profile**

Binding of BIBF 1120 to the VEGFR2 and PDGFRα and β kinase domain

BIBF 1120 was designed to bind to the ATP-binding site of the VEGFR-2. The expected binding mode was confirmed by cocrystallization with recombinant VEGFR-2 kinase and X-ray diffraction (resolution 2.1 Å), demonstrating that BIBF 1120 binds to the ATP-binding site in the cleft between the N- and C-terminal lobes of the kinase domain. The binding mode to the PDGFRα and β was not explored. However, sequence comparisons between the VEGFR-2 and the PDGFRα and β kinase domain suggest a similar binding mode with the glutamate residue at an equivalent position (PDGFRα: Glu609, PDGFRβ: Glu615) [U11-1947]

In vitro kinase assays (U02-1109, U02-1310, U08-1683, U12-2457)

The *in vitro* potency and selectivity of BIBF 1120 was determined in enzymatic assays using human recombinant kinase domains (see Table 1). BIBF 1120 is a potent inhibitor of PDGFRα/β, with IC50 = 59 nM and 60 nM, respectively. BIBF1120 is also a potent inhibitor of the VEGFR-1, -2 and -3 kinases with IC50 values of 34 nM, 21 nM, and 13 nM, respectively. BIBF 1120 inhibits the FGFR family with IC50 values: FGFR-1, 69 nM; FGFR-2, 37 nM; FGFR-3, 137 nM; FGFR-4, 610 nM.

More than 20 other kinases were also analysed and showed no inhibition by the compound with the exception of three members of the Src family of tyrosine kinases: Src (IC50 156 nM), Lck (IC50 16 nM), and Lyn (IC50 195 nM).

Table 1: Potency and selectivity of nintedanib in vitro

Kinase	BIBF 1120 IC50 [nM]
huVEGFR-1	34
huVEGFR-2	21
muVEGFR-2	13
VEGFR-3	13
FGFR-1	69
FGFR-2	37
FGFR-3	137
FGFR-4	610
PDGFRα	59
PDGFRß	60
InsR	>4000
IGF1R	>1000
EGFR	>50000
HER2	>50000
CDK1	>10000
CDK2	>10000
CDK4	>10000
Lck	16
Lyn	195
Src	156

Cellular activity (U02-1109, U08-1946, U03-1488)

The inhibitory effect of BIBF 1120 on *in vitro* PDGFR tyrosine kinase phosphorylation and cell proliferation and migration was explored in both normal human lung fibroblasts and lung fibroblasts explanted from patients with IPF. BIBF 1120 inhibited PDGF-BB-stimulated PDGFRα and β autophosphorylation with EC50 values of 21.6 nmol/L and 38.7 nmol/L, respectively and PDGF-BB-stimulated cell proliferation with an EC50 of 64 nmol/L. BIBF 1202, the metabolite of BIBF 1120, inhibited PDGFRα and β autophosphorylation with EC50 values of 5717 nmol/L and 23,510 nmol/L, respectively (265-fold and 607-fold less potent than BIBF 1120).

In human lung fibroblasts from patients with IPF, BIBF 1120 inhibited PDGF-BB-, bFGF-, and VEGF-stimulated cell proliferation in a concentration dependent manner with EC50values of 11 nmol/L, 5.5 nmol/L and less than 1 nmol/L, respectively (Table 2). In human lung fibroblasts from non-fibrotic controls, BIBF 1120 inhibited PDGF-BB-, bFGF-, and VEGF-stimulated cell proliferation in a concentration dependent manner with EC50 values of 13 nmol/L, 0.6 nmol/L and less than 1 nmol/L, respectively (Table 2). BIBF 1120 inhibited PDGF-BB-, bFGF- and VEGF-stimulated fibroblast migration in a concentration dependent manner in human lung fibroblasts from patients with IPF and non-fibrotic control donors (Table 2).

Table 2: Potency [EC50, nmol/L] and selectivity of BIBF 1120 in in vitro cellular assays

	Inhibition of proliferation of human lung fibroblasts; mean					
Donor	Control	Control	Control	IPF	IPF	IPF
Stimulus	PDGF-BB	bFGF	VEGF	PDGF-BB	bFGF	VEGF
BIBF 1120						
EC_{50} [nmol/L]	13	0.6	<1	11	5.5	<1

	Inhibition of migration of human lung fibroblasts; mean					
Donor	Control	Control	Control	IPF	IPF	IPF
Stimulus	PDGF-BB	bFGF	VEGF	PDGF-BB	bFGF	VEGF
BIBF 1120						
Significant inhibition at [nmol/L] [1)]	≥1000	≥100	≥1000	≥100	≥1000	≥100

1) $p<0.05$ versus growth factor-stimulated control

BIBF 1120 resulted in a dose-dependent decrease in the TGF-ß2-induced αSMA expression in two primary lung fibroblast isolates with estimated IC50 values in the range of 100 nmol/L to 1 µmol/L. Inhibition of fibroblast to myofibroblast transformation was likely not due to inhibition of TGF-ß signalling as BIBF 1120 does not block TGF-ß mediated SMAD2 phosphorylation.

To examine the duration of BIBF 1120 induced inhibition of PDGFRα and β, washout experiments were conducted in normal human lung fibroblasts exposed to BIBF 1120 for 30 min at 50 nmol/L. Cells were subsequently washed and transferred into new cell culture dishes. After 4 days BIBF 1120 still showed an inhibition of the PDGF-BB-induced PDGFRα and β autophosphorylation by 36.3% and 18.9%, respectively. When cells were washed multiple times after incubation with BIBF 1120, inhibitory activity

on the PDGFRs was still apparent after 8 h (16.9-27.3%). Even after 24 h some remaining inhibitory activity could be demonstrated (8.6-16.2%).

Radioligand receptor assay (U02-1084)

Affinities for various receptors were determined by radioligand receptor assays for BIBF 1120 at 5 µM. Out of 50 receptors tested, BIBF 1120 inhibited A3 adenosine receptors by 66%, NK2 receptors by 84%, 5HT1B receptors by 102% and L-type Ca2+ channels by 65%. The applicant considers that the measured receptor affinity suggests a possibility that BIBF 1120 at higher plasma concentrations (5 µM and above) may induce a decrease in blood pressure due to interactions with L-type Ca2+ channels. However, no specific binding was detected at 3 µmol/L when the radioligand receptor assays to determine specific binding of BIBF 1120 to 5HT1B receptors was repeated.

***In vivo* pharmacology profile**

The *in vivo* efficacy of BIBF 1120 was explored in three animal models of pulmonary fibrosis, bleomycin-induced lung fibrosis in mice and rats and silica-induced lung fibrosis in mice (U06-1451, U06-1479, U12-2437 and U12-2066). BIBF 1120 was administered orally, once daily in both a preventive regimen starting directly after bleomycin or silica stimulation till the end of the experiment and a therapeutic regimen starting after the onset of the fibrotic lung alteration in all models. In general, BIBF 1120 reduced lung inflammation and lung fibrosis in the different animal models. The parameters explored and the extent of inhibitory activity was different in each model. A daily dose of 24.9 - 83 mg/kg BIBF 1120 in mice and 8.3 – 41.5 mg/kg in rats was efficacious and tolerated when administered for 10 to 30 days. In summary, BIBF 1120 reduced lung inflammation demonstrated by reduced lymphocyte counts in the bronchoalveolar lavage fluid (BALF), interleukin-1 ß, chemokine (C-X-C motif) ligand 1/keratinocyte chemoattractant detected in lung tissue, diminished percentage of myeloid dendritic cells in lung tissue and semiquantitative histologic analysis of H&E-stained micrographs of the lungs. BIBF 1120 treatment diminished lung fibrosis demonstrated by reduced tissue inhibitor of metalloproteinase (TIMP)-1 and total lung collagen levels in lung tissue and by semiquantitative histologic analysis of the lungs and by reduction of messenger RNA expression of fibrosis-related marker genes (transforming growth factor (TGF)-ß1; procollagen I). A qualitative overview of the results is given in Table 3.

Table 3: Qualitative summary of the in vivo efficacy of BIBF 1120 in animal models of lung fibrosis (U06-1451, U06-1479, U12-2437 and U12-2066)

Study	Bleomycin-induced lung fibrosis				Silica-induced lung fibrosis	
Species	Rat		Mouse		Mouse	
Model	preventive	therapeutic	preventive	therapeutic	preventive	therapeutic[1)]
Readout						
Histology						
Fibrosis	↓	↓	↓	↓	↓	↓
Inflammation	n.d.	n.d.	↓	↓	↓	↓
Granuloma	n.d.	n.d.	n.d.	n.d.	↓	↓
Lung tissue						
TGFb mRNA	↓	↓	n.d.	n.d.	n.d.	n.d.
Procollagen-1 mRNA	↓	↓	n.d.	n.d.	n.d.	n.d.
Total collagen	n.d.	n.d.	O	↓	↓	↓
IL-1b	n.d.	n.d.	↓	↓	↓	↓
IL-6	n.d.	n.d.	n.d.	n.d.	n.d.	↓
KC	n.d.	n.d.	O	O	↓	↓
TIMP-1	n.d.	n.d.	↓	↓	↓	↓
BALF						
Total cells	n.d.	n.d.	O	O	O	O
Macrophages	n.d.	n.d.	O	O	O	O
Neutrophils	n.d.	n.d.	n.d.	n.d.	↓	↓
Lymphocytes	n.d.	n.d.	↓	↓	↓	↓

↓= significant reduction (independent of dose used)
O= no significant effect (independent of dose used)
n.d. = not determined
[1)] therapeutic treatment starting on Day 10

Secondary pharmacodynamic studies

Effect on CNS

Irwin Test: BIBF 1120 chloride was administered in oral doses of 50, 100 and 300 mg/kg to male mice. General overt and covert behaviour and body temperature were assessed at 15, 30, 60 minutes, and 24 hours post-administration. There was no effect on any of the tested behavioural parameter and on body temperature. A yellow discoloration of urine was noted 60 min following the 100 and 300 mg/kg dose.

Nocturnal motility: BIBF 1120 chloride was administered orally in doses of 50, 100 and 300 mg/kg in groups of 7 mice. There was no inhibition or activation of locomotion by BIBF 1120 at any of the doses tested as compared to vehicle-treated animals (U02-1589).

Electrophysiological assessment in vitro (U02-1288): Two assays (hERG and action potential configuration) assessing the effects of BIBF 1120 base on the electrophysiological parameters *in vitro*. In the hERG assay, concentrations of 0.1, 1.0, 3.0 and 10.0 µM was tested in triplicate and the mean fraction of HERG current (I/I_0) obtained was 0.92, 0.83, 0.53 and 0.25 respectively. BIBF 1120 base had an IC_{50} value of 4.0 µM on hERG-mediated potassium current in HEK293 cells.

Action potential configuration: In isolated papillary muscles from guinea pigs, the effect of 0.1, 0.3, 1.0, 3.0 and 10.0 µM BIBF 1120 base on action potential duration (ADP) to 10%, 30% and 90% repolarisation (ADP_{10}, ADP_{30} and ADP_{90} respectively), resting membrane potential, maximal velocity oof phase 0 upstroke, AP overshoot, AP amplitude and the force of concentration was tested (N=5). In the current study setting, BIBF 1120 base had no effect on APD_{90} in concentrations up to 10 µM, or any other measured parameters. No effect was observed on myocardial repolarisation at human therapeutic plasma concentrations.

Effect on Cardiovascular and Respiratory function

In the study performed in conscious rats (U02-1398), chronically instrumented rats received a single oral dose of 0, 10, 30 or 100 mg/kg BIBF 1120 CL, and the systolic arterial pressure, heart rate, temperature, motility and respiration rate and volume were recorded. Systemic arterial blood pressure increased dose-dependently. This effect lasted up to the end of the seven hour post-administration observation period. The increase in systolic systemic blood pressure was about 15 mm Hg in the highest dose group. No effects were observed for the remaining parameters measured.

Anaesthetised domestic pigs *(study U2-1674-02)* were administered increasing doses of BIBF 1120 chloride by intravenous infusion, starting at 3.0 mg/kg, escalating to 10 and 30 mg/kg in 30 minute intervals. The following parameters were measured and determined: systolic and diastolic arterial blood pressure, maximal left ventricular dP/dt (LVdP/dtmax), heart rate and ECG-intervals (QT, PR, QRS) from the electrocardiogram. Decrease in systolic and diastolic blood pressure (see figure 1 below) and in LVdP/dt-max (see figure 3 below) was observed after starting the infusion of the highest dose (30 mg/kg). These effects reversed after the end of dosing. No relevant changes were observed in the electrocardiographic parameters (QT-, QRS-, and PR interval).

Effect on Renal and hepatic function in rats

Metabolic markers of renal and liver function were measured in both serum (Day 7 only) and urine (Days 1 and 6) in rats *(study U02-1260)* treated orally with BIBF 1120 chloride at doses of 10, 30 or 100 mg/kg for 7 days. After 7 days there was an up to 1.6-fold increase in serum glutamic-pyruvic transaminase (GPT) in the animals given 100 mg/kg. Also in this dose group, there was an increase of similar magnitude in serum triglyceride concentration. Serum electrolytes were largely unchanged except for a mild increase in calcium at 100 mg/kg.

BIBF 1120 caused a modest increase in urine volume and urine sodium (1.3-fold and 2.3-fold, respectively) between 4 and 8 hours post administration of 100 mg/kg on Day 1. There was also a 1.5-fold increase in beta-N-acetylglucosaminidase (beta-NAG) between 4 and 8 hours post-administration on Day 1 and a ~3-fold increase in Ca^{2+}-output between 4 and 8 hours at 30 and 100 mg/kg. At Day 6, the effects on urine volume, sodium and calcium were absent.

Effect on Gastrointestinal function in rats (U02-1248, U02-1258 and U02-1259)

Gastric function and gastrointestinal motility were assessed in male and female rats (N=5 per sex) treated orally with 0, 10, 30 or 100 mg/kg of BIBF 1120 chloride (U02-1258). The doses of 10 and 30 mg/kg induced no statistically significant effects on gastric emptying. At 100 mg/kg a significant inhibition of gastric emptying was observed). Effects on gastric acid output, total acidity, gastric pH and volume following intraduodenal administration of 0, 10, 30 or 100 mg/kg BIBF 1120 chloride to groups of 7-8 male rats was assessed (U02-1248). No effects on gastric acid output, total acidity, gastric pH and volume were observed.

The effects of BIBF 1120 chloride on gastrointestinal transit was investigated following administration of 0, 10, 30 or 100 mg/kg BIBF 1120 chloride PO to male and female animals (5/sex/group). The gastrointestinal transit was determined as the percentage of the intestine length traversed by the test meal. BIBF 1120 did not influence gastrointestinal transit at 10 mg/kg PO, but at 30 and 100 mg /kg, intestinal transit was does-dependently reduced (U02-1259).

Safety pharmacology programme

There was no stand-alone GLP cardiovascular safety study, however, cardiovascular parameters have been assessed in non-GLP studies described in secondary pharmacodynamics section performed in rats and anaesthetized domestic pigs (U02-1398 and U02-1674). The following safety pharmacology core battery assessment was performed according to GLP, either as part of a repeat dose study (cardiovascular function in Cynomolgus monkeys) or in single dose studies (CNS and respiratory effects in rats).

Effect on Cardiovascular function (Cynomolgus monkeys - as part of the 4 week repeat dose toxicity study U03-1326, GLP)

In the Cynomolgus monkeys study, dose levels were 0, 3, 15 and 60 mg/kg/day. Electrocardiography (ECG) was recorded for all animals pre-treatment, prior to dosing on Day 1 as well as 2 and 24 hours after treatment on Day 1. In week 4 of treatment, all animals in groups 1 to 3 had ECG's performed 2 and 24 hours after treatment. Only 2 Group 4 animals were examined, as the remaining animals in this group had been terminated on Days 14 and 15 of the study due to clinical signs, and the two remaining animals had been of dosing since Day 15 (e.g. 2 weeks recovery). Blood pressure (systolic and diastolic) measurements were also performed.

Slight fluctuations were observed in the beats per minute heart rate (HR) on Day 1 pre-dose (HR 192-270), where most animals exhibited increased heart rate compared to the measurement performed earlier in the pre-dose period (HR 156-258). In the high dose group a minor increase in heart rate at 60 mg/kg/day by 5.7% versus the control group on Day 1 at 2 h post dosing. No other relevant effects on electrocardiographic parameters were found.

Blood pressure data showed a slight tendency to decreased mean systolic pressure in the high-dose males and females on Day 1, 2 hours after dosing resulting from the slightly reduced individual values of 2 males and 3 females. After 24 hours, their values returned to levels similar to the pre-dose values except for female no. 453. Since a slight trend to decreased systolic pressure was also observed in the control group and similar values were also observed during the pre-dose period, this finding is considered not to be related to treatment.

Effect on respiratory function (in rats using study U03-1465)

In this study, doses of 3, 20 and 100 mg/kg BIBF 1120 (as base) as a single PO dose was administered to male and female Wistar rats (8/sex/group). Morphine sulphate (200 mg/kg) was used as a positive control, to ensure that the assay was performing as expected. The respiratory parameters; respiration rate, tidal volume and minute volume, were recorded pre-dose, at 30, 90, 150 and 300 minutes after dosing, as well as 24 hours after dosing. The rats were placed in the chambers for approximately 16 minutes at each observation time point (from 8 minutes before the time point to 8 minutes after). All groups (including the control group) showed the highest group mean respiration rate prior to treatment, approximately 350 breaths/minute, and the lowest group mean respiration rates were recorded at 150 minutes after dosing (158-218 breaths/minute). However, the only statistically significant difference observed between the control and treated groups, were at 30 and 90 minutes post dosing in the positive control group, treated with morphine sulphate.

No marked or statistically significant changes following administration of BIBF 1120 were observed with regards to respiration rate, tidal volume or minute volume when compared to the vehicle treated animals.

Effects on general behaviour, body temperature and spontaneous locomotor activity in rats (U02-1537, GLP)

BIBF 1120 ES was administered PO to rats (4 animals/sex/group) at doses of 0, 3, 20, 100 mg/kg. Subjective observations performed to assess the behaviour and physiological state of the animals were performed prior to dosing, and at 30, 90, 150 and 300 minutes as well as 24 hours after treatment. Assessment of locomotor activity and body temperature (measured rectally) was also performed at the same time points. The animals were kept under observation for 7 days after treatment to record signs of toxicity or mortalities.

Oral administration of BIBF 1120 ES at doses of 3, 20 and 100 mg/kg (as base) produced no significant test article-induced changes in the behaviour or physiological state of rats. One female rat treated with 20 mg/kg BIBF 1120 exhibited slight tremor and piloerection at 30 and 90 minutes and slight tremor at 150 minutes post treatment. As only one animal at the intermediate dose level exhibited these mild changes, it was considered to be incidental, and not related to treatment. In addition, no significant effects on locomotor activity or body temperature were recorded in this study.

Pharmacodynamic drug interactions

No investigations on pharmacodynamic drug interactions have been submitted.

2.3.3. Pharmacokinetics

The non-clinical pharmacokinetics and drug metabolism of BIBF 1120 were studied in mice, rats, Cynomolgus monkeys and Rhesus monkeys and were compared to the pharmacokinetics and drug metabolism of BIBF 1120 in humans. The species and strains were identical with those used in pharmacology and toxicity studies. A number of liquid chromatography tandem mass spectrometry (LC-MS/MS) assays was developed and validated in order to quantify BIBF 1120, the major metabolites BIBF 1202 (M1) and BIBF 1202 glucuronide (M2) as well as CDBB 213 (BIBF 1120 Anilin) in plasma samples from several species. A number of non-validated methods were utilized for sample analyses in some range finding and PK studies; these methods followed the same general assay concept as the validated methods.

Absorption

In vitro studies of BIBF 1120 absorption in cells showed that permeability through bio-membranes was high, e.g. within minutes, the BIBF 1120 radioactivity was associated with the cell fraction in the test system, both at 37°C and 4°C the transport process was most likely passive.

Bioavailability was low in humans (4.7%) as well as the non clinical species approximately 11% (rat) to 23.8% (rhesus monkey). Intestinal P-gp activity was suspected to contribute to the low bioavailability due to incomplete absorption form the intestinal tract. In addition, first pass metabolism in the liver and intestine further contribute to the low bioavailability observed.

Distribution

The plasma protein binding of BIBF 1120 was high in mice, rats and humans, at 97% to 98.5%, and slightly lower in the non-human primates Rhesus and Cynomolgus monkeys (91% to 93%). Tissue distribution studies showed that the high binding to plasma protein did not restrict BIBF 1120 to the vascular compartment, but rather rapid and extensive distribution of BIBF 1120 was apparent in rat tissues at 5 minutes after IV administration. Repeated oral dosing (30 mg/kg [14C]BIBF 1120) for 13 days showed a slight accumulation in some tissues (testes, salivary gland, epididymides and liver), albeit a similar accumulation in plasma concentrations was not apparent.

Placental transfer of BIBF 1120 was not examined, although maternal exposure was determined in embryo-foetal development studies, no exposure data was generated for the foetuses, and no conclusions on the possible placental transfer can be made. Excretion of BIBF 1120 into milk was examined in female Wistar rats on Day 12 of lactation, and the average concentration at 1 hour after dosing was approximately 10-fold lower than the plasma concentration (269 and 2260 ng/mL respectively). The total estimated BIBF 1120 radioactivity secreted to milk over a 24 hour period was 0.18-0.5%.

