25 September 2014
EMA/CHMP/726072/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Vargatef

International non-proprietary name: nintedanib

Procedure No.: EMEA/H/C/002569/0000

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Administrative information

Name of the medicinal product:	Vargatef
Applicant:	Boehringer Ingelheim International GmbH Binger Strasse 173 55216 Ingelheim GERMANY
Active substance:	NINTEDANIB
International Nonproprietary Name/Common Name:	NINTEDANIB
Pharmaco-therapeutic group (ATC Code):	Not yet assigned
Therapeutic indication:	In combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first line chemotherapy.
Pharmaceutical form:	Capsule, soft
Strengths:	100 mg and 150 mg
Route of administration:	Oral use
Packaging:	Blister (Alu/Alu)
Package sizes:	120 (60 x 2) capsules (multipack), 120 capsules and 60 capsules

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List of abbreviations

14C	Carbon 14
ADCA	Patients with adenocarcinoma
ADCA <9months	Patients with adenocarcinoma and <9 months since start of first-line therapy
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALKP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
aPTT	Increased activated partial thromboplastin time
AR	Assessment Report
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical classification system
ATP	Adenosine triphosphate
AUC	Area under the time concentration curve
b.i.d.	Bis in die, twice daily
BCRP	Breast cancer resistance protein
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte, German Health Authority
BI	Boehringer Ingelheim
BIBF 1120	Nintedanib
bid	Twice daily
BMI	Body mass index
BSA	Body surface area
CEA	Carcinoembryonic antigen
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent clearance
CL/Fss	Apparent clearance at steady state
C_{max}	Maximum observed plasma concentration
COPD	Chronic obstructive pulmonary disease
CP	Carboplatin/paclitaxel
CR	Complete response
CRA	Clinical research associate
CRC	Colorectal cancer
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical trial report
CV	Coefficient of variance
CYFRA-21-1	Cytokeratin Subunit 19
CYP	Cytochrome P450
DCE-MRI	Dynamic Contrast-enhanced Magnetic Resonance Imaging
DHC	Ductus hepaticus communis
DIC	Disseminated intravascular coagulation
DLT	Dose limiting toxicity
DMC	Data monitoring committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

ECOG PS	ECOG performance score
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
EQ-5D	Health Status Self-Assessment Questionnaire
F	Absolute bioavailability
FF	Final formulation
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
Flt-3	FMS-like tyrosine kinase 3
fT3	Free triiodothyronine
fT4	Free thyroxine
FU	Follow-up
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
gCV	Geometric coefficient of variation
GFR	Glomerular filtration rate
GGT	γ-Glutamyl transferase
GLUT1	Glucose transporter 1
gMean	Geometric mean
h	Hour(s)
HPLC-MS/MS	High performance liquid chromatography, tandem mass spectroscopy
HR	Hazard ratio
HRPC	Hormone refractory prostate cancer
HRQoL	Health related quality of life
HSA	Human serum albumin
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalised ratio
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ITT	Intention-to-treat
IV	Intravenous administration
IVRS/IWRS	Interactive voice/web-based response system
Ka	First order absorption constant
kg	kilogram
KM	Kaplan-Meier
L	Litre
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate dehydrogenase
LoQ	List of Questions
LVSI	Laboratory values of special interest
MCT4	Monocarboxylate transporter 4
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N	Sample size
N/A	Not applicable
na	Not available
NC	Not calculated
NONMEM	Non-linear mixed effect modelling
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association

OATP	Organic anion transporting peptide
OECD	Organisation for Economic co-operation and development
OR	Odds ratio
OS	Overall survival
P25	25th percentile
P75	75th percentile
PD	Progressive disease
PD	Pharmacodynamic
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
PKS	Pharmacokinetic set
PopPK	Population pharmacokinetic
PR	Partial response
PT	Prothrombin time
PTC	Percutaneous transhepatic cholangiography
PTT	Partial thromboplastin time
q.d.	Quaque die, once daily
QLQ	Quality of life questionnaire
QLQ-C30	Quality of life questionnaire – Core 30
QLQ-LC13	Quality of life questionnaire – lung cancer module
QoL	Quality of life
QT interval	The ECG interval from the start of the QRS complex to the end of the T-wave
QTc	Heart rate-corrected QT interval (general term)
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAF	Safety analysis set
SCC	Patients with squamous cell carcinoma
SCC ≥7.5 cm	Patients with squamous cell carcinoma and baseline sum of longest diameters ≥7.5 cm
SD	Stable disease
SLD	Sum of longest diameter (of the target lesions)
SMQ	Standardized MedDRA Query
Src kinase	Src tyrosine kinase
SS	Screened set
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life
TKI	Tyrosine kinase inhibitor
t_{max}	Time of occurrence of C_{max}
TNM	Tumour, lymph node, metastasis
TS	Treated set
TSAP	Trial statistical analysis plan
TSH	Thyroid stimulating hormone
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UGT1A1	UDP glucuronosyltransferase 1A1
UICC	Union Internationale Contre le Cancer
ULN	Upper limit of normal
V/F	Apparent volume of distribution
V2ss/F	Apparent volume of distribution at steady state
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 30 September 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Vargatef, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 May 2011.

The applicant applied for the following indication in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first line chemotherapy.

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(s) [CW/1/2011] on on the granting of a class 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 did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for 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 am Rhein
GERMANY

1.3. Steps taken for the assessment of the product

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

Rapporteur: Christian Schneider Co-Rapporteur: Ingunn Hagen Westgaard

The application was received by the EMA on 30 September 2013.

- The procedure started on 23 October 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 January 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 January 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 6 February 2014.
- During the meeting on 20 February 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 February 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 May 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 June 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 10 July 2014.
- During the CHMP meeting on 24 July 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 August 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2nd September 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 11 September 2014

Updated Joint Rapporteur/Co-Rapporteur Assessment Report on the responses provided by the applicant, dated 12 September 2014

- During the meeting on 25 September 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 Vargatef.

2. Scientific discussion

2.1. Introduction

Lung cancer is the most common cancer worldwide, with nearly 1,825,000 new cases diagnosed in 2012 (13% of the total). Lung cancer incidence rates are highest in Northern America and lowest in Middle Africa, but this partly reflects varying data quality worldwide. In Europe, lung cancer is the fourth most common cancer, with more than 410,000 new cases diagnosed in 2012 (12% of the total); the highest World age-standardised incidence rates for lung cancer in EU are in Hungary for men and Denmark for women; the lowest rates are in Sweden for men and Ukraine for women. Lung cancer is the leading cause of cancer deaths in men and the second leading cause of cancer deaths in women worldwide, estimated to be responsible for nearly one in five (1.59 million deaths, 19.4% of the total). Because of its high fatality (the overall ratio of mortality to incidence is 0.87) and the relative lack of variability in survival in different world regions, the geographical patterns in mortality closely follow those in incidence.
Non-small cell lung cancer accounts for approximately 85% of lung cancer cases. Broad histological subtypes of adenocarcinoma and squamous cell carcinoma each account for about 30 to 50% of NSCLC cases. The majority of patients with lung cancer are diagnosed after the disease has progressed to a more advanced stage. At diagnosis, 10% to 15% of patients have locally advanced cancer i.e. stage IIIB, and 40% of patients have metastatic cancer, i.e. stage IV. The prognosis for advanced stage disease has not changed significantly in the past 20 years. With an overall 5-year survival rate of 9-13%, the treatment of NSCLC remains a major clinical challenge.

In patients with locally advanced or metastatic disease, systemic chemotherapy is considered the therapeutic mainstay and is usually a platinum-combination therapy. Targeted therapies used for the first-line treatment of patients with NSCLC include inhibitors of the epidermal growth factor receptor (EGFR) such as erlotinib and gefitinib as well as bevacizumab, a monoclonal antibody against the vascular endothelial growth factor (VEGF). However, bevacizumab is not indicated for use in patients with NSCLC of squamous histology due to the increased risk of bleeding observed in these patients.

Despite responses and transient tumour regression on first-line treatment, the tumour will relapse in almost all patients. Currently, erlotinib, pemetrexed, and docetaxel are approved as monotherapies for the second-line treatment of locally advanced or metastatic NSCLC. In addition, gefitinib is approved for the treatment of patients with tumours harbouring activating EGFR mutations, irrespective of the line of treatment.

Despite the availability of second-line treatment options for patients with locally advanced or metastatic NSCLC, further treatment options are required to improve therapeutic outcome by prolonging the time until progression, to ameliorate signs and symptoms of the disease, and to prolong the overall survival of patients.

About the product

Nintedanib is a small molecule TKI triple angiokinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), fibroblast growth factor receptors (FGFR 1-3) kinase activity and platelet-derived growth factor receptor (PDGFR) α and β 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 and survival of endothelial as well as perivascular cells (pericytes and vascular smooth muscle cells). In addition Flt-3, Lck and Src kinases are inhibited. Nintedanib inhibits mitogenactivated protein kinase and Akt signalling pathways in 3 cell types contributing to angiogenesis, i.e. endothelial cells, pericytes, and smooth muscle cells, resulting in inhibition of cell proliferation. Based on its antiangiogenic action, nintedanib is expected to slow tumour growth. The inhibition of tumour autocrine and paracrine growth factor loops involving vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (FGF) is expected to inhibit tumourgenesis.

The Applicant initially claimed the following indication:

"Vargatef is indicated in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first line chemotherapy."

The final indication following a CHMP review of this application is:

Vargatef is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.
The recommended dose of Vargatef is 200 mg (2 capsules of 100 mg) taken orally twice daily; administered approximately 12 hours apart, preferably with food, on days 2 to 21 of a standard 21-day docetaxel treatment cycle, i.e. with Vargatef not to be taken on the same day of the administration of the docetaxel chemotherapy (= day 1). If a dose of nintedanib is missed, administration should resume at the next scheduled time at the recommended dose. The individual daily doses of nintedanib should not be increased beyond the recommended dose to make up for missed doses. The recommended maximum daily dose of 400 mg should not be exceeded. Patients may continue therapy with nintedanib after discontinuation of docetaxel for as long as clinical benefit is observed or until unacceptable toxicity occurs.

Treatment with Vargatef should be initiated and supervised by a physician experienced in the use of anticancer therapies.

Type of application and aspects on development

- Legal basis

This application concerns a centralised procedure and is submitted in accordance with article 8(3) of Directive 2001/83/EC.

- 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 (interim analysis of the PFS endpoint).

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.

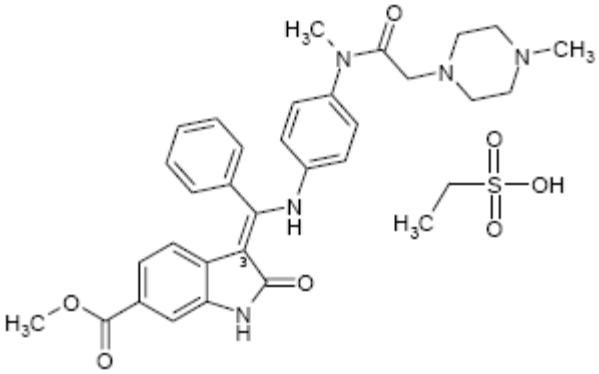
Other ingredients are medium-chain triglycerides, hard fat, lecithin, gelatin, glycerol (85 %), titanium dioxide, iron oxide red, iron oxide yellow and black ink. The black ink of the capsule has the following composition: shellac glaze, iron oxide black and propylene glycol.

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 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 production 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 formualtions. 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 proposedThe 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 Vargatef 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 Vargatef (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

On the molecular level, nintedanib is considered to inhibit the signaling cascade mediating angiogenesis by binding to the adenosine triphosphate (ATP) binding pocket of the VEGFR-2 kinase domain, thus interfering with cross-activation via autophosphorylation of the receptor homodimers. Besides inhibition of neo-angiogenesis, tumour regression may also be achieved by inducing apoptosis of tumour blood vessel endothelial cells. Inhibition of receptor kinases may also interfere with autocrine and paracrine stimulation of tumour angiogenesis via activation loops involving VEGF, PDGF, and bFGF utilized by perivascular cells such as pericytes and vascular smooth muscle cells.

Primary pharmacodynamic studies

In vitro studies

The in vitro activity of nintedanib was investigated in both enzymatic and cellular assays for vascular endothelial growth factor receptor 2 (VEGFR-2) inhibition. In order to characterize the potency of nintedanib for inhibition of VEGFR-2, its IC50 was determined in an enzymatic VEGFR-2 kinase assay and in a VEGF driven endothelial cell proliferation assay. The selectivity of this compound was tested with respect to inhibition of basic fibroblast growth factor (bFGF) mediated endothelial cell proliferation and inhibition of tumour cell lines proliferation.

Sf9-DELFIA assays were used to explore the inhibitory effect of BIBF 1120 on murine VEGFR-2 (flk-1), VEGFR-1 and VEGFR-3. The efficacy of nintedanib on blocking VEGFR-2 phosphorylation was tested by western blot hybridization.