Metabolism

BIBF 1120 showed high clearance in all species. Metabolic elimination was the major clearance pathway, with m1 (BIBF 1202) as the primary metabolite excreted via in faeces in all species. Approximately 10 to 30 % of the orally administered BIBF 1120 was recovered unchanged in the faeces of the nonclinical species, and approximately 20 % was recovered in human faeces. In the tabularised presentation of the major metabolites in plasma (as % of sample radioactivity), the metabolite M7 is listed to represent 11.6%. The remaining metabolites following oral administration of BIBF 1120 was present in smaller amounts less than 10% for most except in mice, where m3 and m4 was present at approximately 10 and 20 % respectively.

Excretion

Excretion and mass balance studies were carried out in mice, rats, Rhesus monkeys and human subjects using [14C]-radio-labelled BIBF 1120. Following both IV and PO dosing, the major fraction of radioactivity was recovered in faeces. Following IV dose, biliary excretion was the major contributing factor, however, following oral dose, the amount secreted in the bile was significantly less. Urinary excretion of BIBF 1120 associated radioactivity was largest following IV dose (approximately 5% of the dose) whereas following PO dose, this was much smaller (1.2, 1.5 and 0.65 % in rat, Rhesus monkey and human respectively). This is probably due to incomplete absorption of BIBF 1120 form the intestinal tract.

Overview of the excretion balance of [14C]BIBF 1120 ethanesulfonate related radioactivity in mouse, rat and Rhesus monkey as well as human (excretion data are given as % of dose)

	Mouse	**Rat**	**Rhesus monkey**	**Human**
Study	U09-2277	U02-1494	U05-1558	U06-1724

Route	p.o.	i.v.	p.o.	i.v.	p.o.	p.o.
Dose [mg/kg]	30	5	30	5	20	100 mg/ subject
Faecal excretion [% of dose]	95.8	89.2	98.5	84.4	85.7	93.4
Biliar excretion [% of dose]	10.1*/20.3 * (m/f)	65.2 *	8.3* (6 h sampling) 15.44 (24 h sampling)	ND	ND	ND
Urinary excretion [% of dose]	2.05	5.1	1.2	4.7	1.5	0.65

1. * anaesthetized animals, dosed intraduodenal

2. ND = not determined

The major route of excretion of BIBF 1120 following IV dose is faecal and biliary with approximately 5% of the dose being excreted via urine. Following PO dose, faecal excretion is higher in the rat, but similar in the Rhesus monkey, and urinary excretion decreases to approximately 1.5 % in the nonclinical species. Biliary excretion is higher following IV administration than PO administration, indicating together with the lower urinary excretion that absorption from the intestinal tract following PO administration is incomplete.

Pharmacokinetic drug interactions

Dose-dependent inhibition of OCT1 by BIBF 1120 was demonstrated, but not of other hepatic transporters tested. The IC50 value of BIBF 1120 for OCT1 was estimated to be 0.88 ìM i.e. 15-fold higher than the maximum plasma concentration of BIBF 1120 (30 ng/mL: 0.06 ìM) after 150 mg oral administration to humans. Therefore, potent inhibition of OCT1 by BIBF 1120 under *in vivo* conditions is considered unlikely.

Efflux transport studies suggest involvement of P-gp in the biliary and urinary excretion of BIBF 1120, while P-gp, MRP2 and BCRP appear to have little role in the biliary and urinary excretion of BIBF 1202.

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

Other pharmacokinetic studies

The pharmacokinetic properties of BIBF 1120 as well as its phase I metabolite BIBF 1202 and the phase II metabolite BIBF 1202-glucuronide were investigated in rats after single intravenous doses (U10-2525). BIBF 1120 was additionally investigated after single oral doses. Pharmacokinetics of BIBF 1120 is characterized by a high volume of distribution (2.86 L/kg for the central compartment and 15.7 L/kg at steady state) and a high plasma clearance of 91.8 (mL/min)/kg.

For BIBF 1202, the volumes of distribution were markedly smaller than those for BIBF 1120 (approximately 0.4 and 0.3 L/kg, respectively), but still considerably greater than the plasma or blood volume of the rat. The clearance of BIBF 1202 was moderate with 25.9 (mL/min)/kg.

The glucuronide of BIBF 1202 was distributed almost instantaneously into a volume of approximately the plasma space of the rat (0.0389 L/kg) and showed an only slightly higher volume of distribution at steady state (V(ss) of 0.0556 L/kg).

The oral administration of BIBF 1120 led to absolute bioavailabilities of 10.9% for BIBF 1120, 2.2% for BIBF 1202 and 2.5% for BIBF 1202-glucuronide. The metabolites BIBF 1202 and BIBF 1202-glucuronide were mainly formed pre-systemically after oral dosing of BIBF 1120.

2.3.4. Toxicology

The toxicology program included studies performed in rodents and non-rodents (dogs, minipigs, cynomolgous and rhesus monkeys).

Single dose toxicity

Single dose toxicity studies were performed in mice and rats, with both oral and intravenous injection (see table 3)

Table 1 Summary of the single dose toxicity studies performed with BIBF 1120

Study ID	Species / Sex / Number / Group	Dose / Route	Approx. lethal dose	Major findings
U04-1066	SCrl:NMRI mice 3/3 M/F	Oral 2000 mg/kg	>2000 mg/kg	None, the dose was well tolerated
U02-1491	Crl:WI(Han) rats 3/3 M/F	Oral 2000 mg/kg	>2000 mg/kg	On day of dosing: Sedation Staggered gait Diarrhoea
U09-1057	Crl:NMRI mice 3/3 M/F	IV 40 mg/kg	>40 mg/kg	None
U09-1058	Crl:WI(Han) rats 3/3 M/F	IV 40 mg/kg	>40 mg/kg	None

Repeat dose toxicity

Sub-acute, sub-chronic and chronic toxicity of BIBF 1120 were assessed in oral repeat-dose toxicity studies in CD-1 mice (up to 13 weeks), in Wistar rats (Crl:WI(Han) and HsdRccHan™:WIST) (up to 26 weeks), in Beagle dogs (up to 2 weeks), in Cynomolgus monkeys (up to 13 weeks) and in Rhesus monkeys (up to 52 weeks) and in intravenous repeat-dose toxicity studies in Crl:WI(Han) rats and Rhesus monkeys (each up to 2 weeks). In addition two exploratory studies were performed in mini-pigs.

In the following, tables summarising the major findings are presented (exploratory and dose escalating studies not included), and the pivotal toxicity studies are referred in more detail.

Non-rodent repeat-dose toxicity studies

Table 2 Repeat-dose toxicity studies performed in rodents.

Study ID (GLP)	Species/ Sex/ Number/ Group	Dose (mg/kg) /Route	Duration	NOEL/ NOAEL (mg/kg/ day)	Major findings
Mouse					
U10-1797 Non-GLP	Mouse (CD-1) 6/6 M/F	0, 10, 30, 100 Oral gavage	14 days	-	All dose groups Food consumption ↓ 100 mg/kg Body weight gain in females ↓
U10-1798 GLP	Mouse (CD-1) 12/12 M/F	0, 10, 30, 100 Oral gavage	13 weeks	<10	All dose groups Bodyweight gain ↓ ≥30 mg/kg RBC↓, haemoglobin↓, MCV↓, reticulocytes ↓, liver weights ↓, thickened epiphyseal plates, swelling of articular chondrocytes 100 mg/kg dentopathy, luteinized follicles, fewer mature corpora lutea

Rat					
U06-1063 GLP (TK non-GLP)	Wistar rat 5/5 M/F	0, 10, 30, 100 Oral gavage	14 days	-	≥30 mg/kg RBC↓, hemoglobin↓ 100 mg/kg Bodyweight gain (M)↓, PCV ↓, reticulocytes ↓, organ weights (liver, heart, spleen)↓, thickened epiphyseal growth plates
U02-1526 non-GLP	Wistar rat 5 M	0, 100, 300, 1000 Oral gavage	14 days	-	All dose groups Bodyweight gain↓, liver weights ↓, thickened epiphyseal growth plate ≥300 mg/kg Panmeylophthisis, atrophy of liver, heart, thymus spleen 1000 mg/kg RBC↓, hemoglobin↓, MCV↓, reticulocytes ↓, ALT↑, AST↑, GGT↑
U10-1799 GLP	Wistar rat 10/10 M/F	0, 5, 20, 60 mg/kg Oral gavage	91 days	< 5	≥5 mg/kg Dentopathy ≥20 mg/kg RBC ↓, PCV ↓, hemoglobin ↓, MCV ↑, MCHC ↓, hepatocellular hemosiderosis, swelling of articular chondrocytes 60 mg/kg Bodyweight gain ↓, ALT ↑, AST ↑, organ weights ↓ (heart, lung, liver, kidneys, spleen)
U04-1812 GLP	Wistar rat 10/10 M/F	0, 3, 20, 100 Oral gavage	28 days	20	100 mg/kg Bodyweight ↓ (recovery secondary to dentopathy) organ weights ↓ (heart, lung, liver, kidneys, thymus), dentopathy, thickened epiphyseal plates
U04-1065 GLP	Wistar rat 20/20 M/F	0, 3, 20, 100 Oral gavage	91 days	3	20 mg/kg hepatocellular hemosiderosis (females), ≥20 mg/kg Dentopathy, swelling of articular chondrocytes, cellular depletion (bone marrow) 100 mg/kg 1 premature decedent, RBC ↓, PCV ↓, hemoglobin ↓, ALT↑, AST↑, GGT↑, thymus weights ↓, thickened epiphyseal plates, hepatocellular hemosiderosis, cellular depletion (spleen), corpora lutea reduced in size/increased in number

U05-1843 GLP	Wistar rat 20/20 M/F	0, 5, 20, 80 Oral gavage	182 days	5	<u>20 mg/kg</u> swelling of articular chondrocytes, <u>≥20 mg/kg</u> RBC ↓, PCV ↓, hemoglobin ↓, organ weights ↓ (thymus, adrenals), hepatocellular hemosiderosis, swelling of articular chondrocytes, corpora lutea reduced in size/increased in number <u>80 mg/kg</u> Premature decedents, bodyweight gain ↓, ALT ↑, dentopathy, thickened epiphyseal plates, cellular depletion (bone marrow, thymus, spleen)
U09-1730 Non-GLP	Wistar rat 10/10	Intravenous 0, 5, 10, 20	14 days	5	<u>≥5 mg/kg</u> Thickened epiphyseal plates, cellular depletion (bone marrow) <u>≥10 mg/kg</u> ALT ↑, AST ↑

In the rodent studies of longer duration than 14 days, dentopathy was observed at dose levels above 20 mg/kg/day and consequently lower body weight and body weight gains were also observed. Due to the observed dentopathies, powdered diet was offered to the animals.

<u>13-week (MTD) study in mice (U10-1798)</u>

The objective of this 13-week toxicity study was to determine the Maximum Tolerated Dose of BIBF 1120, when administered to mice over 13 weeks, and to aid the selection of dose levels for a subsequent carcinogenicity study. BIBF 1120 was administered at dosages of 0, 10, 30 or 100 mg/kg/day for 13 weeks to four groups of animals, each comprising 12 male and 12 female CD-1 mice. In order to obtain blood samples for toxicokinetics, a further 8 males and females were allocated to the control group, and 12 male and females to the treated groups. During the study, clinical condition, bodyweight, food consumption, haematology, blood chemistry, toxicokinetics, organ weight, gross pathology and histopathology investigations were undertaken.

At the end of the 13-week administration period, discoloured white incisors were noted from Week 7 for animals given 100 mg/kg/day. A broken tooth was also recorded in Weeks 10/11 for one female receiving 100 mg/kg/day. Overall body weight gain was lower than that of controls for all treated groups in a dose-related manner (males/females: 0.74X/0.75X controls at 10 mg/kg/day, 0.59X/0.85X controls at 30 mg/kg/day and 0.55X/0.54X controls at 100 mg/kg/day). Haematology investigations revealed low red blood cell count (max. effect 0.86X control), low reticulocyte counts for females receiving 30 or 100 mg/kg/day (max. effect 0.63X control) and high mean cell haemoglobin and mean cell volume (max. effect 1.2X control) for animals receiving 30 or 100 mg/kg/day. Platelet counts were low (max. 0.80X control) for males and females receiving 100 mg/kg/day.

Blood chemistry investigations revealed slightly high bilirubin concentrations for males receiving 100 mg/kg/day BIBF 1120 without a histopathological correlate. Total protein and albumin concentrations were slightly low resulting in a slightly low albumin to globulin ratio for females receiving 100 mg/kg/day (max. effect 0.94X control).

Absolute, body weight-relative and brain weight-relative liver weights were low for all treated female groups (max. 0.75X control) and, to a lesser extent, for males receiving 30 or 100 mg/kg/day BIBF 1120 (max. 0.84X control). Absolute, body weight-relative and brain weight-relative heart weights were low for females receiving 100 mg/kg/day BIBF 1120 (max. 0.81X control).

Histopathological changes were thickening of the growth plate (due to increased hypertrophic chondrocytes) and increased swelling of chondrocytes in the basal layers of the articular cartilage in femur and tibia, cellular depletion in the bone marrow, dentopathy of the incisor teeth, increased extramedullary haematopoiesis in the spleen and liver, diffuse cortical hypertrophy in the adrenals, and decreased numbers of mature corpora lutea and increased numbers of luteinised follicles in the ovaries.

In summary, oral administration of BIBF 1120 to CD-1 mice at doses of 10, 30 or 100 mg/kg/day for 13 weeks was associated with changes in the bone and bone marrow, teeth and spleen of both sexes, in the liver and adrenals of males, and in the ovaries of females receiving 100 mg/kg/day. The dosage of 30 mg/kg/day was considered to be close to the MTD. NOAEL was not established.

26-week toxicity study in CrlGlxBrlHan:WI rats (U05-1843)

Groups of 20 male and 20 female Han Wistar rats received daily oral doses of 0, 5, 20 and 80 mg/kg/day BIBF 1120 over a period of 26 weeks, followed by an 8 week recovery period. In order to obtain blood samples for toxicokinetics, a further 6 males and females were allocated to each group, and a further 10 male and females were allocated to the control and high dose groups to allow for a treatment free period (recovery) at the end of the study. During the study, mortality, clinical condition, bodyweight, food consumption, ophthalmoscopy, haematology, blood chemistry, toxicokinetics, organ weight, gross pathology and histopathology investigations were performed.

5 mg/kg/day dose group: No evident adverse effects considered to be drug-related were observed.

20 mg/kg/day dose group: Two animals (one male, one female) were prematurely sacrificed due to poor general condition with histopathological changes indicating a severe (incidental) chronic progressive nephropathy and liver hemosiderosis. In males, body weight gain was slightly reduced. Clinically, 3/20 males and 9/20 females had broken incisors (regularly growing back and breaking again) and almost all animals showed swelling and reddening of the gingiva. Thymus weight in males was slightly reduced. Histopathologically, in some animals there were minimal to slight drug-related effects on the liver, spleen, kidneys, bone marrow, thymus, ovaries, epiphyseal growth plates, articular cartilage and incisors. All these findings were dose-related. They are described below together with those of the 80 mg/kg/day dose group.

80 mg/kg/day dose group: Five males and three females were found dead or were prematurely sacrificed due to poor general condition caused by broken incisors and resulting reduced food consumption. The remaining animals were prematurely sacrificed on day 165/166 (except recovery animals) due to poor general condition and lack of body weight gain in males. In males, there was no body weight gain from Day 50 on.

Findings from both the 20 and 80 mg/kg/day dose groups: Clinical pathology investigations revealed a mild, reversible decrease in red blood cell parameters (red blood cell count, hematocrit and hemoglobin) and an increase in reticulocytes. White blood cell count and platelet count were also slightly increased. Clinical chemistry revealed a mild increase in the activity of ALT, aldolase and GLDH in both sexes. Urinalysis revealed strongly increased protein concentration and presence of white blood cells in some animals. At the end of the recovery period, the activity of aldolase was still increased in both sexes. Microscopically, there were drug- and dose-related effects on the liver, spleen, kidneys, adrenals, bone marrow, thymus, ovaries, epiphyseal growth plates, joint cartilage, incisors and the main bile duct with adjacent organs. The major findings were graded as moderate or severe. Almost all findings were completely reversible or ameliorated during the recovery period (high-dose group).

Findings which were not observed or not as prominent in previous toxicity studies in rats were periportal hemosiderosis in the liver, moderate or severe mineralisation of the capsule and trabecules in the spleen, severe dilatation of the main extra-hepatic bile duct probably induced or aggravated by a narrow duodenal orifice of the duct and accompanied by a moderate to severe inflammation and a pronounced hyperplasia of the ductal epithelial cells, minimal to mild signs of unspecific tubular injury in the kidneys, slight to severe peliosis/angiectasis and, only in males, diffuse hyperplasia of the adrenal cortex, slight to severe cellular depletion in the bone marrow, minimal to mild lymphoid depletion in the spleen, moderate involution of the thymus and reduced size and sparse vascularisation of corpora lutea (often associated with an increase in number) in the ovaries.

Table 3 Summary of Non-rodent repeat-dose toxicity studies

Study ID (GLP)	Species/Sex/ Number/Group	Dose (mg/kg) /Route	Duration	NOEL/NOAEL (mg/kg/day)	Major findings
U05-2450 GLP	Dog 2/2 M/F	0, 3, 10, 30, 1000 Oral gavage	14 days	< 3 mg/kg/day	≥3 mg/kg diarrhea, food consumption↓, large intestine goblet cells ↓, ≥10 mg/kg 1 animal euthanized Intestinal mucosa: erosions, villous atrophy, epithelial cell damage ≥30 mg/kg Clinical signs: severe diarrhea Vomiting, salivation and paralysis/abnormal gait All animals euthanized ALT/AST↑ cellular depletion (bone marrow, lymphoid tissue), gall bladder inflammation All dose groups Bodyweight/bodyweight gain↓, cholesterol↑, thickened epiphyseal plates
U03-1707 Non-GLP Dose escalating study	Cynomolgus monkey 1/1 M/F	0, 20, 40, 80 Oral gavage	Up to 10 days per dose level		All dose groups (not consistent between sexes) RBC↓, PCV ↓ WBC↓, reticulocytes↑, platelets↑, monocytes↑ 40 mg/kg ALT↑ 80 mg/kg Diarrhea, vomiting, yellow skin AST ↑, ALT ↑

U04-1067 Non-GLP Dose escalating study	Cynomolgus monkey 1/1 M/F	0, 20, 40, 80, 160 Oral gavage	One week per dose level One day at 160 mg/kg		<u>≥ 40 mg/kg</u> Diarrhea, vomitus, RBC ↓, hemoglobin ↓, reticulocytes ↑, PCV ↓, platelets ↑, ALT ↑, AST ↑ <u>80 and 160 mg/kg</u> Bodyweight↓, food consumption↓ spleen weight ↓
U03-1326	Cynomoglus monkey 3/3 M/F 2/2 recovery animals	0, 3, 15, 60 Oral gavage	28 days + 2 week recovery	3 mg/kg/day	<u>15 mg/kg</u> Occasional diarrhea, vomitus <u>60 mg/kg</u> Diarrhea, vomitus, bodyweight ↓, RBC ↓, hemoglobin ↓, reticulocytes ↑, PCV ↓, platelets ↑, ALT ↑, AST ↑, epithelial atrophy, villous atrophy (small intestine), cellular depletion (thymus, lymph nodes, spleen, bone marrow)
U05-2245	Cynomolgus monkey 3/3 M/F 2/2 recovery animals	0, 3, 15, 30/20 Oral gavage	13 weeks +4 week recovery	3 mg/kg/day	<u>≥15 mg/kg</u> Bodyweights/bodyweight gains ↓, cellular depletion (bone marrow) <u>30/20 mg/kg</u> thymic weights↓, cellular depletion (thymus, bone marrow)
U05-2452 Non-GLP Dose escalating study	Rhesus monkey 1/1 M/F	5mg/kg IV 10 mg/kg PO 20, 40, 60, 80, 120 mg/kg 40/mg/kg	1 day 3 to 4 days or up to a week 14 days	-	<u>≤10 mg/kg</u> Bilirubin ↑ <u>≥40 mg/kg</u> Diarrhea, bodyweights ↓, ALT ↑, AST ↑, GLDH ↑, GGT ↑ <u>120 mg/kg</u> Premature decedent
U05-2427	Rhesus monkey 3/3 M/F 2/2 recovery animals	0, 10, 20, 60	28 days + 4week recovery	10 mg/kg/day	<u>≥10 mg/kg</u> Yellow coloured faeces <u>20 mg/kg</u> RBC↓, HB↓ <u>60 mg/kg</u> Bodyweights ↓, diarrhea, vomitus, ALT ↑, AST ↑, GGT ↓
U07-1875	Rhesus monkey 4/4 M/F	10, 20, 60/45/30	52 weeks		<u>All dose groups</u> Thickened epiphyseal plates Adrenal zona fasciculata atrophy (10mg/kg: males) <u>≥20 mg/kg</u> Bodyweight gain ↓ Spleen weight (females)↓ <u>60/45/30 mg/kg</u> 1M/1F euthanized Diarrhea, albumin ↓, total protein ↓,

13-week toxicity study in Cynomolgus monkey (U05-2245).

Groups of 3 males and 3 females received doses of 0, 3, 15 or 30 mg/kg/day BIBF 1120 by oral gavage. A further 2 male and 2 female monkeys were assigned to the Control and high dose groups which were retained for a 4 week recovery period following the 13 week treatment period. During the study, clinical condition, bodyweight, food consumption, ophthalmic examination, ECG, haematology, blood chemistry, toxicokinetics, urinalysis, organ weight, macroscopic and microscopic pathology investigations were performed.