Results in terms of potency of nintedanib for selected kinases are in table 1.

Table 1 In vitro potency (IC50 nM) and selectivity of BIBF 1120 in kinase assays

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

In order to determine the duration of receptor inhibition induced by nintedanib, washout experiments were performed. VEGFR-2 transfected NIH3T3 cells were exposed to BIBF 1120 for a limited period of time. Nintedanib was washed off and VEGFR-2 activation/phosphorylation was analyzed after various periods of time. After 8 h, 24 h, or 32 h without BIBF 1120, the cells were stimulated with VEGF and receptor activation was analyzed.

Nintedanib exhibited a strong VEGFR-2 inhibitory activity in vitro. In a HUVEC proliferation assay was demonstrated that a short pulse (2 hrs) of nintedanib treatment followed by an (up to) 46 hrs "washout" period was sufficient to block cell proliferation
BIBF 1202, the main metabolite of BIBF 1120, inhibits VEGFR-2, FGFR1 and PDGFRα with IC50 values of 62 nM, 240 nM and 433 nM, respectively. VEGF-stimulated HUVEC cell proliferation is inhibited with an EC50 value of 133 nM. Thus, BIBF 1202 inhibits angiokinase activity with lower potency than BIBF 1120.

Nude mice carrying established FaDu tumors were treated with 30 mg/kg/day intraperitoneally (IP) of either BIBF 1120 or BIBF 1202. After 20 days, the BIBF 1120 treated tumors had not even doubled their volume, whereas the BIBF 1202 treated tumors had increased their volumes by a factor of >10 (similar to the mock-treated control tumors) compared to the size of the tumors at the start of treatment (Figure X) (BIBF 1120 chloride and BIBF 1202 were used in these experiments; U05- 1930). In conclusion, no in vivo activity of BIBF 1202 could be observed.

Plasma concentrations of BIBF 1202 and BIBF 1120 were analysed at the end of the in vivo efficacy experiments 2, 5 and 24 hours after the last administration. The Cmax for BIBF 1202 was 5.1 +/- 2.1 µM and for BIBF 1120 0.96 +/- 0.19 µM.

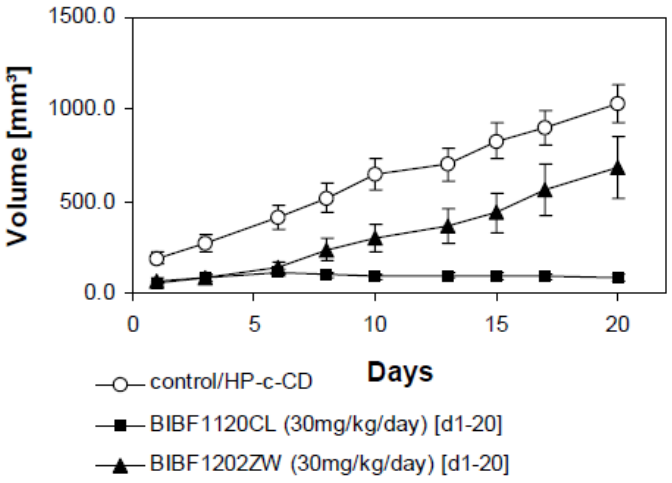


Figure 1 Anti-tumour efficacy of BIBF 1120 and BIBF 1202 on FaDu Xenografts in nude mice.

The effects of BIBF 1120 on intracellular signalling were assessed in short-term cellular assays by Western blotting using phospho-specific antibodies to signalling molecules such as MAPK, Akt and Caspase 3.

In HUVEC endothelial cells, apoptosis was preceded by inhibition of MAPK and Akt phosphorylation (Figure 2A). The apoptosis marker cleaved caspase 3 was up-regulated in a concentration-dependent manner in both VEGF- and bFGF- stimulated HUVEC (U08-1946).

Pericytes, important for vessel maturation and stabilization, are known to express PDGF receptors. BIBF 1120 inhibited proliferation of PDGF-BB-stimulated bovine retinal pericytes (BRP) with an EC50 of 79 nM (Table 2). Signaling pathway analysis demonstrated that activation of MAPK following stimulation with 5% serum plus PDGF-BB could be blocked by BIBF 1120 at concentrations down to 100 nM. Stimulation of BRP with 5% serum plus bFGF blocked MAPK phosphorylation but not concentration-dependently.

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The kinase domain of VEGFR-2 was recombinantly expressed as a GST fusion protein in a baculovirus expression system. After cleavage of the GST-tag, the kinase domain was in vitro phosphorylated and cocrystallized with the ligand. Diffraction data of the VEGFR-2 kinase crystals in complex with BIBF 1120 were collected.
The X-ray structure of VEGFR-2 kinase in complex with the ligand BIBF 1120 (Figure below) was solved at a resolution of 2.1 Å. The crystal contains one monomer of VEGFR-2 kinase in the asymmetric unit. BIBF 1120 is bound at the ATP-binding site in the cleft between the N- and C-terminal lobes of the kinase domain.

In vivo studies

The in vivo anti-tumour efficacy of BIBF 1120 was analysed at different doses (10-100 mg/kg daily orally) in three different tumour models. The main results are as follows:

- Human FaDu xenografts on nude mice showed complete growth arrest at doses of 100 mg/kg (T/C=11%) and 2x50 mg/kg (T/C=15%) and even at 1x50 mg/kg (T/C=27%) a statistically significant anti-tumour effect was observed.
- Caki-1 tumour xenografts also responded well to the treatment with BIBF1120 at doses of 100 mg/kg (T/C=13%) and 50 mg/kg (T/C=35%).
- Using the syngeneic GS9L rat tumour model BIBF1120 demonstrated anti-tumour efficacy at doses of 50 mg/kg (T/C=30%) and 25 mg/kg (T/C=45%).
- Treatment of Caki-1 tumours with 100 mg/kg/day for five days resulted in the reduction of tumour vessel density of about 80%

Table 2 In vivo anti-tumour effects of BIBF 1120 in cancer models.

Model	Derivation	Dose [mg/kg/d]	T/C value [%]*
FaDu	HNSCC	100	11
		50	14[#] / 27
		2 x 50	15
		25	46[#]
		10	82[#]
Caki-1	Kidney	100	16
		50	25
		10	71
GS-9L[$]	Glioma	50	30
		25	45
		10	74

*Nude mice bearing established human xenografts (0.05 - 0.1 cm^3 volume) were treated once or twice daily with BIBF 1120 p.o. (10 – 100 mg/kg) or vehicle control. For T/C values, the median tumour volume of each treatment group was compared to the median of the control group at the end of the experiment.
[#]Results of an independent experimental series.
[$]GS-9L is a syngeneic rat tumour glioma model that has grown s.c.