Because of clinical signs of diarrhea and loose/liquid faeces in animals given 30 mg/kg/day, the high dose was lowered to 20 mg/kg/day after a 3-day off treatment period. At 15 and 30/20 mg/kg/day the animals showed reduced body weight gain or body weight loss. Pertinent histopathological changes were decreased cellularity of the thymic cortex and fatty replacement of the bone marrow. Though also present in some control animals, their incidence and severity were increased in treated animals and showed a dosage-related trend. All bone marrow smears, however, were considered to be normal for cellularity, distribution and morphology.

52-week toxicity study in Rhesus monkey (U07-1875)

Groups of 4 male and 4 female Rhesus monkeys received doses of 0, 10, 20 or 60 mg/kg/day BIBF 1120 by oral gavage for 52 weeks. Additionally 2 males and 2 females were allocated to the control and high dose groups and were allowed a 4-week treatment free period at the end of the study to observe recovery. As a result of adverse clinical signs seen in high dose animals, this group had a 20 day off-dose period following the first 4 weeks of treatment. The high dose was reduced stepwise from 60 to 45 and then to 30 mg/kg/day. Three weeks of treatment were added at the end of the study with the remaining animals from this group.

During the study, clinical condition, bodyweight, ophthalmic examination, EGC, haematology, blood chemistry, toxicokinetics, urinalysis, immunology, organ weights, macropathology and histopathology investigations were performed.

In the high dose group one male and one female were killed due to severe clinical signs including liquid faeces, vomiting, pale gums, salivation, hypoactivity, thin build and hunched posture. Similar effects were also observed in the other high dose animals. Mixed *coliform Spp*. (particularly *E. coli*) and/or *Campylobacter Spp.* bacteria were detected in the rectum and/or faeces, and may have contributed to the severity of liquid faeces. Reduced body weight was observed in all treated groups, but only statistically significant at the two highest dose levels. Statistically significant reductions of large unstained cells were observed in all groups, while only at the top dose for basophils, erythrocytes and platelets. Blood chemistry showed elevated levels of chloride (all doses) and reduced levels of albumin and total protein (highest dose). Growth plate thickening in the femur, atrophy of adrenal zone fasciculata and reductions in spleen weight were present in all dose groups, while significant reductions in lung and bronchi weight were seen at the highest dose only. No other effects than growth plate thickening in the femur was still present at the end of recovery. Electrocardiography, ophthalmoscopy, urinalysis, peripheral blood leukocyte analysis and macroscopic pathology did not indicate any treatment-related changes.

In addition, two mini-pig studies were performed in order to evaluate the sensitivity of this non-rodent species to liver enzyme elevations induced by BIBF 1120 which have been observed in patients.

Oral exploratory 2-day toxicity study in mini-pigs (U11-1349, non-GLP)

An oral dose of 50 mg/kg BIBF 1120 was administered on 2 consecutive days to 1 male and 1 female mini-pig. Slight increases in the activity of AST, ALT and GLDH and decreases in bilirubin and triglycerides on Day 2 were considered of no biological relevance.

Oral 7-day toxicity study in mini-pigs (U07-2343, non-GLP)

Oral doses of 0, 50, 70 and 100 mg/kg/day BIBF 1120 were administered to a total of 3 male animals, and 0, 40, and 50 mg/kg/day to a total of 3 female animals. The maximum continuous administration per dose was 7 days. Toxicokinetic measurements demonstrated substantial exposure (C(max) of 538 ng/mL and AUC(0-24h) of 9010 ng·h/mL at 100 mg/kg/day in the males). Five of 6 animals had to be sacrificed. Despite of the severe clinical signs, only inconsistent increases in AST (up to 123.4 U/L) and ALT (up to 86.4 U/L) were observed at the end of the treatment period. No other significant changes of liver parameters were observed (AP, gamma-GT, LDH, bilirubin).

Genotoxicity

Overview of the genotoxicity studies performed with BIBF 1120 in the table 6:

Type of test / study ID / GLP	**Test system**	**Concentrations / Concentration range / Metabolising system**	**Results Positive / negative / equivocal**
Gene mutations in bacteria U02-1481 GLP	Salmonella strains TA 1537, TA 98, TA 100, TA 1535, TA 102	3, 10, 30, 100, 300, 500, 1000, 2500 µg/plate 3-2500 µg/plate +/- S9	Negative
Gene mutations in mammalian cells U12-1512 GLP	Mouse lymphoma L5178 $tk^{+/-}$	+/- S9	Negative
Chromosomal aberrations *in vivo* U02-1650 GLP	Rat, micronuclei in bone marrow	+/- S9	Negative

Carcinogenicity

Carcinogenicity studies have not been included in the submission of the MAA (See Discussion on non-clinical aspects).

Reproduction Toxicity

A summary of studies performed is given in table 7

Table 7 Summary table of the performed studies:

Study type / Study ID / GLP	Species; Number Female / group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg &AUC)
Male fertility U10-1128 GLP	Rat 24 M/F per group	Oral gavage 0, 3, 20, 100 mg/kg/day	M: 92 days prior to mating F: vehicle GD 1-6	<u>Paternal toxicity</u> ≥20 mg/kg Food consumption↓ Body weight & gain ↓ Dentopathies↑ <u>Early embryonic development</u> 3 mg/kg/day Total and early resorptions ↑ 20 mg/kg/day Corpora lutea ↓ However, the differences observed, are within the means in evaluation studies (Viertel 2004 and 2005)	Paternal toxicity: 3 mg/kg/day Male reproductive performance and early embryonic development: 100 mg/kg/day
Embryo-fetal development					
Embryo-fetal development U07-1710 Non-GLP	Rat 10 F per group	Oral gavage 0, 30, 75, 180 mg/kg/day	F: GD 7-16	Complete loss of embryos ≥ 30 mg/kg/day	-
Embryo-fetal development U07-1814 Non-GLP	Rat 10 F per group	Oral gavage 0, 5, 10, 20 mg/kg/day	F: GD 7-16	≥ 5 mg/kg/day Skeletal variations ↑ 10 mg/kg/day Dysmorphogenesis of blood vessels ↑ 20 mg/kg/day: complete resorption of embryos	-
U13-1420-01 Dose range finding study Non-GLP	Rabbit 6 F per Group	Oral gavage 0, 3, 7, 15, 30, 75, 180 mg/kg/day	F: GD 6-18	15 mg/kg/day Brachydactylia ≥75 mg/kg/day Abortions Resorption rate ↑ Sternal malformation↑ Deviations of heart and vertebrae↑	Proposed doses for a subsequent study: 15, 30 and 60 mg/kg/day

Fertility and early embryonic development

Male fertility and subsequent early embryonic development was investigated following administration of BIBF 1120 at 0, 3, 20 and 100 mg/kg/day PO to male rats. Treatment started 92 days before mating. The females received treatment with vehicle only from gestation day 1 through 6. Clinical signs, food consumption, body weight were recorded for the parental animals. Copulation, fertility and gestation rates were recorded.

In the treated males, loose and broken teeth were observed at 20 and 100 mg/kg (4/24 and 23/24 animals respectively), and decreased food consumption and bodyweight fluctuations (mid dose group) and body weight loss (high dose group) was observed from 20 mg/kg/day BIBF 1120. With respect to reproductive parameters, all males in all groups mated successfully, and copulation, fertility and gestation indices were all 100% in both control group as well as the treated groups. Litter parameters (resorptions, resorption rate and pre-implantation loss) were comparable between control and treated groups. Slight decrease in the mean number of corpora lutea (20 mg/kg) and slight increases in the mean numbers of total resorptions, early resorptions and resorption rate (all at 3 mg/kg) were within the ranges of means in the evaluation studies of Viertel et al. (2004 and 2005).

Embryo-fœtal development

Two studies were performed in rats to assess the effects of BIBF 1120 on embryofetal development. In the first study doses of 30, 75 and 180 mg/kg were used, and complete loss of embryos was observed at all dose levels. Another study, with lower doses of 5, 10 and 20 mg/kg/day with the dosing period spanning from gestation day 7 to 16 was performed. In this study, complete resorption of the embryos was observed at 20 mg/kg and at the lower doses, skeletal variations (5 and 10 mg/kg), as well as dysmorphogenesis of blood vessels (10 mg/kg) were observed.

A dose range study was performed in female rabbits treated with BIBF 1120 by oral gavage with 0, 3, 7, 15, 30, 75, 180 mg/kg/day (6 animals per group) from GD 6 to 18. Maternal toxicity was observed in the high dose group (180 mg/kg/day), 1 animal found dead and 2 euthanized due to poor general condition on GD 15. Unusually yellow urine was observed from doses of 75 mg/kg/day. Embryotoxicity was observed form 75 mg/kg/day, where increased resorption rate was observed, and 2 females had complete abortions. Complete fetal resorption was also observed at 180 mg/kg/day. No fetal or maternal toxicity was demonstrated at 30 mg/kg/day or below. A teratogenic effect was observed in the 75 mg/kg/day group. The results in this preliminary study support a dose proposal of 15, 30 and 60 mg/kg/day for low-, mid- and high-dose levels in a subsequent pivotal embryofetal toxicity study.

Toxicokinetics

Blood samples for exposure and toxicokinetics were taken in most of the toxicology studies; results of AUC and Cmax obtained in the studies summarised in table X. For the calculation of exposure multiples, the oral dosage of 250 mg bid as Maximum Recommended Human Dose (MRHD).

See below a table 8 summarising the toxicokinetic studies (PO treatment, except Study U09-1730):

Study ID **Species** **N**	**Daily Dose (mg/kg)**	**AUC (ng.h/ml)**		**Cmax (ng/mL)**	
		♂	♀	♂	♀
Rodents					
U10-1797 Mouse 6M/6F	10 30 100	233 1410 6650	242 1790 5940	42.7 197 1610	57.3 348 1070

U10-1798 Mouse 12M/12F	**10** 30 100	**225** 1280 5630	**231** 1350 3840	**57.7** 262 1450	**56.2** 241 600
U06-1063 Rat 4M/4F	10 30 100	40 274 434	20 178 85#	7 30 46	4 20 14#
U10-1799 Rat 10M/10F	**5** 20 60	**22.7** 163 302	**26.1** 195 446	**4.16** 24.4 45.6	**6.48** 37.6 33.7
U04-1812 Rat 10M/10F	3 **20** 100	12.6 **149** 1340	8.46 **119** 1750	8.40 **58.0** 256	5.64 **46.5** 370
U04-1065 Rat 20M/20F	**3** 20 100	**2.31** 213 1130	**8.38** 220 2150	**1.21** 57.4 147	**3.07** 67.8 346
U05-1843 Rat 20M/20F	**5** 20 80	**16.4** 184 1240	**29.2** 316 1030	**5.12** 41.1 173	**9.70** 78.4 168
U09-1730 *IV* Rat 10M/10F	**5** 10 20	**388** 1130 3000	**336** 1230 3150	**399** 943 1800	**317** 784 1980
Non-rodents					
U05-2450 Beagle Dog GLP 2M/2F	**3** 10 30 100	**223** 1404 5609 13326	**782** 1903 5949 9787	**17** 173 532 1176	**80** 156 540 789
U03-1326 Cynomolgus monkey 3M/3F	**3** 15 30	**158** 1600 4980	**185** 1030 4740	**15.1** 135 299	**158** 1600 4980
U05-2245 Cynomolgus monkey 3M/3F	**3** 15 30/20	**305** 1370 1870	**345** 1310 1320	**38.5** 140 170	**37.2** 131 119
U05-2427 Rhesus monkey 3M/3F	**10** 20 60	**357** 755 2830	**529** 1360 3620	**51.4** 131 222	**75.2** 151 285
U07-1875 Rhesus monkey 4M/4F	**10** 20 60/45/30	**786** 831 1100	**506** 1220 1660	**77.6** 92.0 92.0	**53.7** 132 160

#plasma samples probably degraded due to multiple freeze/thaw cycles
Numbers in **bold** indicate NOAEL or LOAEL

Local Tolerance

The local tolerance of BIBF 1120 was assessed in 5 studies, where both dermal tolerance (U05-1395), potential for eye irritation (U03-1151), injection either intravenous (U08-1862), intramuscular (U08-1862), intra-arterial (08B041) or paravenous (U08-1863) were assessed. In addition a study was performed to assess the haemolytic potential of BIBF 1120 formulated in a solution for infusion (09B032).

In the local tolerance studies performed BIBF 1120 was found to be well tolerated following dermal application, in an aqueous solution (0.5 g solubilised in water applied topically to skin of rabbits); ocular application of 20 mg powdered administered once in the conjunctival sac of rabbits; intravenous administration in rabbits (2 mg/mL in 5 % glucose). Nintedanib was found to cause local irritation following intra-arterial administration in rabbits (2 mg/mL in 5% glucose); paravenous administration in rats (2 mg/mL in 5% glucose); intramuscular administration in rabbits (2 mg/mL in 5% glucose). The haemolytic potential was found to be very low, as only hemolysis of up to 0.5% was observed when 2.0 mg/mL BIBF 1120 was applied.

Other toxicity studies

Immunotoxicity

Immunological investigations (phenotyping of lymphoid subpopulations in blood, spleen and thymus, as well as determination of spleen natural killer cell activity) were performed in the 4-week toxicity study in rats (U04-1812), in the 13-week toxicity study in Cynomolgus monkeys (U05-2245) and in the 52-week toxicity study in Rhesus monkeys (U07-1875).

In male rats of the 4-week toxicity study (U04-1812), a decreased T- to B-lymphocyte ratio in the peripheral blood and spleen of all animals given the high dose level of 100 mg/kg/day, an approximate 30% decrease in T-helper cells (CD3+CD4+) of the blood and a slight increase in natural-killer cell activity in the spleen were observed.

In the 13-week toxicity study in Cynomolgus monkeys (U05-2245), no changes of CD4 and CD8 positive T cells and NK cells were observed. In peripheral blood, a mild reduction of B cells was noted in study week 13. No changes were present at the end of the recovery period.

In the 52-week toxicity study in Rhesus monkeys (U07-1875), no consistent changes of peripheral blood monocytes, B and T cell subsets and NK cells were observed. There were also no changes in the percentages of splenic B and T cell subsets and NK cells and no statistically significant changes in NK cell function. In animals at 60/45/30 mg/kg/day, however, there was evidence of a decrease in the absolute numbers of all cell types per gram of spleen tissue. No changes of any parameter including NK cell function were present at the end of the recovery period.

Metabolites

The major human metabolite is BIBF 1202 (free acid) and BIBF 1202 glucuronide, contributing up to 32 and 47% of total radioactivity following 100 mg BIBF 1120. Toxicokinetic analyses have revealed substantial systemic exposure to BIBF 1202 and BIBF 1202 glucuronide in the general toxicity studies. However, due to low formation of BIBF 1202 in the in vitro genotoxicity studies with BIBF 1120, BIBF 1202 was tested separately in the *in vitro* genotoxicity assays (see table below).

Table 9 *In vitro* genotoxicity studies with BIBF 1202

Type of test (study ID)	**Test system (strain)**	**S9**	**Concentration range**	**Results**	**GLP**
Ames test (U12-1640)	*S.typhimurium* (TA 98, TA 100, TA 102, TA 1535, TA 1537)	±	50-500 µg/plate	negative	Yes
TK locus test (U12-1997)	Mouse lymphoma L5178Y $tk^{+/-}$ cells	±	5-50 µg/ml	negative	Yes

Impurities

A number of potential impurities were identified, classified and genotoxic investigations performed where specified according to alerts and classification. Genotoxic impurities which might be present in DS were always below 3 ppm corresponding to the TTC of 1.5 µg/day at a maximum daily dose of 250 mg bid of BIBF 1120, which is the highest dose level in any of the indications of nintedanib. Therefore, none of these genotoxic impurities have been specified.

The impurity CDBB 213 is an intermediate of chemical synthesis and potential degradant of BIBF 1120. It has an aromatic amine moiety, which is in general a structural alert for mutagenicity. It may be formed under acidic conditions. In the case of delayed gastric emptying, soft gelatine capsules with BIBF 1120 may stay in the acidic milieu of the stomach for up to 7-8 hours. Based on in vitro data, it is estimated that this may result in a maximum degradation of BIBF 1120 to CDBB 213 of approximately 3%. Assuming a maximum daily dose of 250 mg bid of BIBF 1120, this percentage of degradation would result in an exposure of maximally ~0.3 mg/kg/day or ~1.15 µmol/kg/day of CDBB 213 in human patients.

CDBB 213 was negative in the bacterial reverse mutation test, the Ames test, but showed clastogenic effects at very high concentrations in the 24h-incubation experiment in the mouse lymphoma assay. CDBB 213 was negative withj respect to genotoxicity endpoints in a 2-week rat toxicity study, where bone marrow micronucleus assay and the Comet assay for the detection of DNA damage in the liver, were assessed. A NOAEL of 1 mg/kg/day was established for CCBB 213 in the 14 day repeat dose toxicity study performed.

Phototoxicity

In accordance with the OECD Guideline 432, a phototoxicity assay was conducted with Balb/c 3T3 cells (U05-2272). A phototoxic threshold concentration of approximately 0.5 µg/mL was estimated. At this concentration, the Photo Effect (PEC) was around the phototoxicity limit of 0.15. A Photo Irritating Factor (PIF) of 18.4 and a Mean Photo Effect (MPE) of 0.554 and 0.560 indicate that BIBF 1120 may have a phototoxic potential.

2.3.5. Ecotoxicity / environmental risk assessment

Table 10 Summary of main study results

Substance (INN / Invented Name): Nintendanib esilate			
CAS-number (if available): 656247-18-6 (ethanesulfonate)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD122 (draft November 2000)	Nonionised form: 3.4 (At pH 7 = 3.0)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log P_{ow}	pH 5: log D = 0.93 pH 7: log D = 2.7 pH 9: log D = 3.34 log P = 3.4	not B
Persistence	DT50 or ready biodegradability	Not ready biodegradable	P
Toxicity	NOEC (Fish, Early Life Stage Toxicity Test/ *Brachydanio rerio*)	0.038 mg/L	not T
PBT-statement :	The compound is considered as P as it is not readily biodegradable.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default	2.5	µg/L	> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Mean of 3 soils: Koc = 194549 Kd = 5376 Mean of 2 sludges: Koc = 5608 (6633 max.) Kd = 1878 (2236 max.) Note: As part of the water/sediment study Kd sediment was calculated to be 539 (max).	
Ready Biodegradability Test	OECD 301B	Not ready biodegradable	Study report No U09-0242-01

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	River (r), pond (p) $DT_{50, water}$ = 0.56 (r) and 0.43 (p) $DT_{50, sediment}$ = not calculated as no or very low degradation was observed $DT_{50, whole\ system}$ = 1.28 (r) and 0.47 (p) Kd values = 1.28 (r) and 0.47 (p)			Nintedanib is rapidly dissipated from the water phase, and adsorbs to the sediment. Once in the sediment, the degradation process is slow, mainly via formation of bound residues and minor metabolites
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	NOEC	≥ 1	mg/L	
Daphnia magna Reproduction Test	OECD 211	NOEC LOEC	0.24 0.81	mg/L	
Fish, Early Life Stage Toxicity Test/*Brachydanio rerio*	OECD 210	NOEC LOEC	0.038 0.12	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50 NOEC	> 1000 ≥ 1000	mg/L	
Phase IIb Studies					
Sediment dwelling organism (*Chironomus riparius*)	OECD 218	NOEC	100	mg/L	

Considering the above data, nindetanib is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

BIBF 1120 was tested for its ability to interfere with essential processes occurring in fibrotic lung diseases like IPF in a variety of in vitro assays and in vivo systems.

The in vivo activity of BIBF 1120, as a single agent, was investigated in mouse and rat models of lung fibrosis. In all experiments BIBF 1120 was always dosed in a preventive, but also in a therapeutic manner, i.e. after onset of fibrotic lung pathology. In all studies, preventive and therapeutic administration of BIBF 1120 reduced both bleomycin and silica induced lung fibrosis and inflammation in mice and rats.

On the molecular level, BIBF 1120 is thought to inhibit the FGFR, PDGFR and VEGFR signalling cascades mediating lung fibroblast proliferation and migration by binding to the adenosine triphosphate (ATP) binding pocket of the intracellular receptor kinase domain. In vitro, the target receptors are inhibited by BIBF 1120 in low nanomolar concentrations. In human lung fibroblasts BIBF 1120 inhibited PDGF-stimulated PDGFR activation determined by receptor autophosphorylation. BIBF1202, the main metabolite of BIBF 1120 was 265-fold and 607-fold less potent than BIBF 1120 in inhibiting the autophosphorylation of PDGFRα and β, respectively. In human lung fibroblasts from patients with IPF BIBF 1120 inhibited PDGF-, FGF-, and VEGF-stimulated cell proliferation with EC50 values of 11 nmol/L, 5.5 nmol/L and less than 1 nmol/L, respectively. BIBF 1202 was not tested in the fibroblast proliferation assay. At concentrations between 100 and 1000 nmol/L BIBF 1120 also inhibited PDGF-, FGF-, and VEGF-stimulated fibroblast migration and TGF-ß2-induced fibroblasts to myofibroblast transformation. The contribution of the anti-angiogenic activity of BIBF 1120 to its mechanism of action in fibrotic lung diseases is currently not clarified.

Therefore, BIBF 1120 is a tyrosine kinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR á and ß) and fibroblast growth factor receptors (FGFR 1-3) kinase activity. BIBF 1120 binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signaling which is crucial for the migration, proliferation and transformation of lung fibroblasts the hallmark cells of IPF. In addition Fms-like tyrosine-protein kinase (Flt)-3, Lymphocyte-specific tyrosine-protein kinase (Lck) and proto-oncogene tyrosine-protein kinase src (Src) are inhibited (see section 5.1 of the SmPC).