Plasma levels were determined as part of the study, after single oral administration of 100 mg/kg in NMRI nu/nu mice and 50 mg/kg in Fischer 344 rats. The calculated plasma levels at the Cmax were ~700nM and ~200nM, respectively

Efficacy of BIBF 1120 in combination with pemetrexed or carboplatin in nude mouse xenograft models of human cancer (U11-1283-01, study no BIRCV07-10)

In a model of non-small-cell lung carcinoma (Calu-6), addition of BIBF 1120 to a regimen of pemetrexed therapy was assessed. In the same study a model of ovarian carcinoma (SKOV-3), addition of BIBF 1120 to a regiment of carboplatin therapy was also evaluated.

In the Calu-6 study (10 animals per group), BIBF 1120 was dosed at 50 mg/kg once daily PO. Pemetrexed was initially dosed at 125 mg/kg qdx5 per week IP; due to intolerability in the combination arm the dose was reduced to 100 mg/kg on day 23. In the SKOV-3 study (7 animals per group, except for 10 in the control group), carboplatin was dosed by IP injection of 75 mg/kg on day 1, followed by oral BIBF 1120 at 25 mg/kg daily on days 2 to 7 of each week.

In the Calu-6 study, T/C values of 36%, 49% and 18% were observed for BIBF 120 monotherapy, pemetrexed monotherapy and combination therapy respectively. In the SKOV-3 study, T/C values of 48%, 82% and 16% were observed for BIBF 1120 monotherapy, carboplatin monotherapy and combination therapy respectively.In both experiments at least additive anti-tumour effects were observed and the treatment groups receiving the combination did not show additional adverse effects.

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)

BOBF 1120ES 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). High metabolism 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 µM i.e. 12.4-fold higher than the maximum plasma concentration of BIBF 1120 (37.9 ng/mL: 0.071 µM) after 200 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.

[14C]BIBW 2992 MA2 was metabolized under formation of U1 (BIBW 2992 MA2 N-oxide) and U2 (N-demethyl BIBW 2992 MA2). BIBF 1120 ES up to a concentration of 50 µM had no apparent effect on the *in vitro* microsomal metabolism of [14C]BIBW 2992 MA2, neither on metabolite formation nor on the metabolic depletion of [14C]BIBW 2992 MA2.

[14C]BIBF 1120 ES was metabolized under formation of U1 (di-demethyl BIBF 1120 ES), U2 (BIBF 1202, i.e. O-demethyl BIBF 1120 ES) and U4 (BIBF 1053, i.e. N-demethyl BIBF 1120 ES). BIBW 2992 MA2 up to a concentration of 50 µM had some minor inhibitory effect on the formation of U1, U2 and U4 and consequently reduced the metabolic turnover of BIBF 1120 ES. However, the effect was only minor and an IC50 could not be calculated as the inhibition was < 50 % at the highest concentration of BIBW 2992 MA2 (50 µM).

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 3 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 4 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	<u>20 mg/kg</u> hepatocellular hemosiderosis (females), <u>≥20 mg/kg</u> Dentopathy, swelling of articular chondrocytes, cellular depletion (bone marrow) <u>100 mg/kg</u> 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.

<u>26-week toxicity study in CrlGlxBrlHan:WI rats (U05-1843)</u>

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 5 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		≥ 40 mg/kg Diarrhea, vomitus, RBC ↓, hemoglobin ↓, reticulocytes ↑, PCV ↓, platelets ↑, ALT ↑, AST ↑ 80 and 160 mg/kg 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:

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

Embryo-foetal development

A summary of studies performed is given in table X

Table 6 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 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 7 *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. 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.

Repeat dose toxicity studies with other agents

Several repeat-dose toxicity studies were conducted with BIBF 1120 in combination with other compounds. Combination partners were the EGFR/HER-2 inhibitor afatinib (U06-1624, U06-1606, U06-1196, U06-1605), the PLK1 inhibitor volasertib (08B038, 08B079) and an Aurora B-inhibitor, BI 811283 (U11-2658, U12-1780). The development of BI 811283 was terminated. The combination studies with afatinib were already included in the submission package for afatinib [cf. Toxicology Written Summary U12-1533).

In summary, combination of BIBF 1120 with afatinib, volasertib and an Aurora B-inhibitor did not reveal any additional, toxicologically meaningful information with respect to the toxicological profile of BIBF 1120 not already known from the non-clinical studies with this compound alone.

2.3.5. Ecotoxicity / environmental risk assessment

Table 8 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

Tumour angiogenesis is an essential feature contributing to tumour growth, progression and metastasis formation and is predominantly triggered by the release of pro-angiogenic factors secreted by the tumour cell (i.e. VEGF and bFGF) to attract host endothelial as well as perivascular cells to facilitate oxygen and nutrient supply through the host vascular system.

Nintedanib was tested for its ability to interfere with essential angiogenic processes in a variety of *in vitro* assays and *in vivo* systems. To evaluate the potential for combination treatment, nintedanib was tested together with docetaxel, vinorelbine, pemetrexed or carboplatin in xenograft models of lung and ovarian cancer.

In preclinical disease models nintedanib, as single agent, effectively interfered with the formation and maintenance of the tumour vascular system resulting in tumour growth inhibition and tumour stasis. In particular, treatment of tumour xenografts with nintedanib led to a rapid reduction in tumour micro vessel density, pericytes vessel coverage and tumour perfusion (see section 5.1 of the SmPC). Affinities for various receptors were determined by radioligand receptor assays for BIBF 1120 at 5 µM. Potent and selective inhibition of human VEGF-2-dependent endothelial cell proliferation (HUVEC and HSMEC) by BIBF 1120 was demonstrated at IC50 values of 21 nM. VEGFR-1 was also significantly inhibited by BIBF 1120 (IC50 of 34 nM). The values presented for HUVEC (bFGF; 290 ± 160) and for VEGFR-3 (13) seems to be different from the data presented in the original study report U02-1109 (341 ± 112 nM and 46 ± 9 nM (Table 2.1.2:1 Pharmacology Written

Summary, respectively). In addition, in Study U02-1310 BIBF 1120 was found to inhibit VEGFR3, PDGFRα and FGFR-l at mean IC50 values of 13, 59 and 69 nM respectively. Therefore the Applicant is asked to: A) Present the correct data for HUVEC and VEGFR-3 or explain why this discrepancy exists. B) The IC50 value for VEGFR-3 in this study differs from the value found in study U02-1109 and the Applicant is asked to elaborate on this discrepancy.

BIBF 1120 exhibited a strong VEGFR-2 inhibitory activity in vitro. In a HUVEC proliferation assay was demonstrated that a short pulse (2 hrs) of BIBF 1120 treatment followed by an (up to) 46 hrs "washout" period was sufficient to block cell proliferation. BIBF 1202 was found to be a potent inhibitor of VEGFR-2 (IC50 = 62 nM) and is equally active (IC50 = 14.5 nM) on the closely related VEGFR-3. The more distantly related members of the kinase-insert domain family, FGFR1 and PDGFRα, were inhibited at higher concentrations (IC50 = 240 and 433 nM, respectively). BIBF 1120 inhibited cellular proliferation of VEGF-stimulated endothelial cells derived from umbilical veins (HUVEC), of PDGF-BB-stimulated human vascular smooth muscle cells (HUASMC) and of PDGF-BB-stimulated bovine retinal pericytes (BRP) with EC50s of 9 nM, 43 nM and 79 nM (mean values), respectively. These proliferative effects were preceded by inhibition of MAPK and Akt phosphorylation. Induction of apoptosis was observed in endothelial and smooth muscle cells, but not in pericytes. The expected binding mode of BIBF 1120 was confirmed by co-crystallization with recombinant VEGFR-2 kinase and X-ray diffraction at a resolution of 2.1 Å.

Therefore, nintedanib is a triple angiokinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR α 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 proliferation and survival of endothelial as well as perivascular cells (pericytes and vascular smooth muscle cells). 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).

BIBF1120 at a dose level of 50 mg/kg twice daily, or 100 mg/kg once daily PO show anti-tumour efficacy in mouse and rat tumour xenograft models with a reduction in tumour vessel density of approximately 80% in Caki-1 tumours in nude mice. The Cmax plasma levels of BIBF 1120 was determined in mice following PO 100 mg/kg PO, and in Fischer 344 rats at 50 mg/kg PO to be approximately 700 and 200 nM respectively.

Treatment with the metabolite BIBF 1202 at a daily dose of 30 mg/kg given IP to FaDu Xenograft-implanted nude mice showed no significant anti-tumour effect.

BIBF 1120 in combination with pemetrexed or carboplatin showed additive anti-tumour effects in Calu-6 and SKOV-3 xenografted tumours in nude mice, without showing additional adverse effects (as measured by body weight changes).

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. The Applicant has investigated ant-tumour efficacy of drug combinations and presented the data in earlier sections.

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 the non clinical species approximately 11% (rat) to 23.8% (rhesus monkey). High metabolism 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-fetal 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 µM i.e. 12.4-fold higher than the maximum plasma concentration of BIBF 1120 (37.9 ng/mL: 0.071 µM) after 200 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.

[14C]BIBW 2992 MA2 was metabolized under formation of U1 (BIBW 2992 MA2 N-oxide) and U2 (N-desmethyl BIBW 2992 MA2). BIBF 1120 ES up to a concentration of 50 µM had no apparent effect on the in vitro microsomal metabolism of [14C]BIBW 2992 MA2, neither on metabolite formation nor on the metabolic depletion of [14C]BIBW 2992 MA2.

[14C]BIBF 1120 ES was metabolized under formation of U1 (di-demethyl BIBF 1120 ES), U2 (BIBF 1202, i.e. O-demethyl BIBF 1120 ES) and U4 (BIBF 1053, i.e. N-demethyl BIBF 1120 ES). BIBW 2992 MA2 up to a concentration of 50 µM had some minor inhibitory effect on the formation of U1, U2 and U4 and consequently reduced the metabolic turnover of BIBF 1120 ES. However, the effect was only minor and an IC50 could not be calculated as the inhibition was < 50 % at the highest concentration of BIBW 2992 MA2 (50 µM).

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 specie 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 200 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. 605 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.According to the ICH S9 carcinogenicity studies are not warranted in the context of the proposed indication for (second line and in combination with docetaxel).

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-fetal 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-fetal 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 Vargatef should be advised to avoid becoming pregnant while receiving treatment with Vargatef and to use adequate contraception during and at least 3 months after the last dose of Vargatef. 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 Vargatef 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 Vargatef.
Female patients should be advised to notify their doctor or pharmacist if they become pregnant during therapy

with Vargatef. If the patient becomes pregnant while receiving Vargatef, she should be apprised of the potential hazard to the foetus. Termination of the treatment with Vargatef 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 Vargatef.

Nintedanib is presented as an oral formulation. The potential for local irritation can be assessed as part of other toxicity tests, and as the intended route of administration (oral gelatine capsules), 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 immunosuppresion 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 9 Clinical trials investigating nintedanib in patients with NSLC

Trial number	Study design[1]	Main characteristics of the patient population	Combination treatments	Patients (n)[2]
Phase I dose escalation trials, combination therapy				
1199.5	O, U, MC, DE	NSCLC, all histologies	Paclitaxel/ carboplatin	26
1199.18	O, U, MC, DE	NSCLC, all histologies	Pemetrexed	26
1199.29	O, U, SC, DE	NSCLC, all histologies, Japanese patients only	Docetaxel	(43)
Phase I/II, combination therapy				
1199.28	Part I: O, U, MC, DE Part II: DB, R, PG, MC	NSCLC, Japanese patients only part I: all histologies, part II: non-squamous histologies	Pemetrexed	(18)
1199.82	Part I: O, U, MC, DE Part II: DB, R, PG, MC	NSCLC, squamous histology	Gemcitabine/ cisplatin	(16)
Phase II, monotherapy				
1199.10	DB, R, PG, MC	NSCLC, all histologies	–	73
Phase III, combination therapy				
1199.13	DB, R, PG, MC	NSCLC, all histologies	Docetaxel	1314
1199.14	DB, R, PG, MC	NSCLC, non-squamous histologies	Pemetrexed	713

[1] Abbreviations: DB=double-blind, DE=dose escalation, MC=multicentre, NSCLC=non-small cell lung cancer, O=open-label, PG=parallel-group, R=randomised, SC=single-centre, U=uncontrolled

[2] For completed trials, the number of entered/randomised patients is given. For trials that were ongoing, the number of entered patients as of 27 May 2013 is provided in parentheses.