The secondary pharmacodynamics of BIBF 1120 was determined in an array of studies where effects of treatment with BIBF 1120 by oral gavage at 10, 30 and 100 mg/kg in most in vivo studies, except the mouse CNS study where doses of 50, 100 and 300 mg/kg, was examined with respect to CNS (general behaviour, body temperature and locomotor activity in mice); Cardiovascular effects (hERG assay in HEK293 cells and action potential configuration in isolated guinea pig papillary muscle cells, as well as in vivo studies in conscious rats and anaesthetized domestic pigs); Gastrointestinal effects, including gastric emptying, output, pH and volume and gastrointestinal transit (in rats); Hepatic and renal function. No relevant effects were shown. The results of the hepatic function assay were therefore not predictive for the hepatotoxic effects of high dosages of BIBF 1120 observed in the clinic (See Discussion on Clinical Safety).

In the core safety pharmacology studies, no significant effects of BIBF 1120 treatment was observed on respiratory parameters or in general behaviour, body temperature and locomotor activity in rats. Similarly, with respect to cardiovascular parameters, only slight and transient increased heart rate was observed in the high dose group 1 and 2 hours after dosing on Day 1 (5.7% increase compared to control group), and a slight tendency to decreased mean systolic pressure in the high-dose males and females on Day 1, 2 hours after dosing resulting from the slightly reduced individual values of 2 males and 3 females.

The lack of any specific pharmacodynamic drug interaction studies is acceptable.

Pharmacokinetic *in vitro* and *in vivo* studies describing the absorption, distribution, metabolism and excretion of BIBF 1120 in the nonclinical species used, as well as *in vitro* metabolism data from human hepatocytes. Pharmacokinetic and metabolism studies on the major metabolites BIBF 1202 and BIBF 1202 glucuronide was also performed.

In vitro studies of BIBF 1120 absorption in cells showed that permeability through bio-membranes was high, e.g. within minutes, the BIBF 1120 radioactivity was associated with the cell fraction in the test system, both at 37°C and 4°C the transport process was most likely passive.

Bioavailability was low in humans (4.7%) as well as in the non-clinical species (from approximately 11% in rat to 23.8% in rhesus monkey). Intestinal P-gp activity was suspected to contribute to the low bioavailability due to incomplete absorption form the intestinal tract. In addition, first pass metabolism in the liver and intestine further contribute to the low bioavailability observed.

The plasma protein binding of BIBF 1120 was high in mice, rats and humans, at 97% to 98.5%, and slightly lower in the non-human primates Rhesus and Cynomolgus monkeys (91% to 93%). Tissue distribution studies showed that the high binding to plasma protein did not restrict BIBF 1120 to the vascular compartment, but rather rapid and extensive distribution of BIBF 1120 was apparent in rat tissues at 5 minutes after IV administration. Repeated oral dosing (30 mg/kg [14C]BIBF 1120) for 13 days showed a slight accumulation in some tissues (testes, salivary gland, epididymides and liver), albeit a similar accumulation in plasma concentrations was not apparent.

Placental transfer of BIBF 1120 was not examined, although maternal exposure was determined in embryo-foetal development studies, no exposure data was generated for the foetuses, and no

conclusions on the possible placental transfer can be made. Excretion of BIBF 1120 into milk was examined in female Wistar rats on Day 12 of lactation, and the average concentration at 1 hour after dosing was approximately 10-fold lower than the plasma concentration (269 and 2260 ng/mL respectively). The total estimated BIBF 1120 radioactivity secreted to milk over a 24 hour period was 0.18-0.5%. In rats, small amounts of radiolabelled nintedanib and/or its metabolites were excreted into the milk (≤ 0.5 % of the administered dose) (see section 5.2 of the SmPC).

BIBF 1120 showed high clearance in all species. Metabolic elimination was the major clearance pathway, with m1 (BIBF 1202) as the primary metabolite excreted via in faeces in all species. Approximately 10 to 30 % of the orally administered BIBF 1120 was recovered unchanged in the faeces of the nonclinical species, and approximately 20 % was recovered in human faeces. In the tabularised presentation of the major metabolites in plasma (as % of sample radioactivity), the metabolite M7 is listed to represent 11.6%. The remaining metabolites following oral administration of BIBF 1120 was present in smaller amounts less than 10% for most except in mice, where m3 and m4 was present at approximately 10 and 20 % respectively.

The major route of excretion of BIBF 1120 following IV dose is faecal and biliary with approximately 5% of the dose being excreted via urine. Following PO dose, faecal excretion is higher in the rat, but similar in the Rhesus monkey, and urinary excretion decreases to approximately 1.5 % in the nonclinical species. Biliary excretion is higher following IV administration than PO administration, indicating together with the lower urinary excretion that absorption from the intestinal tract following PO administration is incomplete.

Dose-dependent inhibition of OCT1 by BIBF 1120 was demonstrated, but not of other hepatic transporters tested. The IC50 value of BIBF 1120 for OCT1 was estimated to be 0.88 ìM i.e. 15-fold higher than the maximum plasma concentration of BIBF 1120 (30 ng/mL: 0.06 ìM) after 150 mg oral administration to humans. Therefore, potent inhibition of OCT1 by BIBF 1120 under *in vivo* conditions is considered unlikely.

Efflux transport studies suggest involvement of P-gp in the biliary and urinary excretion of BIBF 1120, while P-gp, MRP2 and BCRP appear to have little role in the biliary and urinary excretion of BIBF 1202.

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

An extensive toxicology program has been performed in rodents and non-rodents. For the selection of the most relevant non-rodent species for long-term toxicity studies, dogs, mini-pigs, Cynomolgus monkeys and Rhesus monkeys were considered. The dog was identified as the most sensitive, however, not considered most relevant due to severe gastro-intestinal effects, since the severe gastrointestinal effects were considered to prevent this species from attaining sufficient long-term exposure necessary to detect potential chronic effects of BIBF 1120 on other organ systems than the GI tract. Further, dogs were determined not to be a suitable species to investigate the liver enzyme elevations observed in patients, since only moderate increases in transaminase activities were observed. These elevations were seen when the dogs were moribund due to the severe adverse gastrointestinal effects (diarrhoea and vomiting). The mini-pig was also considered not to be an appropriate species to study liver enzyme elevations observed in the clinical setting, as this species showed severe clinical signs, but only slight and inconsistent increases in AST and ALT at the end of the treatment period. The Cynomolgus and Rhesus monkey also showed gastro-intestinal effects, although not to the same degree as the dog, and was therefore chosen as the non-rodent species most relevant for the toxicology program.

The single dose of 40 mg/kg BIBF 1120 IV or 2000 mg/kg orally was well tolerated in mice and rats. In rats treated with 2000 mg/kg orally general, nonspecific, signs of toxicity were observed on the first day of treatment, e.g. sedation, staggering gait and diarrhoea, but the signs subsided and all animals proceeded to planned necropsy. No changes were observed at gross pathology of the animals. No single

dose studies were performed in non-rodents. This is acceptable according to ICH guideline M3(R2), acute toxicity information from two mammalian species dosed both via the clinical route and a parenteral (in this case IV) route.

The toxicity profile of BIBF 1120 was explored in both mice (up to 13 weeks) and rats (up to 26 weeks). In the long-term studies LOAEL (mouse) and NOAEL (rat) of <10 and 5 mg/kg/day were found. The most prominent treatment related findings which were considered to be related to the pharmacodynamic activity of BIBF 1120 as a VEGFR-2 inhibitor was: dentopathies of the continuously growing incisors which in turn contributed to the lower body weight and body weight gains observed, the thickening of the growth plates in long bones, PAS-positive hyaline intracytoplasmic granules in podocytes and glomerular endothelium of the glomeruli of the kidneys and the reduced size/increased number of corpora lutea and presence of luteinized follicles in the ovaries and lastly cellular depletion of the bone marrow which may be related to the various roles VEGF has in hematopoiesis.

Single dose toxicity studies in rats and mice indicated a low acute toxic potential of nintedanib. In repeat dose toxicology studies in rats, adverse effects (e.g. thickening of epiphyseal plates, lesions of the incisors) were mostly related to the mechanism of action (i.e. VEGFR-2 inhibition) of nintedanib. These changes are known from other VEGFR-2 inhibitors and can be considered class effects (see section 5.3 of the SmPC).

In Cynomolgus monkeys, 13 weeks treatment with BIBF 1120 by oral gavage at doses of 3 to 30 mg/kg/day revealed treatment-related changes with a dosage-related trend: 30 mg/kg/day was not tolerated; 3 mg/kg/day was well tolerated clinically but resulted in histopathological changes of the thymus and bone marrow. Evidence of recovery was seen in animals which had received 30/20 mg/kg/day after 4 weeks without treatment. NOAEL was not established in this study. BIBF 1120 administered by oral gavage to Rhesus monkeys for 52 weeks at 60/45/30 mg/kg/day caused treatment-related liquid faeces, vomiting and bodyweight loss. The presence of potentially pathogenic bacteria in the gastrointestinal tract may have exacerbated the severity of liquid faeces and led to the premature death of two high dose animals. Reduced bodyweight gains were observed in animals receiving 20 mg/kg/day which were considered adverse. Histopathologically, growth plate thickening in the femur/tibia and sternum, that was pharmacologically mediated, was seen at all dose levels. All treatment-related changes showed complete or partial reversibility. Changes seen at the 10 mg/kg/day dose level were either slight (i.e., not considered adverse), of unknown relationship to treatment, or were pharmacologically mediated, and as such this dosage level was considered to be the NOAEL.

Diarrhoea and vomiting accompanied by reduced food consumption and loss of body weight were observed in toxicity studies in non-rodents.

There was no evidence of liver enzyme increases in rats, dogs, and Cynomolgus monkeys. Mild liver enzyme increases, which were not due to serious adverse effects such as diarrhoea were only observed in Rhesus monkeys.

Toxicokinetic and pharmacokinetic data confirm that the non-clinical species were exposed at or above expected therapeutic levels with regards to BIBF 1120 as well as the main metabolites BIBF 1202 and BIBF 1202 glucuronide. AUC is considered to be the most appropriate parameter since non-clinical toxicity mainly was seen upon repeated administration. In the toxicology studies, the observed NOAEL's give rise to low exposure multitudes close to or below 1. This is acceptable in the context of the proposed indication of second line treatment of locally advanced or metastatic NSCLC. For the calculation of exposure multiples, the oral dosage of 250 mg bid as Maximum Recommended Human Dose (MRHD). However, for the current application 150 mg bid is specified as the MRHD in the SmPC. The dose-normalized geometric mean $AUC_{(0\text{-}12h,ss)}$ of BIBF 1120 in advanced cancer patients was 1.21 ng*h/mL (U11-1639). Thus a geometric mean daily exposure of twice the AUC(0-12h,ss), i.e. 363 ng*h/mL, can be assumed in humans.

The genotoxic potential of BIBF 1120 was assessed by three studies. An determining the potential of BIBF 1120 to cause gene mutations in bacteria, a study assessing the frequency of gene mutations in mammalian cells (), and an in vivo study in rats assessing micronuclei in bone marrow cells, indicative of the potential of BIBF 1120 to cause chromosomal aberrations. BIBF 1120

Genotoxicity studies indicated no mutagenic potential for nintedanib.

No evidence of carcinogenic potential was identified following long term administration of 30 mg/kg/day and 10 mg/kg/day BIBF 1120 in mice and rats respectively.

The submitted studies on reproductive toxicity are considered adequate. Based on preclinical investigations there is no evidence for impairment of male fertility (see section 4.6 and 5.3 of the SmPC). There are no human or animal data on potential effects of nintedanib on female fertility available.

A study of male fertility and early embryonic development to implantation in rats did not reveal effects on the male reproductive tract and male fertility following oral treatment with BIBF 1120 at 3, 20 and 100 mg/kg. However, slight effects on the early embryonic development, e.g. slightly decreased number of corpora lutea and slight increases in the mean numbers of total resorptions, early resorptions and resorption rate (all at 3 mg/kg). These observed differences between the treated groups and the control group were however within the ranges of means in the evaluation studies of Viertel et al. (2004 and 2005).

In rats, embryo-foetal lethality and teratogenic effects were observed at exposure levels below human exposure, at the MRHD of 250 mg twice daily (b.i.d.). Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels. The studies performed to assess embryo-fetal development in rats, showed that BIBF 1120 at doses exceeding 20 mg/kg resulted in complete resorption of the embryos. At lower doses skeletal variations (from 5 mg/kg) and dysmorphogenesis of blood vessels (10 mg/kg) were observed. The embryotoxicity observed is not surprising, as BIBF 1120 inhibits angiogenesis. The dose range finding study performed in rabbits showed embryo-foetal lethality and teratogenic effects from 75 mg/kg/day (Day 1 C_{max} 498 ng/mL and AUC_{0-24} 2290 ng*h/mL).

In rabbits, embryo-foetal lethality was observed at an exposure approximately 8 times higher than at the MHRD. Teratogenic effects on the aortic arches in combination with the heart and the urogenital system were noted at an exposure 4 times higher than at the MRHD and on the embryo-foetal development of the axial skeleton at an exposure 3 times higher than at the MRHD.

The SmPC text sufficiently describes the observed embryo toxicity in sections 4.4, 4.6 and 5.3, and women and men of childbearing potential are advised to use adequate contraception.

Nintedanib may cause foetal harm in humans (see section 5.3). Women of childbearing potential being treated with Ofev should be advised to avoid becoming pregnant while receiving treatment with Ofev and to use adequate contraception during and at least 3 months after the last dose of Ofev. Since the effect of nintedanib on the metabolism and efficacy of contraceptives has not been investigated, barrier methods should be applied as a second form of contraception, to avoid pregnancy.

There is no information on the use of Ofev in pregnant women, but pre-clinical studies in animals have shown reproductive toxicity of this active substance (see section 5.3). As nintedanib may cause foetal harm also in humans, it should not be used during pregnancy unless the clinical condition requires treatment. Pregnancy testing should be conducted at least prior to treatment with Ofev.
Female patients should be advised to notify their doctor or pharmacist if they become pregnant during therapy with Ofev. If the patient becomes pregnant while receiving Ofev, she should be apprised of the potential hazard to the foetus. Termination of the treatment with Ofev should be considered.

There is no information on the excretion of nintedanib and its metabolites in human milk.
Pre-clinical studies showed that small amounts of nintedanib and its metabolites (≤ 0.5 % of the administered dose) were secreted into milk of lactating rats. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Ofev.

Nintedanib is presented as an oral formulation (oral gelatine capsules). The potential for local irritation can be assessed as part of other toxicity tests, and as the intended route of administration, t the local effects on the GI canal can be considered adequately addressed in the repeat dose studies. In the 5 local tolerance studies and the study on haemolytic potential of BIBF 1120 showed that BIBF 1120 was well tolerated following dermal application in aqueous solution, ocular application in the conjunctival sac and following intravenous administration (5% glucose) in rabbits. Whereas, on the other hand BIBF 1120 was causing local irritation following intra-arterial, intra muscular and paravenous administration in 5% glucose.

Immunological investigations were performed on the 4-week repeat dose toxicity study in rats, in the 13-week toxicity study in Cynomolgus monkey and in the 52-week study in Rhesus monkeys. No consistent adverse effects on the immune system of the nonclinical species were observed. Similarly, no signs of immunosuppression were observed in these studies.

The metabolite BIBF 1202 is negative in genotoxicity studies in vitro. No *in vivo* studies have been performed. However, toxicokinetic data indicate substantial exposure to BIBF 1202 and BIBF 1202 glucuronide following dosing with BIBF 1120. Therefore, no further toxicity studies with BIBF 1202 or BIBF 1202 glucuronide is required.

The impurity CDBB 213, an intermediate of chemical synthesis and potential degradant of BIBF 1120 was negative in the bacterial reverse mutation test, the Ames test, and in a 2-week rat toxicity study, where bone marrow micronucleus assay and the Comet assay for the detection of DNA damage in the liver, but showed clastogenic effects at very high concentrations in the 24h-incubation experiment in the mouse lymphoma assay. A NOAEL of 1 mg/kg/day was established for CCBB 213 in the 14 day repeat dose toxicity study performed.

The OECD Guideline 432 specifies that; a PIF value > 5, and a MPE value >0.15 predicts phototoxicity. Consequently, the 3T3 NRU test indicates that nintedanib is phototoxic. However, as no phototoxic potential has been seen in existing human data, the positive in vitro finding is considered to be of low clinical relevance.

Nintedanib is not expected to pose a risk to the environment. However, as a precautionary measure the Applicant has included the statement: “Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment” in the PL.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate. The relevant information has been included in the SmPC (sections 4.4, 4.6, 5.1, 5.2, 5.3).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 11: Clinical trials of nintedanib to investigate efficacy and safety in patients with idiopathic pulmonary fibrosis

Trial/ Phase	Duration [1]	Trial Description	N [2]	Doses studied [3]	Trial status/ report no. [4]
1199.30/ II	52 weeks	Randomised, double-blind, placebo-controlled trial; period 1	428	Placebo; nintedanib 50 mg qd, 50 mg bid, 100 mg bid, 150 mg bid	Completed [U11-1225]
		Optional active blinded treatment phase after 52 weeks [5]; period 2	286	Nintedanib 50 mg qd, 50 mg bid, 100 mg bid, 150 mg bid	
1199.35/ II		Open-label extension of trial 1199.30	198	Nintedanib 50 mg qd, 50 mg bid, 100 mg bid, 150 mg bid Patients started at dose they were receiving at end of study 1199.30. Three months after trial initiation, all patients were offered to escalate to nintedanib 150 mg bid.	Ongoing [U13-2558]
1199.31/ IIa	14 and 28 days	Randomised, double-blind, placebo-controlled trial in Japanese patients; stratification according to concomitant pirfenidone use	50	Placebo; nintedanib 50 mg bid, 100 mg bid, 150 mg bid	Completed [U11-2158]
1199.40/ II		Open-label extension of trial 1199.31	20	Nintedanib 150 mg bid (as add-on treatment to pirfenidone)	Ongoing [U13-2767]
1199.32/ III	52 weeks	Randomised, double-blind, placebo-controlled trial	513	Placebo; nintedanib 150 mg bid	Completed [U13-2381]
1199.34/ III	52 weeks	Randomised, double-blind, placebo-controlled trial	548	Placebo; nintedanib 150 mg bid	Completed [U13-2382]
1199.33/ III		Open-label extension of trials 1199.32 and 1199.34	750 [6]	Nintedanib 150 mg bid, 100 mg bid [7]	Ongoing [U13-2559]
1199.187/ IIIb	52 to 78 weeks	Randomised, double-blind, placebo-controlled trial	275 [6]	Placebo; nintedanib 150 mg bid	Ongoing [8]

qd - once daily; bid - twice daily

[1] For the open-label extension trials there was no minimum or maximum treatment duration.

[2] Number of treated patients.

[3] Starting dose; dose reductions were allowed in all trials, except trial 1199.31.

[4] For the completed trials, final clinical trial reports are included in this application dossier. For the ongoing trials, except trial 1199.187, interim clinical trial reports are included.

[5] Patients randomised to placebo were switched in a blinded manner to nintedanib 50 mg qd; other patients continued to receive the same dose as at the end of period 1.

[6] Planned number of patients.

[7] Patients randomised to placebo in the parent trial (1199.32 or 1199.34) were switched to nintedanib. Patients' treatment allocation in the parent trials (placebo or nintedanib 150 mg bid) remained blinded until completion and unblinding of the parent trials. Patients continued receiving the same dose (100 mg bid or 150 mg bid) as at the end of the parent trial. After unblinding of the parent trials, placebo patients could increase the dose to 150 mg bid.

[8] Recruiting since Dec 2013.

Clinical trials for evaluation of efficacy in IPF patients

Table 12: summary of clinical trials submitted in support of efficacy

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
1199.32	98 centres in 13 countries	Phase III confirmatory; randomised, double-blind, placebo-controlled	Oral nintedanib 150 mg b.i.d.; dose reduction to 100 mg b.i.d. possible	To investigate the efficacy and safety of nintedanib compared with placebo over 52 weeks in IPF	**Randomised:** 515 Nintedanib:309 Placebo: 206 **Treated:** 513 Nintedanib:309 Placebo: 204	52 weeks treatment duration;28 day follow-up	80.7% male 19.3% female Median age 68yr (min/max 42yr/87yr)	Patients ≥40 years, diagnosed with IPF within last 5 years; baseline DL_{CO} 30% to 79% of predicted and baseline FVC ≥50% predicted	Annual rate of decline in FVC (adjusted) expressed in mL/year
1199.34	107 centres in 17 countries	Phase III confirmatory; randomised, double-blind, placebo-controlled	Oral nintedanib 150 mg b.i.d.; dose reduction to 100 mg b.i.d. possible	To investigate the efficacy and safety of nintedanib compared with placebo over 52 weeks in IPF	**Randomised**: 551 Nintedanib:331 Placebo:220 **Treated**:548 Nintedanib: 329 Placebo: 219	52 weeks treatment duration;28 day follow-up	77.9% male 22.1% female Median age 67yr (min/max 42yr/89yr)	Patients ≥40 years, diagnosed with IPF within last 5 years; baseline DL_{CO} 30% to 79% of predicted and baseline FVC ≥50% predicted	Annual rate of decline in FVC (adjusted) expressed in mL/year
1199.30	92 centres in 25 countries	Phase II, dose-finding, randomised, double-blind, placebo-controlled	Nintedanib 50 mg q.d., 50 mg b.i.d., 100 mg b.i.d., 150 mg b.i.d. (starting doses); dose reductions to dose below where possible	To investigate the efficacy and safety of 4 doses of nintedanib compared with placebo over 52 weeks in IPF	**Randomised:** 432 Nintedanib 50 mg qd: 87 50 mg bid: 86 100 mg bid: 86 150 mg bid: 86 Placebo: 87 **Treated:** 428 Nintedanib 50 mg qd: 86 50 mg bid: 86 100 mg bid: 86 150 mg bid: 85 Placebo: 85	52 weeks treatment period; 14 day follow up	74.8% male 25.2% female Mean age (± SD) 65± 8.6 yr	Patients ≥40 years, diagnosed with IPF within last 5 years; baseline DL_{CO} 30% to 79% of predicted and baseline FVC ≥50% predicted	Annual rate of decline in FVC (adjusted) expressed in L/year

2.4.2. Pharmacokinetics

Absorption

Nintedanib reached maximum plasma concentrations approximately 2 - 4 hours after oral administration as soft gelatin capsule under fed conditions (range 0.5 - 8 hours).