Based on the overall safety profile from all phase I and phase II studies, a nintedanib dose of 200 mg b.i.d. administered approximately 12 hours apart, on days 2 to 21 of a standard 21-day docetaxel treatment cycle, was selected for the combination with standard therapy of docetaxel (75mg/m2) in the phase III trial 1199.13. This starting dose could be reduced in two steps in case of intolerable AEs. If a dose of nintedanib is missed, administration should resume at the next scheduled time at the recommended dose. The individual daily doses of nintedanib should not be increased beyond the recommended dose to make-up for missed doses and the recommended maximum daily dose of 400 mg should not be exceeded (see SmPC section 4.2).

Patients may continue therapy with nintedanib after discontinuation of docetaxel for as long as clinical benefit is observed or until unacceptable toxicity occurs.

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 10).

Table 10: 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 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

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), liver metastases, ECOG performance score, 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 LUME-Lung-1 trial these effects are not considered clinically relevant. However, close monitoring is recommended in patients with several of these risk factors (see SmPC sections 4.4 and 5.2).

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). 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. Pharmocokinetic 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.

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. $AUC_{T,ss}$ 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. Studies in paediatric populations have not been performed.

The number of elderly patients included in PK trials is reported in the table below.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	720/2380	185/2380	2/2380

An inverse correlation between body weight and exposure to nintedanib was observed. $AUC_{T,ss}$ 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 (see SmPC section 5.2).

No studies in paediatric populations investigating the PK of nintedanib have been performed. Safety data for Black and African American patients are limited (see SmPC sections 4.2 and 5.2).

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 Vargatef should be carefully considered.

Co-administration of nintedanib with docetaxel (75 mg/m²) did not alter the pharmacokinetics of either medicine to a relevant extent.

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 11: 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 triple angiokinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR α 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 proliferation and survival of endothelial as well as perivascular cells (pericytes and vascular smooth muscle cells). 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

Tumour angiogenesis is an essential feature contributing to tumour growth, progression and metastasis formation and is predominantly triggered by the release of pro-angiogenic factors secreted by the tumour cell (i.e. VEGF and bFGF) to attract host endothelial as well as perivascular cells to facilitate oxygen and nutrient supply through the host vascular system. In preclinical disease models nintedanib, as single agent, effectively interfered with the formation and maintenance of the tumour vascular system resulting in tumour growth inhibition and tumour stasis. In particular, treatment of tumour xenografts with nintedanib led to a rapid reduction in tumour micro vessel density, pericytes vessel coverage and tumour perfusion.

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) measurements showed an anti-angiogenic effect of nintedanib in humans. It was not clearly dose dependent, but most responses were seen at doses of ≥ 200 mg. Logistic regression revealed a statistically significant association of the anti-angiogenic effect to nintedanib exposure. DCE-MRI effects were seen 24 - 48 h after the first medicine intake and were preserved or even increased after continuous treatment over several weeks. No correlation of the DCE-MRI response and subsequent clinically significant reduction in target lesion size was found, but DCE-MRI response was associated with disease stabilization (see SmPC sections 5.1 and 5.2).

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).

However, no thorough QT-trial of nintedanib administered in combination with docetaxel was conducted.

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.

PK-efficacy analyses were not performed for clinical endpoints (see SmPC section 5.2).

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.

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. The target population may be severely affected by their malignant disease and food intake could be difficult. As a consequence, section 4.2 of the SmPC states that capsules of nintedanib must be taken orally, preferably 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 Vargatef 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. Both for efficacy and safety the exposure-response relationships were rather weak, but in a given patient maximising exposure may be desirable from a benefit-risk perspective. Thus, the recommended posology, starting with a dose of 200 mg bid and then adapted according to the proposed dose reduction schemes seems reasonable. The dose reduction scheme is proposed in the SmPC which also recommends continuous monitoring of safety and tolerability in patients with more than one covariate that may lead to increased exposure to nintedanib.

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.

The applicant has committed to provide data on in-vitro OAT1 and OAT3 inhibition post approval by Q4 2014.

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.

No obvious association between exposure and adverse events is apparent from a descriptive analysis of available data.

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).

Neither DCE-MRI response nor soluble levels of VEGF and bFGF could be associated with treatment effect after administration of nintedanib in at least three months. The biomarker research programme proposed as part of the ongoing clinical development programme for nintedanib will focus on the assessment of a larger panel of soluble plasma biomarkers, IHC of tumour cell proliferation and tumour MVD, mutational analysis of oncogenic driver mutations and nintedanib/angiogenesis-related target genes and gene expression analyses. It is to be updated annually for submission to the CHMP on a yearly basis. In accordance with the published data about circulating angiogenic factors (CAFs) it is planned to quantify a comprehensive panel of ~60 plasma markers in further studies with nintedanib in different indications including NSCLC. Furthermore, multiple genes (60) have been identified to have an oncogenic role and possibly play a role in angiogenesis, and the predictive value of these genes will be investigated further. (see Conclusion on clinical efficacy and Annex II)

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, as well as nintedanib combined with docetaxel in lung cancer patients, 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)

- Submission of results from trial PK1407T: In vitro evaluation of the interaction of nintedanib with human OAT transporters to determine the interaction potential of BIBF 1120 toward OAT1 and OAT3. The final report is expected by Q4 2014
- 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).

2.5. Clinical efficacy

The applicant submitted two Phase III trials to support the European Marketing Authorisation for Vargatef (nintedanib) for the treatment of non-small cell lung cancer, one pivotal study (1199.13) and one supportive study (1199.14).

2.5.1. Dose response study(ies)

A wide range of nintedanib monotherapy doses were investigated in phase I and II trials, from 50 to 450 mg q.d. and from 150 to 300 mg b.i.d. In phase I dose escalation trials (trials 1199.1, 1199.2, and 1199.3), the maximum tolerated dose was determined as 250 mg b.i.d. The predominant dose limiting toxicities were gastrointestinal AEs and fully reversible elevations in liver enzymes (ALT, AST, GGT) not accompanied by relevant bilirubin increases. Based on the nintedanib monotherapy data, a dose threshold for liver enzyme increases was observed at approximately 250 mg b.i.d., with higher frequencies of liver enzyme increases at nintedanib doses >200 mg b.i.d. compared to doses of ≤200 mg b.i.d. According to data from the trials 1199.1, .2, and .3, splitting the cumulative daily dose into 2 doses per day increased the tolerability of nintedanib, compared with once-daily dosing. In phase I trials combining nintedanib with pemetrexed, docetaxel, paclitaxel/carboplatin, or mFOLFOX6 (trials 1199.4, 1199.5, 1199.6, 1199.18, 1199.51), the recommended dose of nintedanib was established as 200 mg b.i.d. The pattern of AEs was comparable to the AE profile observed in phase I monotherapy trials except for the chemotherapy-related AEs. Based on the overall safety profile from all phase I and phase II studies, a nintedanib dose of 200 mg b.i.d. was selected for the combination with standard therapy of docetaxel (75mg/m2) in the phase III trial 1199.13. This starting dose could be reduced in two steps in case of intolerable AEs.