Results of the absolute bioavailability analysis in healthy volunteers for $AUC_{0-\infty}$ and AUC_{0-tz} are presented below:

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

Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism. Dose proportionality was shown by increase of nintedanib exposure (dose range 50 - 450 mg once daily and 150 - 300 mg twice daily). Steady state plasma concentrations were achieved within one week of dosing at the latest.

The effect of food on exposure to nintedanib was investigated in study 1199.17. In a single-dose open study of 16 male volunteers, the effect of a high fat meal (as administered 30 minutes before drug administration) on a single 150mg of nintedanib was investigated (see Table 14).

Table 14: Geometric mean (and gCV%) pharmacokinetic parameters of BIBF 1120 BS after single oral administration of 150 mg nintedanib capsule under fasted and fed conditions to healthy male volunteers

BIBF 1120 capsule		Fasted	Fed
Parameter	**Unit**	**N=14**	**N=15**
t_{max}[1]	[h]	2.00 (1.48-3.98)	3.98 (1.50-6.05)
C_{max}	[ng/mL]	11.1 (60.3%)	13.2 (61.6%)
$AUC_{0-\infty}$	[ng·h/mL]	98.4 (33.0%)[2]	119 (53.9%)
AUC_{0-24}	[ng·h/mL]	79.0 (34.8%)[2]	90.2 (52.9%)

[1] median and range
[2]: N = 11
Source Data: Table 15.5.2.1: 1 and 2

After food intake, nintedanib exposure increased by approximately 20 % compared to administration under fasted conditions (CI: 95.3 - 152.5 %) and absorption was delayed (median t_{max} fasted: 2.00 hours; fed: 3.98 h) (see SmPC section 5.2).

Distribution

Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution during the terminal phase (Vz: 1050 L, 45.0 % gCV) was observed.

The in vitro protein binding of nintedanib in human plasma was high, with a bound fraction of 97.8 %. Serum albumin is considered to be the major binding protein. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.869 (see SmPC section 5.2).

Elimination

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

Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways with CYP 3A4 being the predominant enzyme involved. The major CYP-dependent metabolite could not be detected in plasma in the human ADME study. *In vitro*, CYP-dependent metabolism accounted for about 5 % compared to about 25 % ester cleavage. In *in vitro* receptor binding assays the metabolite BIBF 1202 has a very similar affinity for the VEGFR-3 receptor to that of the parent drug (IC_{50} 14.4 nM versus 13 nM). In addition, despite the assertion that BIBF 1202 has low membrane permeability, the EC_{50} of BIBF 1202 in an assay of VEGF-stimulated cellular proliferation (unspecified cell type) was 80 nM which is comparable to peak steady state levels of BIBF 1202 in humans treated with oral nintedanib at 150 mg b.i.d.

In preclinical *in vivo* experiments, BIBF 1202 did not show efficacy despite its activity at target receptors of the substance.

Total plasma clearance after intravenous infusion was high (CL: 1390 mL/min, 28.8 % gCV). Urinary excretion of the unchanged active substance within 48 h was about 0.05 % of the dose (31.5 % gCV) after oral and about 1.4 % of dose (24.2 % gCV) after intravenous administration; the renal clearance was 20 mL/min (32.6 % gCV). The major route of elimination of drug related radioactivity after oral administration of [14C] nintedanib was via faecal/biliary excretion (93.4 % of dose, 2.61 % gCV).

The contribution of renal excretion to the total clearance was low (0.649 % of dose, 26.3 % gCV).

The overall recovery was considered complete (above 90 %) within 4 days after dosing. The terminal half-life of nintedanib was between 10 and 15 h (gCV % approximately 50 %) (see SmPC section 5.2).

Dose proportionality and time dependencies

Dose-proportional behaviour of C_{max} and AUC was concluded based on several studies in cancer patients investigating doses from 50 to 450 mg qd (1199.1 and 1199.3) and from 150 to 300 mg bid in studies that included patients with idiopathic pulmonary fibrosis (1199.1, 1199.2, 1199.19, 1199.30). In the meta-analyses of PK studies in patients with cancer and IPF there was no evidence of drift in dose proportionality for nintedanib and no difference in the fraction metabolised to BIBF 1202 and BIBF 1202 glucuronide over the investigated dose range. Nintedanib showed dose proportionality for all investigated PK parameters. CL/F of nintedanib did not change after multiple dosing compared to single administration. The PK of nintedanib can therefore be considered linear with respect to time (i.e. single-dose data can be extrapolated to multiple-dose data). Accumulation upon multiple administrations was 1.04-fold for Cmax and 1.38-fold for AUC_T. Nintedanib trough concentrations remained stable for more than one year (see SmPC section 5.2).

Special populations

The pharmacokinetic properties of nintedanib were similar in healthy volunteers, cancer patients, and patients of the target population. Exposure to nintedanib was not influenced by gender (body weight corrected), mild and moderate renal impairment (estimated by creatinine clearance), , alcohol consumption, and P-gp genotype.

Population PK analyses indicated moderate effects on exposure to nintedanib depending on the following intrinsic and extrinsic factors. Based on the high inter-individual variability of exposure observed in the clinical trials these effects are not considered clinically relevant.

Hepatic impairment

Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90 %, see elimination). The safety, efficacy, and pharmacokinetics of nintedanib have not been investigated in patients with hepatic impairment classified as Child Pugh B and C (moderate and severe hepatic impairment respectively). Three studies in patients with hepatic impairment are currently ongoing (**1199.37, 1199.39** and **1199.120**). The applicant is asked to complete the principal studies - **1199.37** and **1199.39** – and to commit to reporting of results by Q1 2015. Therefore, treatment of patients with moderate and severe hepatic impairment with nintedanib is not recommended.

Hepatic impairment and its potential effects on the PK of nintedanib were explored in several analyses based on transaminase and bilirubin levels. These included the Phase II/III PopPK, studies 1199.3 and 1199.19, and the two exploratory PopPK analyses. Pharmacokinetic data for nintedanib was collected in patients with abnormalities in hepatic parameters defined by elevations in AST, ALT and bilirubin levels. A trend to elevated exposure was observed in patients with AST- and ALT-values (up to 10 x ULN) and elevated bilirubin levels (up to 1.5 x ULN) at baseline as compared to patients with normal AST, ALT and bilirubin levels. In patients with ALT or AST > 10 x ULN and bilirubin > 1.5 x ULN, data were too limited to draw conclusions (see SmPC section 5.2).

Renal impairment

No dedicated study in renally impaired patients has been performed. The contribution of renal excretion after oral administration of nintedanib both as unchanged drug (about 0.05% of dose) and as drug related radioactivity was minor (about 0.6% of dose). As a consequence, adjustment of the starting dose in patients with mild to moderate renal impairment is not required.

The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 ml/min creatinine clearance). Treatment of patients with severe renal impairment is not recommended.

Gender, ethnicity, body weight, age

No formal studies were conducted to examine gender, ethnicity, weight or age. Although females appeared to have higher nintedanib exposure compared to males, once body weight was accounted for, gender was found to not significantly affect the PK of nintedanib.

In the Phase II/III PopPK analysis age, race and body weight were found to affect the PK of nintedanib. Simulations revealed that none of the individual covariate effects alone identified in the Phase II/III PopPK analysis caused a change in exposure that exceeded the observed variability range of nintedanib. Relevant increases in simulated exposure were only found when considering more than one covariate.

Exposure to nintedanib increased linearly with age. AUCô,ss decreased by 16 % for a 45-year old patient (5th percentile) and increased by 13 % for a 76-year old patient (95th percentile) relative to a patient with the median age of 62 years. The age range covered by the analysis was 29 to 85 years representing approximately 5 % of the population were older than 75 years.

An inverse correlation between body weight and exposure to nintedanib was observed. AUCô,ss increased by 25 % for a 50 kg patient (5th percentile) and decreased by 19 % for a 100 kg patient (95th percentile) relative to a patient with the median weight of 71.5 kg.

The geometric mean exposure to nintedanib was 33 % higher in Chinese, Taiwanese, and Indian patients while it was 22 % lower in Koreans compared to Caucasians (body weight corrected). However, based on the high inter-individual variability of exposure these effects are not considered clinically relevant. Data from black individuals was very limited but in the same range as for Caucasians. Safety data for Black and African American patients are limited (see SmPC sections 4.2 and 5.2).

No studies in paediatric populations investigating the PK of nintedanib have been performed. IPF has not been reported in children. The EMA granted a product-specific waiver for paediatric development of nintedanib in IPF on 29th October 2010 (EMA/644826/2010). Studies in children are therefore not required.

Pharmacokinetic interaction studies

Two well-designed conducted and reported DDI studies in healthy volunteers have been performed to assess the clinical relevance of potent P-GP inhibition and induction on the PK of nintedanib.

Co-administration with the potent P-gp inhibitor ketoconazole increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on Cmax in a dedicated drug-drug interaction study. In a drug-drug interaction study with the potent P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3 % based on AUC and to 60.3 % based on C_{max} upon co-administration with rifampicin compared to administration of nintedanib alone. If co-administered with nintedanib, potent P gp inhibitors (e.g. ketoconazole or erythromycin) may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of nintedanib. Management of side effects may require interruption, dose reduction, or discontinuation of therapy with nintedanib.

Potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. Co-administration with Ofev should be carefully considered.

Nintedanib was administered in combination with pirfenidone to Japanese patients with IPF in a parallel group design study (1199.31). Exposure to nintedanib decreased to 68.3% based on AUC and to 59.2% based on Cmax n the group where pirfenidone was co-administered (inter-individual comparison). Nintedanib did not have a relevant effect on the PK of pirfenidone (intra-individual comparison). The applicant will perform a drug to drug interaction study with pirfenidone and the final report will be submitted end of 2016.

The potential for interactions of nintedanib with hormonal contraceptives was not explored (see SmPC section 4.5).

Pharmacokinetics using human biomaterials

Inhibition of glucuronidation reactions by nintedanib and BIBF 1202 was investigated in vitro using human liver microsomes or expressed UGT enzymes [U06-1744]. The IC50 for UGT 1A1 dependent ß-estradiol metabolism was 24.5 µM for nintedanib and >200 µM for BIBF 1202. UGT 2B7 dependent ß-estradiol metabolism was inhibited by nintedanib with an IC50 of 77.6 µM and an IC50 >200 µM for BIBF 1202.

Results of transporter inhibition experiments are reported in the table below.

Table 4: Transporter inhibition of nintedanib and its metabolites

	Nintedanib		BIBF 1202		BIBF 1202 glucuronide	
Transporter	**Substrate**	**Inhibitor/IC_{50}**	**Substrate**	**Inhibitor/IC_{50}**	**Substrate**	**Inhibitor/IC_{50}**

Uptake						
OATP-1B1	No	No (>10 µM*)	Yes	14 µM	No	nd
OATP-1B3	No	No (>10 µM*)	No	79 µM	No	nd
OATP-2B1	No	No (>10 µM*)	Yes	50 µM	No	nd
OCT-1	Yes	0.88 µM	No	16 µM	No	nd
OCT-2	No	No (>30 µM*)	No	No (>100 µM*)	nd	nd
Efflux						
P-gp	Yes	Weak; 72.9% of control[#]	No	No (>30 µM*)	nd	nd
MRP-2	No	No (>30 µM*)	No	No (>30 µM*)	Yes	nd
BCRP	No	Weak; 36.6% of control[#]	No	Weak; 71.8% of control[#]	Yes	nd

The *in vitro* evaluation of the drug drug interaction (DDI) potential for nintedanib and its metabolites, the free acid moiety BIBF 1202 and its glucuronide BIBF 1202 glucuronide does not suggest a clinically relevant potential for nintedanib mediated DDI related to, P450 enzymes 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 4A11. Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways. The likelihood of drug-drug interactions with nintedanib based on CYP metabolism is therefore considered to be low (see SmPC section 4.5).

2.4.3. Pharmacodynamics

Mechanism of action

Nintedanib is a tyrosine kinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR á and ß) and fibroblast growth factor receptors (FGFR 1-3) kinase activity. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signaling which is crucial for the migration, proliferation and transformation of lung fibroblasts. In addition Fms-like tyrosine-protein kinase (Flt)-3, Lymphocyte-specific tyrosine-protein kinase (Lck) and proto-oncogene tyrosine-protein kinase src (Src) are inhibited.

Primary and Secondary pharmacology

Transforming Growth Factor ß1, -ß2 and -ß3 (TGFß1, ß2 and ß3) and well as the circulating proteins Krebs von den Lungen-6 (KL-6) and IL-8 may be markers for the course of IPF and were therefore evaluated in Study 1199.30 – the results are shown tabulated below.

Marker	**Rapporteur's comment**
TGFβ1	Levels increased from baseline to study end with no evident difference between placebo and active treated patients except at the 150 mg b.d and 50 mg b.d. doses where the increase was statistically significantly lower than placebo.
TGFβ2 and 3	Only quantifiable in 1/3 of patients at baseline. No evaluation of data done
IL-8	No difference from placebo
KL-6	Baseline values below 1000 U/mL may be a favourable prognostic marker

Blood samples were taken to evaluate potential biomarkers in Studies 1199.30, 1199.32 and 1199.34. The results in study 1199.30 are presented and discussed (Document U13-1590)..

Effects of nintedanib on the QT-interval were determined as a part of study 1199.26 which was a randomised, open-label, parallel-group Phase II study comparing the efficacy and tolerability of

nintedanib versus sunitinib in previously untreated patients with renal cell cancer where observation regarding QT-prolongation was the main purpose of the interim report (enrolled patients =113; analysed for primary QTc endpoint= 64).

In this study single oral doses of 200 mg nintedanib as well as multiple oral doses of 200 mg nintedanib administered twice daily for 15 days did not prolong the QTcF interval. The largest meantime-matched increase of QTcF at steady state was 3.1 ms (two-sided 90% CI: -0.2, 6.4).

In exploratory pharmacokinetic (PK)-adverse event analyses, higher exposure to nintedanib tended to be associated with liver enzyme elevations, but not with gastrointestinal adverse events.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic properties of nintedanib were similar in healthy volunteers, cancer patients, and patients of the target population. The PK studies are orientated towards oncology uses rather than IPF in the type of study and numbers studied but the IPF database is adequate.

Under fed conditions the extent of absorption of nintedanib was increased around 20%. As the decrease in systemic exposure under fasted conditions is small, it can be assumed that in case nintedanib is taken without food on single occasions the impact on the overall steady state exposure of nintedanib will be limited. Section 4.2 of the SmPC states that capsules of nintedanib must be taken orally, with food, swallowed whole with water, and must not be chewed or crushed.

Three different types of capsules were administered to healthy male volunteers. Bioequivalence has only been established between two capsule formulations (slow and fast dissolution). However, no clinical bioequivalence has been established between these two capsule formulations and the final formulation (intended commercial formulation). Although clinical bioequivalence between the final formulation and the two capsules (slow and fast) has not been established in an appropriate bioequivalence study, the applicant has described and justified in a sufficient way the lack of bioequivalence studies between the two capsule formulations (slow and fast dissolving) and the final formulation (intended commercial formulation).

Less than 1 % of a single dose of nintedanib is excreted via the kidney (see section 5.2). Adjustment of the starting dose in patients with mild to moderate renal impairment is not required (see SmPC sections 4.2 and 5.2).

Nintedanib has not been investigated in patients with moderate and severe hepatic impairment. Hepatic impairment and its potential effects on the PK of nintedanib were explored in several analyses based on transaminase and bilirubin levels. These included the Phase II/III PopPK, studies 1199.3 and 1199.19, and the two exploratory PopPK analyses. All investigations indicated higher exposure to nintedanib in patients with elevated laboratory values. The applicant will submit the final data from the on-going trials investigating hepatic impairment (1199.37 by Q1 2015, 1199.39 by Q1 2015 and 1199.120 by Q1 2016) and discuss the possible influence of hepatic impairment on the PK of nintedanib when available (see RMP).

Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90 %). No adjustment of the starting dose is needed for patients with mild hepatic impairment based on clinical data (Child Pugh A). The safety, efficacy, and pharmacokinetics of nintedanib have not been investigated in patients with hepatic impairment classified as Child Pugh B and C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with Ofev is not recommended (see SmPC sections 4.2, 4.4 and 5.2).

No formal studies were conducted to examine gender, ethnicity, weight or age. In the Phase II/III PopPK analysis, age, race and body weight were found to affect the PK of nintedanib. Simulations revealed that none of the individual covariate effects alone identified in the Phase II/III PopPK analysis caused a change in exposure that exceeded the observed variability range of nintedanib. No a priori dose adjustments are required based on intrinsic factors like age, race and body weight as the variability of exposure observed is not considered clinically relevant.

The Applicant has discussed dose adjustment in individuals with more than one covariate present. Data showed a significant proportion of patients with more than one covariate present would still have nintedanib plasma concentrations in the range observed in patients with no covariate present. The recommended posology, starting with a dose of 150 mg bid and then adapting according to the proposed dose reduction schemes as outlined in the SmPC seems reasonable. .

Since the effect of nintedanib on the metabolism and efficacy of contraceptives has not been investigated, barrier methods should be applied as a second form of contraception, to avoid pregnancy.

Nintedanib is a substrate of P-gp however it was shown not to be a substrate or inhibitor of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2, or MRP-2 in vitro. Nintedanib was also not a substrate of BCRP. Only a weak inhibitory potential on OCT-1, BCRP, and P-gp was observed in vitro which is considered to be of low clinical relevance. The same applies for nintedanib being a substrate of OCT-1.

The applicant has provided an in-depth discussion on the possible inhibition of intestinal inhibition of CYP3A4, P-gp and BCRP. Based on *in vitro* data, nintedanib is considered a weak inhibitor of BCRP and P-gp. No *in vitro* Ki value against P-gp (max tested concentration 30 µmol/L) was established The crude estimate of gut concentration (dose/250 ml) is likely a large overestimation as 1) the solubility of nintedanib decreases rapidly with increasing pH and the solubility of nintedanib in different buffer solutions at pH values of ≥ 6 is 0.001 mg/ml (approx. 1.85 µM) and 2) as nintedanib is intended to be administered with food.

Further argumentation has also been provided in order to address the inductive effect of nintedanib on oral contraceptives. According to the EMA guideline on drug interactions “a potential human teratogen needs to be studied *in vivo* for effects on contraceptive steroids if the drug is intended for use in fertile women, regardless of the *in vitro* induction study results.” Therefore, the lack of a drug-drug interaction study investigating the inductive effect of nintedanib on oral contraceptives is acceptable given the current indication and patient population of nintedanib. However, if future approval for additional indications, where nintedanib is to be used in women of childbearing potential, is sought, it is important that a drug-drug interaction study investigating the inductive effect of nintedanib on oral contraceptives is performed. In the mean-time, a recommendation to use a barrier method as a second form of contraception has been included in the SmPC.

A clinically relevant drug-drug-interaction based on inhibition of UGT after oral administration of nintedanib is considered less likely as all IC50 values are substantially higher than the therapeutic plasma concentrations.

Drug-drug interactions between nintedanib and CYP substrates, CYP inhibitors, or CYP inducers are not expected, since nintedanib, BIBF 1202, and BIBF 1202 glucuronide did not inhibit or induce CYP enzymes in preclinical studies nor was nintedanib metabolized by CYP enzymes to a relevant extent (see SmPC section 5.2).

The rapporteur considers the issue of co-treatment with pirfenidone to be primarily one of clinical safety and efficacy rather than pharmacokinetic, a drug-to-drug interaction study with pirfenidone is going to be performed and the final report will be submitted by the end of 2016.

The correlation between exposure to nintedanib with elevations of liver enzymes or bilirubin can be tackled by reducing the exposure with down-titration of the nintedanib dose.

QT-prolongation is a recognised class effect of previously authorised TKIs (Shah et al., 2013), and the omission of a thorough QT study to investigate possible QT-prolongation of nintedanib has been justified. Additional wording has been included in the SmPC sections 4.4 and 5.1 in order to reflect the possible relation between TKIs and QT-prolongation.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology documentation submitted in support of the application for marketing authorisation of nintedanib is considered satisfactory.

The CHMP considers the following measures necessary to address issues related to clinical pharmacology: (see RMP)

- Data on nintedanib treatment in patients with hepatic impairment from trials 1199.37 and 1199.39 (final report due Q1 2015) and trial 1199.120 in Japanese patients (final report due Q1 2016).
- A drug-to drug interaction study with pirfenidone will be performed and the final report is expected by end of 2016.

2.5. Clinical efficacy

Two pivotal Phase III trials (**1199.32** and **1199.34**) and a supportive dose-finding Phase II trial (**1199.30**) were submitted in support of clinical efficacy of nintedanib in IPF. Based on the Phase II safety and dose-finding trial **1199.30**, a nintedanib dose of 150 mg bid was selected for the confirmatory trials (**1199.32** and **1199.34).** In the event of adverse effects, the dose could be reduced to 100 mg bid.

Trials **1199.32** and **1199.34** provided a placebo-controlled assessment of the efficacy of nintedanib in IPF over a 52 week treatment duration. Additional supportive data for persistence of efficacy beyond this time point is provided by the optional, blinded active extension period for trial **1199.30**. Trials **1199.32** and **1199.34** were also submitted to a pre-specified pooled analysis for the purpose of investigating survival.

2.5.1. Dose response studies

Determination of maximum tolerated dose in oncology trials:

The maximum tolerated dose for oral nintedanib as monotherapy had previously been established from Phase I oncology trials and was determined to be 250 mg b.i.d. in Caucasians and 200 mg b.i.d. in Japanese patients.

Based on the phase I dose escalation trials with nintedanib monotherapy in patients with solid tumours, the maximum tolerated dose (MTD) was determined as 250 mg b.i.d. in Caucasians and 200 mg b.i.d. in Japanese patients. The predominant adverse events were nausea, diarrhoea, vomiting, abdominal pain and fatigue of mostly low to moderate intensity. Dose-limiting toxicities (DLTs) were mainly liver enzyme elevations which showed a marked dose-dependency. Liver enzyme elevations were reversible upon

treatment discontinuation. Most cases of liver enzyme elevations occurred at doses of 250 mg b.i.d. and above, while the incidence was low at doses ≤200 mg b.i.d.

Phase II dose-finding study in IPF (1199.30)

A Phase II dose-finding study **(1199.30)** was conducted in patients with IPF to investigate the efficacy and safety of 4 nintedanib doses (50 mg q.d., 50 mg b.i.d., 100 mg b.i.d. and 150 mg b.i.d.) by oral administration versus placebo over a 52 week treatment period with an optional active treatment extension. The study was of a randomised, placebo-controlled, double-blind, parallel design. Higher dosage arms were progressively included following Data Monitoring Committee review and approval. The main inclusion criteria were the same as for the subsequent Phase III pivotal studies. The primary efficacy endpoint was annual rate of decline in FVC (over 52 weeks). Secondary efficacy endpoints included acute IPF exacerbations and quality of life as measured by the SGRQ.

The difference from placebo in the annual rate of decline in FVC was 0.016 L for 50 mg q.d. (95% CI -0.086,0.118), -0.020 L for 50 mg b.i.d. (95% CI -0.119, 0.080), 0.028 L for 100 mg b.i.d. (95% CI -0.071, 0.128) and 0.131 L for 150 mg b.i.d. (95% CI 0.027, 0.235).

A closed testing procedure was pre-specified for the primary analysis of the endpoint in order to prevent inflation of the type 1 error. The closed testing assigned equal weight to each dose group and every intersection between all dose groups and placebo was tested. A dose was determined to be significantly different from placebo (at the 5% level) only if p-values for all tests of all the combinations including this dose against placebo were less than 0.05.

The p-value for the 150 mg b.i.d. dose was 0.0639 using the closed testing procedure and therefore did not reach statistical significance. However, when a less stringent hierarchical testing procedure was used, the difference between nintedanib 150 mg b.i.d. and placebo reached nominal statistical significance (p = 0.0136). The hierarchical testing procedure was used as a pre-specified sensitivity analysis which tested for significance at the highest dose, proceeding to the dose below only if significance was shown.

The efficacy of nintedanib 150 mg b.i.d. in IPF was further supported by a reduced incidence of acute IPF exacerbation compared to placebo (2.3% in the nintedanib group versus 13.8% in the placebo group), hazard ratio (HR) 0.158 (p=0.0161) in favour of nintedanib. Moreover, nintedanib 150 mg b.i.d. was associated with a statistically significant and clinically relevant improvement in the change from baseline in SGRQ total score at 52 weeks (6.12 points over placebo, p=0.0071).

There was also a trend to enhanced survival with nintedanib: the incidence of deaths from any cause was numerically lower in the nintedanib 150 mg b.i.d. group (8.1%) than in the placebo group (10.3%), HR at 52 weeks of 0.732 (95% CI 0.271, 1.977) in favour of nintedanib although this was not statistically significant. Among respiratory-related deaths (numbers derived by blinded adjudication by an external committee) there was also a trend to improved survival over the 52 week duration: 9.2% in the placebo group versus 2.3% in the nintedanib 150 mg b.i.d. group, HR 0.225 (95% CI 0.048, 1.065).

2.5.2. Main studies

Study 1199.32 was a 52 week, double blind, randomised, placebo-controlled evaluation of the safety and efficacy of oral nintedanib, 150 mg twice daily, on annual forced vital capacity decline, in patients with idiopathic pulmonary fibrosis (IPF).

Methods

The principal objective was to investigate the efficacy and safety of nintedanib 150 mg twice daily versus placebo in patients with IPF over 52 weeks.

Primary endpoint

The primary efficacy endpoint was the annual rate of decline in FVC (expressed in mL over 52 weeks).

The key secondary endpoints were:

Change from baseline in SGRQ total score at 52 weeks (expressed in points)

Time to first acute IPF exacerbation (days) over 52 weeks an acute exacerbation was defined as; unexplained worsening or development of dyspnoea within 30 days, new diffuse pulmonary infiltrates on chest X-ray, and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since the last visit. Exclusion of alternative causes as per routine clinical practice.

Inclusion criteria

Eligible patients were at least 40 years old, with IPF diagnosed (according to ATS/ERS criteria less than 5 years prior to Visit 2 and HRCT within 52 weeks of Visit 1 and biopsy (the latter if needed to fulfil ATS/ERS criteria) centrally reviewed and consistent with diagnosis. They had FVC ≥ 50 % of predicted normal value; Males: FVC predicted (L) = 5.76 x height (meters)- 0.026 x age (years) -4.34 Females: FVC predicted (L) = 4.43 x height (meters)- 0.026 x age (years) -2.89. For both genders single breath DLCO 30 - 79% of predicted.

Exclusion criteria

The exclusion criteria included a series of medical conditions that might have interfered with the performance of the study. The criteria also covered some drugs that might have interfered with the activity of the study medication. Continuous oxygen supplementation at randomisation (defined as ≥ 15 hours supplemental oxygen per day, active infection at screening or randomisation, significant laboratory test abnormality, Pregnant women or women who were breast feeding or of child bearing potential not using a highly effective method of birth control for at least one month prior to enrolment.

Statistical analysis

The primary efficacy endpoint (annual rate of decline in FVC) was analysed using a random coefficient regression model (random slopes and intercepts) including gender, age, and height as covariates.

The key secondary endpoint, the change from baseline in SGRQ total score at 52 weeks was analysed using a Mixed Effects Model for Repeated Measures (MMRM), with baseline SGRQ total score as a covariate.

The key secondary endpoint, time to first acute exacerbation over 52 weeks was analysed using the log rank test and a Cox model, including gender, age and height as covariates, to determine the hazard ratio.

The proportion of FVC responders and SGRQ responders was analysed using a logistic regression. All other continuous endpoints were analysed using MMRM and all other time to event endpoints were analysed using a log rank test and Cox model. Superiority of nintedanib 150 mg bid over placebo was tested using a hierarchical procedure for the primary and two key secondary endpoints in order to deal with multiplicity. The consecutive steps of the hierarchy were only considered if the previous step was significant at the 1-sided 2.5% level (the order of testing differed in the US and the EU).

The efficacy and safety analyses were based on the treated set (TS). The TS consisted of patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

The sample size was calculated to provide at least 90% power to detect a difference between the treatment groups in the annual rate of FVC decline of 100 mL. Based on the Phase II data, the common standard deviation was assumed to be 300 mL. Assuming 2% of patients would be non evaluable, the sample size was calculated as 194 patients in the placebo group and 291 patients in the nintedanib 150 mg bid group if using a 2 group t-test at a 1-sided 2.5% level.

Results

Seven hundred and eighteen patients were screened of whom 515 were randomised; 157 were screening failures (patients who did not meet inclusion/exclusion criteria) and 46 were not randomised for other reasons, 206 were randomised to placebo and 309 to nintedanib 150 bd. In the placebo arm 174 patients (85.3%) completed the study and 260 (84.1%) completed the study in the nintedanib arm.

Demographics

The majority of patients were male (80.7%). The largest proportion of patients was Caucasian (64.9%), followed by Asian patients (20.9%). The mean and median values for age were similar between the treatment groups (total mean: 66.9 years; median: 68.0 years). The distribution of patients by age category showed some imbalances, with a higher proportion of younger (<65 years) and elderly patients (≥70 years) and a lower proportion of patients between 65 to <75 years in the nintedanib treatment group than in the placebo group. Most patients were ex-smokers (70.2% nintedanib; 70.6% placebo) or current smokers (6.8% nintedanib; 4.4% placebo), while approximately one quarter of patients never smoked. A summary of key demographic characteristics is presented in Table 4.

Time since IPF diagnosis was comparable across treatment groups. The majority of patients were diagnosed with IPF within 3 years prior to randomisation, with a mean time from diagnosis of 1.63 years. The majority of patients had an HRCT assessment which was 'consistent with UIP' (97.4% nintedanib; 97.1% placebo). All patients who had an HRCT assessment rated as 'possible UIP' had a lung biopsy available for central review which confirmed the diagnosis Overall, 38.2% of patients had centrilobular emphysema, based on qualitative assessment of HRCT.

Selected efficacy outcomes are shown in Table 5, and the time course of FVC decline is in Figure 4. In the placebo arm 10 (4.9%) patients died due to a respiratory cause over 52 weeks and in the nintedanib arm the equivalent figure was also 10 (3.2%) (p = 0.35). The hazard ratio for time to death due to respiratory cause over 52 weeks was 0.61 (95% CI: 0.25, 1.47; p = 0.3515). The proportion of patients who died or received a lung transplant or qualified for a lung transplant over 52 weeks was numerically lower in the nintedanib group (14.9%) than in the placebo group (18.1%). The hazard ratio for the time to death or lung transplant or qualifying for lung transplant over 52 weeks was 0.81 (95% CI 0.52, 1.25; p = 0.3558).

The adjusted mean absolute change from baseline to Week 52 in DLCO (mmol/min/kPa) was -0.380 for nintedanib and -0.365 for placebo. No significant difference was observed between the treatment groups (-0.015 [95% CI: -0.191, 0.161; p = 0.8650]).

Table 4 Baseline data by treatment group. Data are mean (s.d.)

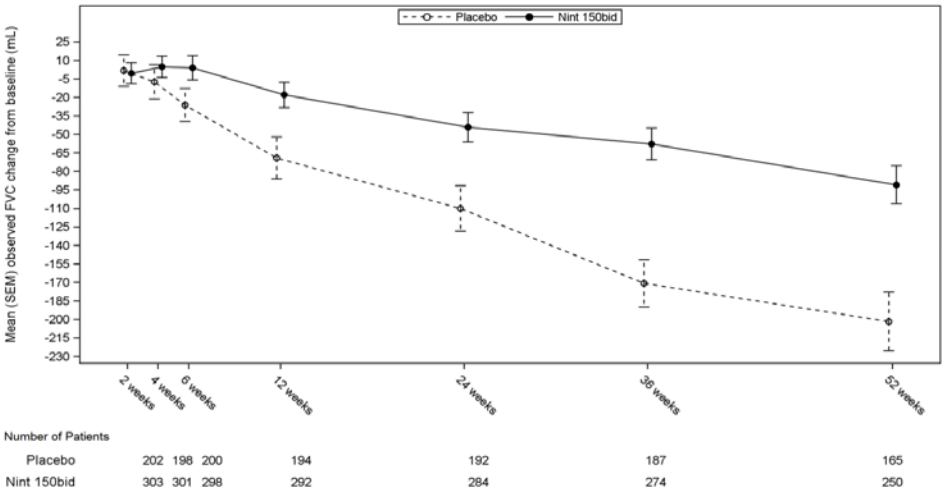
	Placebo	Nintedanib 150 bd
Number of patients	204	309
% male	79.9	81.2
Age (years)	66.9 (8.2)	66.9 (8.4)
BMI (kg/m^2)	28.12 (4.63)	28.63 (4.52)

FVC (mL)	2844.5 (820.1)	2756.8 (735.1)
FVC % predicted	80.53 (17.34)	79.47 (17.03)
DLco (mmol/min/kpa)	3.96 (1.11)	3.96 (1.20)
SGRQ total score	39.79 (18.48)	39.55 (17.63)

Table 5 Efficacy outcomes by treatment group. Data are adjusted mean (s.e.)

	Placebo	Nintedanib 150 bd
	Primary endpoint	
Number of patients	204	309
Rate of decline FVC (mL/year)	-239.91 (18.71)	-114.65 (15.33)
Comparison to placebo	-----	p <0.0001
	Key secondary endpoints	
Change in SGRQ total score	4.39 (0.96)	4.34 (0.799)
Comparison to placebo	-----	p = 0.966
Number (%) with an acute exacerbation	11 (5.4)	19 (6.1)
Comparison to placebo	-----	p = 0.6728
	Other endpoints	
Change in FVC % predicted -	-5.98 (0.47)	-2.76 (0.41)
Comparison to placebo	-----	P<0.0001
DLco mmol/min/KPa	-0.365 (0.075)	-0.380 (0.064)
Comparison to placebo	-----	p = 0.87

Figure 4 shows the time-course of FVC decline over 52 weeks by treatment arm.



Dose reductions (temporary or permanent) were reported for 26.5% of patients in the nintedanib group and 4.9% of patients in the placebo group. The mean duration of exposure to the reduced dose was 4.28 months for the nintedanib group and 3.65 months for the placebo group. The majority of dose reductions were due to drug-related AEs: 95.6% of dose reductions in the nintedanib group and 90.0% of dose reductions in the placebo group. Most patients who had at least 1 dose reduction in the nintedanib group (60/82 patients) and placebo group (6/10) had their first dose reduction within the first 6 months of treatment.

The proportion of patients with AEs leading to premature treatment discontinuation was higher in the nintedanib group (21.0%) compared with the placebo group (10.8%).

Study 1199.34 was a 52 week, double blind, randomised, placebo-controlled evaluation of the safety and efficacy of nintedanib 150 mg twice daily, on annual forced vital capacity decline, in patients with idiopathic pulmonary fibrosis (IPF).

Methods

The primary objective was to assess the reduction in lung function decline, as measured by a change in the annual rate of decline in FVC.

Primary endpoint

The primary efficacy endpoint was the annual rate of decline in FVC (expressed in mL over 52 weeks).

The key secondary endpoints were:

Change from baseline in SGRQ total score at 52 weeks (expressed in points)

Time to first acute IPF exacerbation (days) over 52 weeks an acute exacerbation was defined as; unexplained worsening or development of dyspnoea within 30 days, new diffuse pulmonary infiltrates on chest X-ray, and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since the last visit. Exclusion of alternative causes as per routine clinical practice.

Inclusion criteria

Eligible patients were at least 40 years old, with IPF diagnosed (according to ATS/ERS criteria less than 5 years prior to Visit 2 and HRCT within 52 weeks of Visit 1 and biopsy (the latter if needed to fulfil ATS/ERS criteria) centrally reviewed and consistent with diagnosis. They had FVC ≥ 50 % of predicted normal value; Males: FVC predicted (L) = 5.76 x height (meters)- 0.026 x age (years) -4.34 Females: FVC predicted (L) = 4.43 x height (meters)- 0.026 x age (years) -2.89. For both genders single breath DLCO 30 - 79% of predicted.

Exclusion criteria

The exclusion criteria included a series of medical conditions that might have interfered with the performance of the study. The criteria also covered some drugs that might have interfered with the activity of the study medication. Continuous oxygen supplementation at randomisation (defined as ≥ 15 hours supplemental oxygen per day, active infection at screening or randomisation, significant laboratory test abnormality, Pregnant women or women who were breast feeding or of child bearing potential not using a highly effective method of birth control for at least one month prior to enrolment.

Statistical analysis

The primary efficacy endpoint (annual rate of decline in FVC) was analysed using a random coefficient regression model (random slopes and intercepts) including gender, age, and height as covariates.

The key secondary endpoint, the change from baseline in SGRQ total score at 52 weeks was analysed using a Mixed Effects Model for Repeated Measures (MMRM), with baseline SGRQ total score as a covariate.

The key secondary endpoint, time to first acute exacerbation over 52 weeks was analysed using the log rank test and a Cox model, including gender, age and height as covariates, to determine the hazard ratio.

The proportion of FVC responders and SGRQ responders was analysed using a logistic regression. All other continuous endpoints were analysed using MMRM and all other time to event endpoints were analysed using a log rank test and Cox model. Superiority of nintedanib 150 mg bid over placebo was tested using a hierarchical procedure for the primary and two key secondary endpoints in order to deal with multiplicity. The consecutive steps of the hierarchy were only considered if the previous step was significant at the 1-sided 2.5% level (the order of testing differed in the US and the EU).

The efficacy and safety analyses were based on the treated set (TS). The TS consisted of patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

The sample size was calculated to provide at least 90% power to detect a difference between the treatment groups in the annual rate of FVC decline of 100 mL. Based on the Phase II data, the common standard deviation was assumed to be 300 mL. Assuming 2% of patients would be non evaluable, the sample size was calculated as 194 patients in the placebo group and 291 patients in the nintedanib 150 mg bid group if using a 2 group t-test at a 1-sided 2.5% level.

Results

Seven hundred and ninety-four patients were screened of whom 551 were randomised; 190 were screening failures (patients who did not meet in/exclusion criteria) and 53 were not randomised for other reasons; three patients were not treated. Of those treated 219 were in the placebo arm and 329 in the nintedanib 150 bd arm. In the placebo arm 179 (81.7%) completed the study and 272 (82.7%) completed the study in the nintedanib arm.

Demographics

The majority of patients were male (77.9%). The largest proportion of patients was Caucasian (50.2%), followed by Asian (39.2%). The mean and median values for age were similar between the treatment groups (total mean: 66.6 years; median: 67.0 years). The distribution of patients by age categories showed some imbalances, with a higher proportion of younger patients (<65 years) and a lower proportion of patients between 65 to <75 years in the nintedanib treatment group compared with the placebo group. Most patients were ex-smokers (66.3% nintedanib; 63.5% placebo) or current smokers (2.4% nintedanib; 4.1% placebo), approximately one third of patients had never smoked.

Time since IPF diagnosis was comparable across both treatment groups. The majority of patients were diagnosed with IPF within 3 years prior to randomisation, with a mean time from diagnosis of 1.60 years. The majority of patients had an HRCT assessment which was 'consistent with UIP' (97.6% nintedanib; 98.2% placebo) as defined by the protocol. All patients who had an HRCT assessment rated as 'possible UIP' had a lung biopsy available for central review which confirmed the diagnosis. Overall, 40.9% of patients had centrilobular emphysema, based on qualitative assessment of HRCT. Baseline characteristics by treatment arm are shown in Table 6.

Table 6 Baseline data by treatment group. Data are mean (s.d.)

	Placebo	Nintedanib 150 bd
Number of patients	219	329
% male	78.1	77.8
Age (years)	67.1 (7.5)	66.4 (7.9)
BMI (kg/m^2)	27.17 (4.49)	27.56 (4.55)
FVC (mL)	2619.0 (787.3)	2672.8 (776.0)
FVC % predicted	78.09 (18.97)	79.99 (18.08)
DLco (mmol/min/kpa)	3.748 (1.32)	3.772 (1.23)
SGRQ total score	39.39 (18.65)	39.46 (20.47)

The proportion of patients with at least one acute IPF exacerbation over 52 weeks, based on all investigator-reported adverse events, was lower in the nintedanib group (3.6%) than in the placebo group (9.6%). The time to event analysis yielded a hazard ratio of 0.38 (95% CI: 0.19, 0.77) and was statistically significant with p = 0.0050, indicating a reduced risk of experiencing a first acute IPF exacerbation in patients in the nintedanib group compared with patients in the placebo group.

Twenty (9.1%) placebo treated patients died over the 52 weeks of the study and 22 (6.7%) nintedanib patients died (p = 0.300). Deaths from a respiratory cause were 11 (5.0%) and 14 (4.3%) in the placebo and nintedanib groups respectively (p = 0.67)

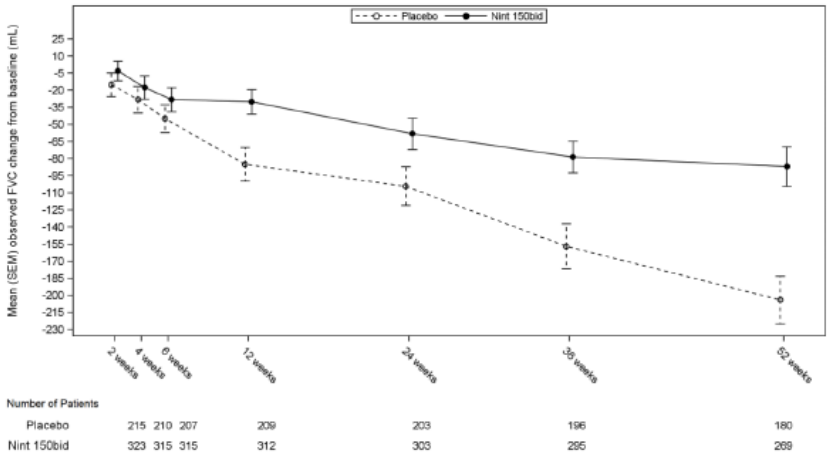
The adjusted mean absolute change from baseline to Week 52 in DLCO (mmol/min/kPa) was -0.286 for nintedanib and -0.400 for placebo. The difference between nintedanib and placebo was 0.113 (95% CI: -0.084, 0.310; p = 0.2600),

Table 7 Efficacy outcomes by treatment group. Data are adjusted mean (s.e.)