2.5.2. Main study

Multicentre, randomised, double-blind, Phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard docetaxel therapy compared to placebo plus standard docetaxel therapy in patients with stage IIIB/IV or recurrent non-small cell lung cancer after failure of first line chemotherapy (LUME Lung 1 – 1199.13)

Methods

Study Participants

Inclusion criteria

Patients could be included in the trial if all of the following criteria were fulfilled:

• Male or female patient aged 18 years or older

• Histologically or cytologically confirmed, locally advanced and/or metastatic NSCLC of stage IIIB or IV (according to American Joint Committee on Cancers [AJCC]) or recurrent NSCLC (all histologies)

• Relapse or failure of 1 first-line prior chemotherapy (in the case of recurrent disease one additional prior regimen was allowed for adjuvant, neoadjuvant, or neoadjuvant plus adjuvant therapy)

• At least 1 target tumour lesion that had not been irradiated within the past 3 months and that could accurately be measured by magnetic resonance imaging (MRI) or CT in at least 1 dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT

• Life expectancy of at least 3 months

• ECOG PS of 0 or 1

• Patient had given written informed consent which must be consistent with international conference on harmonisation – good clinical practice (ICH-GCP) and local legislation

Exclusion criteria

If any of the following criteria applied, the patient was barred from entering the trial:

• More than 1 prior chemotherapy regimen for advanced and/or metastatic or recurrent NSCLC

• More than 1 chemotherapy treatment regimen (either neoadjuvant or adjuvant or neoadjuvant plus adjuvant) prior to first-line chemotherapy of advanced and/or metastatic or recurrent NSCLC

• Previous therapy with other VEGFR inhibitors (other than bevacizumab) or docetaxel for treatment of NSCLC

• Persistence of clinically relevant therapy-related toxicities from previous chemotherapy and/or radiotherapy

• Treatment with other investigational drugs or treatment in another clinical trial within the past 4 weeks before start of therapy or concomitantly with this trial

• Chemo-, hormone-, radio- (except for brain and extremities) or immunotherapy or therapy with monoclonal antibodies or small tyrosine kinase inhibitors within the past 4 weeks prior to treatment with the trial drug i.e. the minimum time elapsed since the last anticancer therapy and the first administration of BIBF 1120 was to be 4 weeks. This criterion was changed with Protocol Amendment 1 (dated 15 May 2009): the exception for radiotherapy of the brain was removed, and no radiotherapy of the brain was permitted within 4 weeks prior to the first administration of BIBF 1120.

• Radiotherapy (except extremities and brain) within the past 3 months prior to baseline imaging

• Active brain metastases (e.g. stable for <4 weeks, no adequate previous treatment with radiotherapy, symptomatic, requiring treatment with anti-convulsants; dexamethasone therapy was allowed if administered as stable dose for at least 1 month before randomisation) or leptomeningeal disease

• Radiographic evidence of cavitary or necrotic tumours

• Centrally located tumours with radiographic evidence (CT or MRI) of local invasion of major blood vessels

• History of clinically significant haemoptysis within the past 3 months (more than 1 tea spoon of fresh blood per day)

• Therapeutic anticoagulation (except low dose heparin and/or heparin flush as needed for maintenance of an indwelling intravenous device) or antiplatelet therapy (except for chronic low-dose therapy with acetylsalicylic acid ≤325 mg per day)

• History of major thrombotic or clinically relevant major bleeding event in the past 6 months

• Known inherited predisposition to bleeding or thrombosis

• Significant cardiovascular diseases (i.e. hypertension not controlled by medical therapy, unstable angina, history of myocardial infarction within the past 6 months, congestive heart failure >New York Heart Association (NYHA) class II, serious cardiac arrhythmia, pericardial effusion)

• Serum creatinine >1.5 times the upper limit of normal

• Proteinuria CTCAE grade ≥2

• Total bilirubin > upper limit of normal (ULN)

• Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) >1.5 x ULN

• Prothrombin time (PT) and/or partial thromboplastin time (PTT) >50% deviation from normal limits

• Absolute neutrophil count (ANC) <1500/µL

• Platelets <100 000/µL

• Haemoglobin <9.0 g/dL

• Significant weight loss (>10%) within the past 6 weeks prior to treatment in the present trial

• Current peripheral neuropathy ≥ CTCAE grade 2 except due to trauma

• Pre-existing ascites and/or clinically significant pleural effusion

• Major injuries and/or surgery within the past 10 days prior to randomisation with incomplete wound healing

• Serious infections requiring systemic antibiotic (e.g. antiviral, antimicrobial, antifungal) therapy

• Decompensated diabetes mellitus or other contraindication to high dose corticosteroid therapy

• Gastrointestinal disorders or abnormalities that could interfere with absorption of the trial drug

• Active or chronic hepatitis C and/or B infection

• Serious illness or concomitant non-oncological disease such as neurologic-, psychiatric-, infectious disease or active ulcers (gastrointestinal tract, skin) or laboratory abnormality that might have increased the risk associated with trial participation or trial drug administration and in the judgment of the investigator might have made the patient inappropriate for entry into the trial

• Patients who were sexually active and unwilling to use a medically acceptable method of contraception (e.g. such as implants, injectables, combined oral contraceptives, some intrauterine devices or vasectomised partner for participating females, condoms for participating males) during the trial and for at least 12 months after end of active therapy

• Pregnancy or breast feeding

• Psychological, familial, sociological, or geographical factors potentially hampering compliance with the trial protocol and follow-up schedule

• Patients unable to comply with the protocol

• Active alcohol or drug abuse

• Other malignancy within the past 3 years other than basal cell skin cancer, or carcinoma in situ of the cervix

• Any contraindications for therapy with docetaxel

• History of severe hypersensitivity reactions to docetaxel or other drugs formulated with polysorbate 80 (Tween 80)

• Hypersensitivity to BIBF 1120 and/or the excipients of the trial drugs

• Hypersensitivity to contrast media

Treatments

Patients were randomized (1:1) to receive nintedanib 200 mg orally in combination with 75 mg/m2 of intravenous iv. docetaxel every 21 days (n = 655) or placebo orally twice daily in combination with 75 mg/m2 of docetaxel every 21 days (n = 659).