	Placebo	Nintedanib 150 bd
	Primary endpoint	
Number of patients	219	329
Rate of decline FVC (mL/year)	-207.32 (19.31)	-113.59 (15.73)

Comparison to placebo	-----	p = 0.0002
	Key secondary endpoints	
Change in SGRQ total score	5.48 (0.90)	2.80 (0.73)
Comparison to placebo	-----	p = 0.0197
Number (%) with an acute exacerbation	21 (9.6%)	12 (3.6%)
Comparison to placebo	-----	P = 0.005
	Other endpoints	
Change in FVC % predicted	-6.15 (0.51)	-3.09 (0.43)
Comparison to placebo	-----	P<0.0001
Change in DLco (mmol/min/kpa)	-0.400 (0.084)	-0.286 (0.073)
Comparison to placebo	-----	P = 0.260

Figure 5 shows the time-course of FVC decline over 52 weeks by treatment arm.



Overall, 29.2% of patients in the nintedanib group had a dose reduction from 150 mg bid to 100 mg bid. These patients received the lower nintedanib 100 mg bid dose for a mean duration of 4.47 months. In the placebo group, 2.7% of patients had dose reductions to 100 mg bid, they received the lower placebo 100 mg bid dose for a mean duration of 2.42 months.

Studies 1199.32 and 1199.34 show a clear and consistent benefit in reducing the decline of FVC by approximately 125 mL/year and 94 mL/year respectively. The time course for the decline in FVC is strikingly similar in both studies (Figures 4 and 5) and the divergent slopes of the decline curves suggests a real benefit over time rather than a once-off benefit which is then maintained over time (in which case the slopes would be parallel). Slightly surprisingly in view of the spirometric effect there was no benefit in terms of gas exchange (DLco) in either study.

Divergences between the studies are a lack of benefit on SGRQ and frequency of IPF exacerbations in Study 1199.32 both of which have a statistically significant advantage over placebo in Study 1199.34, which study may represent reality is impossible to say. However, statistically significant benefits for both variables were present in the 150 mg bid treatment arm compared to placebo in the dose ranging study.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 8 Overview of main efficacy variables by study. Data are adjusted means for nintedanib with the mean placebo value subtracted. Shaded squares indicate a statistically significant benefit. Data preceded by a minus sigh indicate a disadvantage for nintedanib.

Study	**1199.30 (150 mg bd)**	**1199.32**	**1199.34**
No. in study	P = 83 N = 85	P = 204 N = 309	P = 219 N = 329
FVC benefit (mL)	131 **	125.26	93.73
SRGQ total score	6.12	0.05	2.69
Exacerbation benefit (HR)	0.16	1.15	0.64
DLco benefit (mmol/min/KPa)	- 0.121	-0.015	0.113
. ** For study 30, the FVC data were collected in L and expressed in mL for this table			

The robustness of the effect of nintedanib in reducing the annual rate of decline in FVC was confirmed in all pre-specified sensitivity analyses. In patients with missing data, the primary analysis assumes that the decline in FVC after the last observed value would be similar to the decline in other patients in the same treatment group, which is unlikely to be true if a subject had stopped taking treatment. In a sensitivity analysis which allowed for the loss of efficacy expected at treatment withdrawal, by assuming assumed that in patients with missing data at week 52 the FVC decline after the last observed value would be the same as in all placebo patients, the adjusted difference in the annual rate of decline between nintedanib and placebo was 113.9 mL/year (95% CI 69.2, 158.5) in INPULSIS-1 and 83.3 mL/year (95% CI 37.6, 129.0) in INPULSIS-2**.**

2.1. Supportive study

Study 1199.31 was a double-blind, randomised, placebo-controlled evaluation of the safety and pharmacokinetics of multiple rising doses of nintedanib at 50 mg b.i.d. (14 days), 100 mg b.i.d. (14 days), and 150 mg b.i.d. (28 days) on top of standard medical care with stratification according to pirfenidone use, in Japanese patients with idiopathic pulmonary fibrosis.

Methods

The principal aims of the study were to investigate the safety and pharmacokinetics of nintedanib in Japanese patients with idiopathic pulmonary fibrosis with and without pirfenidone background treatment.

Main criteria for inclusion:

Diagnosis of IPF according to Japan Respiratory Society (JRS) guideline Forced vital capacity (FVC) ≥50%, diffusing capacity for carbon monoxide (DLCO) 30-79%. For patients on pirfenidone, treatment with a steady dose (1800 mg/day) for at least 3 months was required. Only for the 150 mg b.i.d. dose group, low dose pirfenidone users (controlled with 1200 mg/day or 600 mg/day) for at least 3 months were allowed to participate.

Exclusion criteria

Patients were not eligible to participate in the study if they met any of the following exclusion criteria; aspartate aminotransferase (AST), alanine aminotransferase (ALT) >1.5 x upper limit of normal range (ULN) at screening. total bilirubin >1.5 x ULN at screening, relevant airways obstruction (i.e., pre-bronchodilator FEV1/FVC <0.7) at screening, continuous oxygen supplementation (defined as ≥15 hours supplemental oxygen per day), active infection at screening or randomisation, neutrophils <1500/mm3 at screening, platelets <100000/mL at screening, haemoglobin <9.0 g/dL at screening, being treated with any of the following concomitant medications, oral corticosteroid medication at unstable doses (i.e., less than 8 weeks on a stable dose) or at doses in excess of the equivalent of 15 mg of prednisone per day or 30 mg every other day, ketoconazole or atazanavir, significant co-morbidity.

Treatments

Study participants were enrolled in 3 different dose groups. In the nintedanib 50 mg b.i.d. and 100 mg b.i.d dose groups (Cohorts 1 and 2), patients were randomised to nintedanib (50 mg b.i.d. and 100 mg b.i.d., respectively) or placebo in a 3:1 fashion, and in the nintedanib 150 mg b.i.d. dose group (Cohort 3), nintedanib 150 mg b.i.d. or placebo in a 3:1fashion for patients with pirfenidone or in a 6:1 fashion for patients without pirfenidone. For the nintedanib 50 mg b.i.d. and 100 mg b.i.d. groups, patients were stratified so that one half was with pirfenidone and the other half was without pirfenidone. For the nintedanib 150 mg b.i.d. dose group, patients randomised to nintedanib were also stratified so that one half was with pirfenidone and the other half without pirfenidone, whereas patients randomised to placebo were stratified so that twice as many were with pirfenidone compared with those without pirfenidone. At least 8 patients were to be on pirfenidone1800 mg per day.

Results

Of the 50 patients, 35 (70.0%) patients were male and 15 (30.0%) were female. The mean age was 65.2 years; 36 (72.0%) patients were ex-smokers; 14 patients (28.0%) had never smoked; and none was a current smoker.

Tab 9 Baseline data by treatment group. Data are mean (s.d.)

	Placebo	50 b.d.	100 bd	150 b.d	total
	Baseline demographics				
No studied	12	6	8	24	50
% male	91.7	66.7	50.0	66.7	70.0
Age (years)	64.1 (10.3)	66.7 (2.9)	67.5 (7.4)	64.7 (8.5)	65.2 (8.2)
	Baseline lung function and other variables				

FVC (L)	2.63 (0.67)	2.14 (0.60)	2.13 (0.55)	2.39 (0.71)	2.38 (0.67)
FVC % predicted (mL/min/mmHg)	72.94 (14.69)	68.41 (9.44)	73.42 (10.42)	76.27 (15.60)	74.07 (13.93)
DLco % predicted	59.19 (13.62)	67.84 (10.54)	58.53 (16.87)	53.02 (13.80)	57.16 (14.38)

Table 10 Pharmacokinetic parameters for nintedanib by dose. Shaded rows are in the presence of pirfenidone 600 mg t.i.d. Data are geometric mean (gCV%) except t_{max}

	50 b.d.	100 bd	150 b.d
AUC_{0-12} h.ng/mL	NC	59.0 (67.2)	152 (60.6)
AUC_{0-12} h.ng/mL	30.0 (8.86)	72.2 (87.1)	131 (154)
C_{max} (ng/mL)	3.90 (264)	13.2 (66.9)	34.9 (62.8)
C_{max} (ng/mL)	5.67 (30.2)	13.3 (117)	26.5 (160)
t_{max} (h) (range)	2.98 (2.0 to 3.97)	4.48 (1.97 to 12.0)	3.9 (1.0 to 6.0)
t_{max} (h) (range)	3.88 (3.0 to 6.0)	4.97 (2.0 to 8.0)	3.9 (3.0 to 6.0)
$t_{½}$ (h)	NC	8.27 (13.9)	8.48 (43.1)
$t_{½}$ (h)	NC	6.95 (16.1)	7.03 (16.0)

Table 11 Pharmacokinetic parameters for BIBF 1202 by dose. Shaded rows are in the presence of pirfenidone 600 mg t.i.d. Data are geometric mean (gCV%) except tmax

	50 b.d.	100 b.d.	150 b.d
AUC_{0-12} h.ng/mL	32.7 (81.6)	40.3 (176)	184 (65.3)
AUC_{0-12} h.ng/mL	21.1 (86.6)	79.9 (90.8)	106 (217)
C_{max} (ng/mL)	4.82 (62.1)	9.34 (66.5)	26.0 (68.7)
C_{max} (ng/mL)	3.50 (85.3)	12.3 (65.9)	17.3 (175)
t_{max} (h) (range)	16.0 (8.0 to 23.9)	12.0 (8.0 to 23.9)	8.0 (5.9 to 23.9)
t_{max} (h) (range)	9.96 (8.0 to 12.0)	10.0 (7.9 to 23.9)	12.0 (8.0 to 23.9)

2.1.1. Discussion on clinical efficacy

Design and conduct of clinical studies

the design and conduct of the studies was good with the dose ranging and Phase III studies carried out to ICH-GCP standards. Study 1199.30 explored an adequately wide range of doses and was large enough and long enough to provide a fairly convincing indication that 150 mg bid was an effective dose. Nintedanib has evident tolerability problems and in consequence it was reasonable not to push the dose above 150 mg bid.

The Phase III studies evaluated a dose which is probably at the upper end of the tolerability range against placebo which is currently the most meaningful comparator. The studies give fairly consistent results for

FVC but inconsistent results for quality of life (SGRQ total score) and IPF acute exacerbations. However, overall the clinical database points to nintedanib being a potentially useful treatment in IPF.

Efficacy data and additional analyses

Studies 1199.32 and 1199.34 show a clear and consistent benefit in reducing the decline of FVC by approximately 125 mL/year and 94 mL/year respectively. The time course for the decline in FVC is strikingly similar in both studies and the divergent slopes of the decline curves suggests a real benefit over time rather than a once-off benefit which is then maintained over time (in which case the slopes would be parallel). Slightly surprisingly in view of the spirometric effect there was no benefit in terms of gas exchange (DLco) in either study.

Divergences between the studies are a lack of benefit on SGRQ and frequency of IPF exacerbations in Study 1199.32 both of which have a statistically significant advantage over placebo in Study 1199.34, which study may represent reality is impossible to say. However, statistically significant benefits for both variables were present in the 150 mg bid treatment arm compared to placebo in the dose ranging study.

The Applicant has analysed the non-Japanese dose ranging and Phase III studies separately, including various sensitivity analyses and in pooled analyses. The methods have been appropriate missing data have generally not been imputed, the number of endpoints has been limited and diverse variables which are not interdependent have been chosen. The hierarchical testing method to counteract multiplicity seems quite conservative. The CHMP does not consider further analysis necessary

2.1.2. Conclusions on the clinical efficacy

Nintedanib shows evidence of reduction of the rate of decline in lung function as indicated by absolute volume FVC. Percentage predicted FVC is preferred endpoint as it standardises the absolute measurement and reduces or eliminates variability due to demographic factors such as age, gender, body size which could be different between different treatment arms; the data on change in predicted normal are consistent with those on absolute volume which is reassuring.

The CHMP support a therapeutic indication which does not specify a stage of disease severity.

The data on quality of life as indicated by SGRQ total score are discordant between the Phase III studies with no difference for nintedanib compared to placebo in Study 1199.32 and a significant benefit in Study 1199.34.

For acute exacerbations of IPF, two out of three studies show a statistical significant benefit for 150 mg bid.

2.2. Clinical safety

Patient exposure

The safety of nintedanib in patients with IPF has been investigated in seven clinical trials; two Phase II trials 1199.30 and 1199.31 (dose ranging and dose ranging in Japanese patients respectively), two Phase III trials 1199.32 and 1199.34, and the three phase II/III open extension trials 1199.33, 1199.35, and 119.40. Table 12 summarises the IPF Safety data base.

Overall, 1061 patients were treated in the phase III studies (referred to as SG1.1 in the rest of the document) of whom 423 received placebo and 638 received nintedanib 150 mg bid. About one fifth of the

patients discontinued treatment prematurely; placebo: 18.9%, nintedanib: 24.5%. The main reason for discontinuation was AE (placebo: 13.9%; nintedanib: 19.9%).

Table 12 Overview of IPF clinical trials

	Duration	Trial description	Patients N	Doses studied	Trial status
1199.30/II	52 weeks	Randomised, double-blind, placebo-controlled trial.	428	Placebo; nintedanib 50 mg qd, 50 mg bid, 100 mg bid, 150 mg bid	Completed
		Optional active blinded treatment phase after 52 weeks	286	Nintedanib 50 mg qd, 50 mg bid, 100 mg bid, 150 mg bid [4]	
1199.35/II		Open extension of trial 1199.30	198	Nintedanib 50 mg qd, 50 mg bid, 100 mg bid, 150 mg bid Patients started at dose they were receiving at end of study 1199.30 period 2. Three months after trial initiation, all patients were offered to escalate to nintedanib 150 mg bid.	Ongoing
1199.31/II	14 and 28 days	Randomised, double-blind, placebo-controlled trial in Japanese patients; stratification according to concomitant pirfenidone use	50	Placebo; nintedanib 50 mg bid, 100 mg bid, 150 mg bid	Completed
1199.40/II		Open-label extension of trial 1199.31	20	Nintedanib 150 mg bid (as add-on treatment to pirfenidone)	Ongoing
1199.32/III	52 weeks	Randomised, double-blind, placebo-controlled trial	513	Placebo; nintedanib 150 mg bid	Completed
1199.34/III	52 weeks	Randomised, double-blind, placebo-controlled trial	548	Placebo; nintedanib 150 mg bid	Completed
1199.33/III		Open-label extension of trials 1199.32 and 1199.34	750	Nintedanib 150 mg bid, 100 mg bid [5]	Ongoing

Table 12a Number of patients exposed to study medication in IPF trials

	Placebo N	Nintedanib N	Total N
52 weeks			
Trials 1199.30 period 1, 1199.32, 1199.34	507	975	1482
No minimum duration			
Trials 1199.30 period 2, 1199.33, 1199.35, 1199.40 [3]	340	645	985
Trials 1199.30 period 2, 1199.33, 1199.35, 1199.40 [4]	-	985	-
Any duration			
Total	519	1013	1532

[4] Patients participating in extension trials who were randomised to placebo in the parent trial are counted under nintedanib (except if they were randomised to nintedanib in trial 1199.31).

[5] Patients participating in trial 1199.31 prior to participating in trials 1199.32 or 1199.34 and randomised to the same treatment group in both trials are not double-counted. Patients participating in extension trial are not double-counted but are only counted once towards the randomised treatment group in the parent trial.

Table 13 Demographics in Safety Group (SG 1.1) Treated Set (TS).

	Placebo	Nintedanib 150 mg bid	Total
Patients, N (%)	423 (100.0)	638 (100.0)	1061 (100.0)
Gender, N (%)			
Male	334 (79.0)	507 (79.5)	841 (79.3)
Female	89 (21.0)	131 (20.5)	220 (20.7)
Race, N (%)			
White	248 (58.6)	360 (56.4)	608 (57.3)
Black	0 (0.0)	2 (0.3)	2 (0.2)
Asian	128 (30.3)	194 (30.4)	322 (30.3)
Missing[1]	47 (11.1)	82 (12.9)	129 (12.2)
Age [years], mean (SD)	67.0 (7.9)	66.6 (8.1)	66.8 (8.0)
Age in categories, N (%)			
<65 years	145 (34.3)	258 (40.4)	403 (38.0)
≥65 years to <75 years	216 (51.1)	263 (41.2)	479 (45.1)
≥75 years	62 (14.7)	117 (18.3)	179 (16.9)
Weight [kg], mean (SD)	78.6 (16.5)	79.2 (16.6)	79.0 (16.6)
Smoking history [N (%)]			
Never smoked	122 (28.8)	174 (27.3)	296 (27.9)
Ex-smoker	283 (66.9)	435 (68.2)	718 (67.7)
Currently smokes	18 (4.3)	29 (4.5)	47 (4.4)

[1] Race was not collected in patients treated at French sites as this is prohibited by French law

Adverse events

Table 14 Summary of AEs in Phase III 52 week studies (SG1.1).

	Placebo N (%)	Nintedanib 150 mg bid N (%)
Patients	423 (100.0)	638 (100.0)
Patients with any AE	379 (89.6)	609 (95.5)
Severe	99 (23.4)	174 (27.3)
Investigator-defined drug-related	120 (28.4)	455 (71.3)
Leading to discontinuation of study medication	55 (13.0)	123 (19.3)
Other significant (as per ICH-E3)	13 (3.1)	156 (24.5)
Serious	127 (30.0)	194 (30.4)
Fatal	31 (7.3)	37 (5.8)
Immediately life-threatening	6 (1.4)	9 (1.4)
Disability/incapacity	2 (0.5)	4 (0.6)
Requiring hospitalisation	103 (24.3)	170 (26.6)
Prolonging hospitalisation	15 (3.5)	11 (1.7)
Other	31 (7.3)	35 (5.5)

Table 15 AE occurring in more than 5% of patients in either treatment group sorted by frequency in the nintedanib 150 mg group Phase III 52 week studies (SG1.1)

System organ class Preferred term	Placebo N (%)	Nintedanib 150 mg bid N (%)
Patients	423 (100.0)	638 (100.0)
Patients with any AE	379 (89.6)	609 (95.5)
Gastrointestinal disorders	168 (39.7)	488 (76.5)
Diarrhoea	78 (18.4)	398 (62.4)
Nausea	28 (6.6)	156 (24.5)
Vomiting	11 (2.6)	74 (11.6)
Abdominal pain	10 (2.4)	56 (8.8)
Abdominal pain upper	15 (3.5)	41 (6.4)
Constipation	17 (4.0)	38 (6.0)
Infections and infestations	228 (53.9)	359 (56.3)
Nasopharyngitis	68 (16.1)	87 (13.6)
Bronchitis	45 (10.6)	67 (10.5)
Upper respiratory tract infection	42 (9.9)	58 (9.1)
Pneumonia	24 (5.7)	29 (4.5)
Respiratory, thoracic and mediastinal disorders	177 (41.8)	254 (39.8)
Cough	57 (13.5)	85 (13.3)
Idiopathic pulmonary fibrosis	61 (14.4)	64 (10.0)
Dyspnoea	48 (11.3)	49 (7.7)
Investigations	69 (16.3)	185 (29.0)
Weight decreased	15 (3.5)	62 (9.7)
General disorders and administration site conditions	106 (25.1)	152 (23.8)
Fatigue	33 (7.8)	40 (6.3)
Chest pain	22 (5.2)	34 (5.3)
Musculoskeletal and connective tissue disorders	95 (22.5)	118 (18.5)
Back pain	29 (6.9)	37 (5.8)
Arthralgia	21 (5.0)	14 (2.2)
Metabolism and nutrition disorders	60 (14.2)	115 (18.0)
Decreased appetite	24 (5.7)	68 (10.7)
Nervous system disorders	65 (15.4)	105 (16.5)
Headache	19 (4.5)	43 (6.7)

As might be expected in a study of a progressive fatal disease almost all patients experienced adverse events. However, investigators attributed causality to treatment more than twice as often in the nintedanib arm compared to placebo (Table 14) above. Review of the SOC categorisation suggests that nintedanib is toxic to the gastrointestinal (GI) tract The different proportion of patients experiencing weight loss by treatment arm probably reflects the GI tolerability and safety problems.

The Inclusion of IPF as an AE is unexpected as it is an inclusion criterion for entrance to the studies. The Applicant has followed a common convention of considering worsening of the disease to be treated as an adverse event. In reality it is a lack of efficacy event. This convention which is probably regulatory driven confuses safety and efficacy. If the medicinal product is effective, as is the case here there are likely to be more 'AEs' due to disease worsening in the placebo arm thus the apparent safety profile of the placebo

arm will appear worse than it actually is. Unfortunately, this is not remediable in the present circumstances.

Serious adverse event/deaths

The analysis of fatal AEs was based on treatment-emergent AEs. This means all AEs with an onset date (or worsening) between the first intake of study medication and 28 days after the discontinuation of study medication were assigned to treatment even if the death due to this AE occurred after the this period. Adverse events leading to death were more frequent in the placebo group (31 patients, 7.3%) than in the nintedanib 150 mg bid group (37 patients, 5.8%) of SG-1.1

Table 16 Adverse events leading to death reported in at least 2 patients in SG 1.1 sorted by frequency in the nintedanib 150 mg bid group

System organ class/	Placebo		Nintedanib 150bid	
Preferred term	N	(%)	N	(%)
Patients	423	(100.0)	638	(100.0)
Patients with AEs leading to death	31	(7.3)	37	(5.8)
Respiratory, thoracic and mediastinal disorders	22	(5.2)	23	(3.6)
Idiopathic pulmonary fibrosis	16	(3.8)	18	(2.8)
Respiratory failure	2	(0.5)	2	(0.3)
Infections and infestations	6	(1.4)	7	(1.1)
Pneumonia	2	(0.5)	5	(0.8)
Respiratory tract infection	2	(0.5)	1	(0.2)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	(0.0)	5	(0.8)
Lung neoplasm malignant	0	(0.0)	2	(0.3)
Cardiac disorders	6	(1.4)	3	(0.5)
Myocardial infarction	1	(0.2)	2	(0.3)
Cardiac arrest	2	(0.5)	0	(0.0)

There was one case of death due to bleeding from a duodenal ulcer in a 66 year old female patient who had lung cancer with liver metastases.

Laboratory findings

LIVER ENZYMES

Table 17 Patients with change from normal range at baseline to values above the reference range during treatment for liver enzymes and total bilirubin in SG-1.1

	Patients with normal baseline value and maximum on-treatment value outside of the reference range	
	Placebo N (%)	Nintedanib 150 mg bid N (%)
ALT	30 (7.2)	169 (27.3)
AST	22 (5.3)	134 (21.4)
ALKP	28 (6.8)	94 (15.3)
GGT	40 (10.4)	225 (39.2)
Total bilirubin	22 (5.3)	48 (7.7)

No patient in the nintedanib group fulfilled the laboratory criteria for potential Hy's law cases i.e. ALT and/or AST ≥3 ULN in conjunction with bilirubin ≥2 ULN within a time span of 30 days after the increase in AST and/or ALT.

HAEMATOLOGY

Table 18 Patients with change from normal range at baseline to outside the reference range during treatment for haematology parameters in SG-1.1

	Patients with normal baseline value and minimum/maximum on-treatment value outside of the reference range	
	Placebo N (%)	Nintedanib 150 mg bid N (%)
Transition to below the normal range		
RBC	35 (9.3)	62 (11.4)
Haemoglobin	39 (10.0)	41 (7.2)
Haematocrit	42 (11.2)	38 (6.9)
MCV	3 (0.8)	4 (0.7)
WBC	5 (1.3)	20 (3.6)
Neutrophils	19 (5.1)	31 (5.5)
Platelets	18 (4.6)	37 (6.2)
Transition to above the normal range		
RBC	9 (2.4)	17 (3.1)
Haemoglobin	16 (4.1)	44 (7.7)
Haematocrit	40 (10.7)	89 (16.2)
MCV	34 (9.4)	137 (24.9)
WBC	97 (25.7)	95 (17.1)
Neutrophils	90 (24.3)	100 (17.8)
Platelets	10 (2.5)	13 (2.2)

BIOCHEMISTRY

Table 19 Patients with change from normal range at baseline to values outside of the reference range during treatment for coagulation and other biochemistry parameters in SG-1.1

	Patients with normal baseline value and minimum/maximum on-treatment value outside of the reference range	
	Placebo N (%)	Nintedanib 150 mg bid N (%)
Transition to below the normal range[1]		
Sodium	34 (8.4)	45 (7.4)
Potassium	18 (4.4)	29 (4.7)
Calcium	22 (5.4)	50 (8.1)
Creatinine	47 (13.4)	102 (19.0)
aPTT	2 (0.6)	4 (0.7)
PT-INR	0 (0.0)	0 (0.0)
Transition to above the normal range[2]		
Sodium	4 (1.0)	12 (2.0)
Potassium	11 (2.7)	25 (4.0)
Calcium	15 (3.7)	28 (4.5)
Creatinine	12 (3.4)	12 (2.2)
aPTT	117 (32.3)	196 (35.3)
PT-INR	116 (30.5)	154 (27.0)

BLOOD PRESSURE

Table 20 Marked changes in blood pressure and pulse rate in SG-1.1

	Placebo N (%)	Nintedanib 150 mg bid N (%)
Patients	423 (100.0)	638 (100.0)
Systolic blood pressure		
Patients with measurements	421 (99.5)	635 (99.5)
Increase	27 (6.4)	61 (9.6)
Decrease	24 (5.7)	29 (4.5)
Diastolic blood pressure		
Patients with measurements	421 (99.5)	635 (99.5)
Increase	45 (10.6)	109 (17.1)
Decrease	38 (9.0)	37 (5.8)
Pulse rate		
Patients with measurements	421 (99.5)	635 (99.5)
Increase	43 (10.2)	69 (10.8)
Decrease	32 (7.6)	73 (11.4)

Analysis includes marked changes at any visit. Marked increase were defined as: SBP>150 mmHg and increase ≥25 mmHg above baseline, DBP>90 mmHg and increase >10 mmHg above baseline, pulse rate >100 bpm and increase >10 bpm above baseline. Marked decrease: SBP<100 mmHg and decrease >10 mmHg below baseline, DBP<60 mmHg and decrease >10 mmHg below baseline, PR<60 bpm and decrease >10 bpm below baseline.

Safety in special populations

No overall analysis of safety in special populations is provided. Pharmacokinetics in renal impairment and hepatic impairment is discussed in the clinical pharmacology of the application as is the effect of intrinsic factors such as weight, gender, and age. Hepatic safety is discussed in other section of this report.

Immunological events

Despite nintedanib's potential for interaction at receptors which mediate the immune response infections do not seem to be more frequent or of a different pattern to those experienced by placebo treated patients; nor are there examples of opportunist infection in the data base. However, as for the potential for hepatic injury, the database is too small to throw up rare events.

Safety related to drug-drug interactions and other interactions

Because of its metabolic route nintedanib appears to have a low potential for drug-drug interaction, probably including pirfenidone but because of the clinical likelihood for coadministration the latter represents an important missing information.

Discontinuation due to adverse events

In the Phase III trials overall about one fifth of the patients discontinued treatment prematurely; placebo: 18.9%, nintedanib: 24.5%. The main reason for discontinuation was AE.

Adverse events leading to discontinuation of study medication were more frequent in the nintedanib 150 mg bid group (19.3%) than in the placebo group (13.0%) of SG-1.1. Adverse events leading to discontinuation by SOC that were more common in the nintedanib than the placebo group by at least 1% were gastrointestinal disorders (placebo: 1.2%, nintedanib: 7.4%) and investigations (0.5% vs. 2.8%). Respiratory, thoracic and mediastinal disorders leading to discontinuation occurred more often in patients receiving placebo (6.6%) than in patients receiving nintedanib (3.1%).

Table 21 Adverse events leading to discontinuation of study medication with an incidence of more than 1% of patients in either treatment group in SG-1.1 sorted by frequency in the nintedanib 150 mg bid group

System organ class/ Preferred term	Placebo N (%)	Nintedanib 150 mg bid N (%)
Patients	423 (100.0)	638 (100.0)
Patients with AEs leading to permanent treatment discontinuation	55 (13.0)	123 (19.3)
Gastrointestinal disorders	5 (1.2)	47 (7.4)
Diarrhoea	1 (0.2)	28 (4.4)
Nausea	0 (0.0)	13 (2.0)
Respiratory, thoracic and mediastinal disorders	28 (6.6)	20 (3.1)
Idiopathic pulmonary fibrosis	21 (5.0)	13 (2.0)
Investigations	2 (0.5)	18 (2.8)
General disorders and administration site conditions	4 (0.9)	10 (1.6)
Infections and infestations	3 (0.7)	9 (1.4)
Metabolism and nutrition disorders	2 (0.5)	9 (1.4)
Decreased appetite	1 (0.2)	9 (1.4)
Cardiac disorders	7 (1.7)	7 (1.1)
Hepatobiliary disorders	1 (0.2)	7 (1.1)

Table 22 Adverse events leading to permanent dose reduction with an incidence of more than 0.5% in any treatment group SG-1.1, sorted by frequency in the nintedanib 150 mg bid group / TS

System organ class/ Preferred term	Placebo N (%)	Nintedanib 150 mg bid N (%)
Patients	423 (100.0)	638 (100.0)
Patients with AEs leading to permanent dose reduction	2 (0.5)	101 (15.8)
Gastrointestinal disorders	0 (0.0)	82 (12.9)
Diarrhoea	0 (0.0)	68 (10.7)

System organ class/ Preferred term	Placebo N (%)	Nintedanib 150 mg bid N (%)
Nausea	0 (0.0)	11 (1.7)
Vomiting	0 (0.0)	7 (1.1)
Abdominal pain	0 (0.0)	6 (0.9)
Investigations	2 (0.5)	12 (1.9)
Weight decreased	1 (0.2)	4 (0.6)
Hepatobiliary disorders	0 (0.0)	6 (0.9)
Hepatic function abnormal	0 (0.0)	4 (0.6)
Metabolism and nutrition disorders	0 (0.0)	5 (0.8)
Decreased appetite	0 (0.0)	4 (0.6)

Post marketing experience

Not applicable.

2.2.1. Discussion on clinical safety

The safety profile of nintedanib is known from its development in various cancer indications as well as the current IPF indication. In the cancer studies it was used at a higher dose than is now proposed for IPF. As there is good evidence that safety and tolerability are worse with higher doses data from the cancer studies cannot be extrapolated to IPF; also the co-medications and co-morbidities in the two situations are quite different. The Applicant's safety analysis is therefore concerned only with the IPF indication and this is appropriate.

The facility for dose reductions and treatment interruptions in the clinical programme was a good one as it mimics what might happen in clinical practice and it permits patient retention in clinical practice. The availability of a 150 mg and a 100 mg strength capsule is also helpful as it will permit dose flexibility in clinical practice.

Three evident safety/tolerability problems emerge from the data; gastrointestinal toxicity in general and diarrhoea in particular, the third being the potential for hepatic injury. The database shows a number of non-diarrhoeal events such as bleeding or a perforating peptic ulcer and a better analysis of these events was made by the applicant. The applicant considers bleeding as an important potential risk for the treatment with nintedanib due to its mode of action.

. The development of diarrhoea in a patient whose pulmonary status limits mobility is highly undesirable for patients and caregivers and is a frequent and causally mediated event in nintedanib treated patients.

The occurrence of elevated transaminases three to fourfold more frequently in nintedanib versus placebo treated patients is of concern and suggests a potential for drug related liver injury. The potential for

nintedanib to cause liver toxicity is the most serious risk associated with the drug and there is a warning in the SmPC regarding the need to monitor hepatic enzymes.

2.2.2. Conclusions on the clinical safety

The majority of the reported adverse events of Nintedanib are considered manageable with dose reductions. The most frequently reported adverse drug reactions (ADRs) specific for nintedanib were gastrointestinal disorders, diarrhoea, increased liver enzyme values (ALT and AST).

All the above side-effects can be dealt with in the product information and the side effect profile presents a picture of acceptable tolerability in most patients.

Because of the clinical likelihood for coadministration with pirfenidone it represents an important missing information. Therefore the applicant commits to perform an open-label nintedanib pirfenidone drug-drug interaction study in patients with IPF

2.3. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.4. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.1 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 1.2 with the following content:

Safety concerns

Table 23 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Diarrhoea Liver enzyme and bilirubin elevations
Important potential risks	Venous thromboembolism Arterial thromboembolism Bleeding Perforation Hepatic failure Treatment of pregnant women and teratogenicity Cardiac failure

	QT prolongation
Missing information	Treatment of patients with hepatic impairment (Child Pugh B/C) Treatment of Black patients Treatment of patients with healing wounds Treatment of patients with severe renal impairment or end stage renal disease Treatment of patients receiving full-dose therapeutic anticoagulation Interaction of OFEV with hormonal contraceptives Concomitant treatment with pirfenidone Treatment of breastfeeding women

Pharmacovigilance plan

Table 24: Ongoing and planned studies in the PhV development plan

Activity / Study title	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of final report**
Trial 1199.200 – nintedanib in volunteers with hepatic impairment.	To assess the pharmacokinetics and safety of nintedanib treatment in patients with hepatic impairment.	Missing information – treatment of patients with hepatic impairment.	Planned	Report archived: May 2016 (first patient in planned for Nov 2014)
Trial 1199.xxx – open-label nintedanib pirfenidone drug-drug interaction study in patients with IPF	To evaluate pharmacokinetics of nintedanib and pirfenidone in patients with IPF	Missing information – concomitant treatment (drug-drug interaction) with pirfenidone	Planned	Report archived: Quarter 4 2016

Risk minimisation measures

Table 25: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Diarrhoea	SmPC Sections 4.2, 4.4, and 4.8 Prescription only medicine; clear labelling, capsule design, and packaging (including information in Braille) to differentiate between different capsule strengths; information on safe use and handling in the SmPC and product information leaflet; readability testing on the printed package leaflet.	None
Liver enzyme and bilirubin	SmPC Sections 4.2, 4.4, and 4.8	None

elevations	Prescription only medicine; clear labelling, capsule design, and packaging (including information in Braille) to differentiate between different capsule strengths; information on safe use and handling in the SmPC and product information leaflet; readability testing on the printed package leaflet.	
Important potential risks		
Venous thromboembolism	SmPC Section 4.4 Prescription only medicine; clear labelling, capsule design, and packaging (including information in Braille) to differentiate between different capsule strengths; information on safe use and handling in the SmPC and product information leaflet; readability testing on the printed package leaflet.	None
Arterial thromboembolism	SmPC Section 4.4 Prescription only medicine; clear labelling, capsule design, and packaging (including information in Braille) to differentiate between different capsule strengths; information on safe use and handling in the SmPC and product information leaflet; readability testing on the printed package leaflet.	None
Bleeding	SmPC Section 4.4 Prescription only medicine; clear labelling, capsule design, and packaging (including information in Braille) to differentiate between different capsule strengths; information on safe use and handling in the SmPC and product information leaflet; readability testing on the printed package leaflet.	None
Perforation	SmPC Section 4.4 Prescription only medicine; clear labelling, capsule design, and packaging (including information in Braille) to differentiate between different capsule strengths; information on safe use and handling in the SmPC and product information leaflet; readability testing on the printed package leaflet.	None
Hepatic failure	SmPC Section 4.4 Prescription only medicine; clear labelling, capsule design, and packaging (including information in Braille) to differentiate between different capsule strengths; information on safe use and handling in the SmPC and product information leaflet; readability testing on the printed package leaflet.	None
Treatment of pregnant women and teratogenicity	SmPC Section 4.4 Prescription only medicine; clear labelling, capsule design, and packaging (including information in Braille) to differentiate between different capsule strengths; information on safe use and handling in the SmPC and product information leaflet; readability testing on the printed package leaflet.	None

Cardiac failure	SmPC Section 4.4 Prescription only medicine; clear labelling, capsule design, and packaging (including information in Braille) to differentiate between different capsule strengths; information on safe use and handling in the SmPC and product information leaflet; readability testing on the printed package leaflet.	None
QT prolongation	SmPC Section 4.4 Prescription only medicine; clear labelling, capsule design, and packaging (including information in Braille) to differentiate between different capsule strengths; information on safe use and handling in the SmPC and product information leaflet; readability testing on the printed package leaflet.	None
Missing information		
Treatment of patients with hepatic impairment (Child Pugh B/C)	SmPC Sections 4.2 and 4.4	None
Treatment of black patients	None	None
Treatment of patients with healing wounds	SmPC Section 4.4	None
Treatment of patients with severe renal impairment or end stage renal disease	SmPC Section 4.2	None
Treatment of patients receiving full-dose therapeutic anticoagulation	SmPC Section 4.4	None
Interaction of OFEV with hormonal contraceptives	SmPC Section 4.4	None
Concomitant treatment with pirfenidone	SmPC Section 4.4	None
Treatment of breastfeeding women	SmPC Sections 4.6	None

2.5. Product information

2.5.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Vargatef (the CHMP adopted an opinion for nintedanib with a different indication. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Studies 1199.32 and 1199.34 show a clear and consistent benefit in reducing the decline of FVC by approximately 125 mL/year and 94 mL/year -respectively. The time course for the decline in FVC is similar in both studies and the divergent slopes of the decline curves suggests a benefit over time rather than an initial once-off benefit which is then maintained over time (in which case the slopes would be parallel). Slightly surprisingly in view of the spirometric benefit there was no benefit in terms of gas exchange (DLco) in either study.

Nintedanib shows persuasive evidence of reduction of the rate of decline in lung function as indicated by absolute volume FVC. Percentage predicted FVC is preferred endpoint as it standardises the absolute measurement and reduces or eliminates variability due to demographic factors such as age, gender, body size which could be different between different treatment arms; the data on change in predicted normal are consistent with those on absolute volume which is reassuring. Divergences between the studies are seen for SGRQ total score andIPF exacerbations. In Study 1199.32 there is no difference between the treatment groups for SGRQ and for exacerbations. In contrast both have a statistically significant advantage over placebo in Study 1199.34, which study may represent reality is impossible to say. However, statistically significant benefits for SGRQ and exacerbation variables were present in the 150 mg bid treatment arm compared to placebo in the dose ranging study.

Uncertainty in the knowledge about the beneficial effects

As indicated above the lung function (spirometry) benefit is consistent over three studies for the 150 mg bid dose, but there is no quality of life or acute exacerbation for active treatment in Study 1199.32.. In the opinion of the CHMP demonstration of the lung function benefit is robust. The pathophysiology and symptoms of IPF are largely or entirely due to loss of lung function and to eventual respiratory failure. Consequently if the rate of deterioration of lung function is slowed indirect or secondary benefits might be expected and this appears to be the case for quality of life and IPF exacerbations. As the disease is quite rapidly progressive it is to be expected that quality of life will deteriorate measurably over the course of a year for both active and placebo groups. It is important that it should not deteriorate more in the active treatment group due to toxicity and the burden of treatment and this may be what was observed in Study 1199.32. Therefore, the fact that nintedanib is preserving approximately 100 mL of lung capacity relative to placebo does not imply that it is slowing progressive disease.

Risks

Unfavourable effects

Three evident safety/tolerability problems emerge from the data; gastrointestinal toxicity in general and diarrhoea in particular, the third being the potential for hepatic injury.

The database shows a number of non-diarrhoeal events such as bleeding or a perforating peptic ulcer. The development of diarrhoea in a patient whose pulmonary status limits mobility is highly undesirable for patients and caregivers and is a frequent and causally mediated event in nintedanib treated patients.

The occurrence of elevated transaminases three to fourfold more frequently in nintedanib versus placebo treated patients is of concern and suggests a potential for drug related liver injury. The potential for nintedanib to cause liver toxicity is the most serious risk associated with the drug and there is a warning in the SmPC regarding the need to monitor hepatic enzymes.

There are also additional suggestions of potentially serious side effects that might become more significant over time and would be consistent with the anti-angiogenic action of the drug. These include a possible increased risk of myocardial infarction, systemic hypertension and bleeding (from the anti-PDGFR activity of the drug). Gastrointestinal perforation is an additional potential risk that has been identified by the Applicant and is related to mechanism of action.

All the above side-effects can be dealt with in the product information and the side effect profile presents a picture of acceptable tolerability in most patients.

Uncertainty in the knowledge about the unfavourable effects

Given the rarity of the condition and the frequent co-morbidities associated with the disease, it can be problematic to decipher side-effects that are genuinely arising from drug treatment and therefore there is substantial noise in the adverse event profile. The population treated with nintedanib in the IPF clinical development is likely to be too small and exposed for too short a time to provide a realistic indication of the likelihood of serious drug related liver injury in clinical practice. However, certain side-effects are clearly linked and these include gastrointestinal side-effects and hepatic enzyme elevation that may lead to ongoing liver damage.

Balance

Importance of favourable and unfavourable effects

The slowing of lung function deterioration is scientifically and clinically interesting targeted therapy in IPF. It was first achieved through the authorisation of pirfenidone.

Change in lung function decline is not directly perceptible by IPF patients therefore the secondary benefits on quality of life and reduction of the frequency of exacerbations are very important. For quality of life an important consideration is ‘first cause no harm’ and this is probably the case for nintedanib two studies show a benefit and one showed no advantage in QoL measurements – probably consistent with the variability of the measurement. Frequency of exacerbations is very important as they may lead to hospitalisation and/or death, and in the case of non-fatal hospitalisation it can be expected to require weeks rather than days to manage.

Diarrhoea in a poorly mobile patient may be a major social and symptomatic problem even if it can be expected to resolve on treatment cessation.

Nintedanib appears to be potentially associated with rare but serious gastrointestinal toxicity, peptic ulcer and the consequences thereof, perforation and haemorrhage.

In view of the frequency of abnormalities of liver function enzymes it is to be expected that symptomatic hepatitis, drug induced liver injury, and probably liver failure will occur in clinical practice, there is a warning in the SmPC regarding the need to monitor hepatic enzymes.

Benefit-risk balance

Discussion on the benefit-risk assessment

Nintedanib is the second pharmacological treatment shown to have a clinical benefit in, and possibly alter the natural history of IPF. As IPF is a disease with a very poor prognosis and a high unmet need, and where intervention at an early stage of disease may have more capacity to prevent irreversible scarring and extend life. Therefore, the positive effect demonstrated on slowing of deterioration in lung capacity can be regarded as very encouraging.

The CHMP consider that it is an important treatment for patients and physicians who wish to avail of it. It is not a curative treatment and its disease modifying potential is modest.

The side effect profile also presents a picture of acceptable tolerability in most patients.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ofev (nintedanib) is not similar to Esbriet (pirfenidone), within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Ofev is indicated in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that nintedanib is qualified as a new active substance at the time of application.