Substance	BIBF 1120	Matching placebo
Pharmaceutical form	Soft gelatine capsule	Soft gelatine capsule
Source	Boehringer Ingelheim Pharma GmbH & Co. KG	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength	100 mg, 150 mg capsules	Matching placebo capsules
Posology	Twice daily, usually in the morning and evening after food intake	Twice daily, usually in the morning and evening after food intake
Route of administration	Oral	Oral
Daily dose	400 mg (200 mg b.i.d.), dose reductions according to Section 9.4.1.4	Daily dose not applicable, dose reductions of matching placebo capsules according to Section 9.4.1.4
Duration of use	Continuous daily dosing until withdrawal criteria were fulfilled (see Sections 9.3.3 and 9.4.1.4), no intake of BIBF 1120 on days of docetaxel administration	Continuous daily dosing until withdrawal criteria were fulfilled (see Sections 9.3.3 and 9.4.1.4), no intake of placebo on days of docetaxel administration

Backbone chemotherapy

Substance	Docetaxel
Pharmaceutical form	Injection concentrate
Source	Aventis Pharma, Dagenham, Essex, United Kingdom
Unit strength	20 mg concentrate
Posology	Once every 3 weeks
Route of administration	Intravenous infusion over 1 hour
Daily dose	75 mg/m^2, dose reduction according to Section 9.4.1.4
Duration of use	Once every 3 weeks until withdrawal criteria were fulfilled (see Sections 9.3.3 and 9.4.1.4)

Co-medication:

To reduce the incidence and severity of fluid retention and the severity of hypersensitivity reactions, all patients were to receive co-medication with oral corticosteroids.

Additional chemo-, immuno-, hormone-, or radiotherapy was not permitted during the treatment period of this trial. For symptom control, palliative radiotherapy was permitted for bone metastases in extremities, provided that radiotherapy did not affect the target lesions, and that the need for radiotherapy did not result from progressive disease.

Objectives

The primary objective of this trial was to evaluate whether nintedanib in combination with standard therapy of docetaxel is more effective than placebo in combination with standard therapy of docetaxel in patients with stage IIIB/IV or recurrent NSCLC after failure of first line chemotherapy.

A secondary aim was to obtain safety information of patients treated with nintedanib in combination with standard therapy with docetaxel.

`Locally recurrent´ was defined as local re occurrence of the tumour without metastases at study entry.

Outcomes / endpoints

Primary endpoint

- PFS by central independent review according to modified RECIST 1.0 criteria

Secondary endpoints

- Overall survival (key secondary endpoint):
    - Patients with adenocarcinoma <9 months since start of first-line therapy
    - Patients with adenocarcinoma
    - All patients
- PFS by investigator
- Tumor response by modified RECIST 1.0
- Clinical improvement (weight and/or ECOG performance score)
- QoL
- Pharmacokinetics of nintedanib and of its metabolites BIBF1202 and BIBF 1202 glucuronide
- Safety

Sample size

The alternative hypothesis assumed that the combination of nintedanib and docetaxel increased median PFS by approximately 28-32% in comparison to combination treatment with placebo and docetaxel, assuming a median PFS of 4 months in patients with an ECOG PS of 0 or 1 who are treated with docetaxel alone. It was calculated that a total of 713 PFS events would be needed to achieve a statistical power of 90%.

Table 12: **Number of PFS events and determination of statistical power**

PFS (median) docetaxel + placebo	PFS (median) docetaxel + BIBF 1120	Increase in median PFS vs. placebo (%)	HR (docetaxel+BIBF 1120 vs. docetaxel+placebo)	Statistical power		
				85%	90%	95%
				Required failures		
4 months	5.1 months	27.5	0.7843	610	713	882
4 months	5.3 months	32.5	0.7547	455	533	658

Calculations performed using EAST-5 software, using the log-rank test, and excluding interim analysis
HR = hazard ratio

Although the sample size used in this trial was expected to provide 80% power for OS, the magnitude and pattern of the effect of any third-line (or higher) anticancer therapy after disease progression could have obscured the treatment effect. The below table shows that 1151 deaths provided a statistical power of 80% to detect an 18% increase in median OS for nintadanib plus docetaxel vs. docetaxel monotherapy (HR = 0.8475). The timing of the final analysis of OS will be adjusted to include as many deaths as possible within a reasonable period of time and will be conducted after 1151 patients have died, but might be performed with fewer deaths within approximately 48 months after the start of the trial.

Table 13: **Statistical power for overall survival**

OS (median) docetaxel+ placebo	OS (median) docetaxel+ BIBF 1120	Increase in median OS vs. placebo (%)	HR (docetaxel+BIBF 1120 vs. docetaxel+placebo)	Statistical power	Required deaths	Required patients
9 months	10.6 months	18	0.8475	80%	1151	1300

Calculations performed using EAST-5 software, using the log-rank test, with 1 interim analysis when 713 PFS events were reached, using an O'Brien-Fleming boundary with a Lan-DeMets spending function for an overall $\alpha = 0.025$ (1-sided)
HR = hazard ratio

Randomisation

Patients were randomised 1:1. Randomisation was done in blocks of 4. Within each country, randomisation was stratified by ECOG PS (0 vs. 1), prior bevacizumab therapy (yes vs. no), tumour histology (squamous vs. non-squamous cell cancer) to balance for the higher bleeding risk associated with squamous cell carcinoma, and brain metastasis at baseline (yes vs. no).

Blinding (masking)

The trial had a parallel-group, double-blind, placebo-controlled design. Neither the patient nor the investigator was informed about the treatment allocation. All personnel of the sponsor and of the CRO who were involved in the conduct of the trial were unaware of the treatment allocation of patients until the final lock of the database.

Statistical methods

The alternative hypothesis of the primary analysis was that the PFS time was longer for patients treated with nintedanib plus docetaxel than for patients who received placebo plus docetaxel. The null hypothesis tested by this trial was: H0: $S_{Nin+Doc}(t) \leq S_{Placebo+Doc}(t)$, for $t > 0$; with S(t) presenting the probability that a patient passes time t without dying or experiencing disease progression. The alpha level was 0.025. This was the same as the effect of nintedanib being tested at the two-sided 0.05 (5%) level if the treatment effect was in favour of nintedanib (e.g. if nintedanib exhibits longer PFS times on average). Two-sided p-values are presented and statistical significance was declared if these were significant at the 0.05 two-sided level if and only if the treatment effect was in favour of nintedanib.

If both the primary and the follow-up PFS analyses showed a statistically significant treatment benefit of nintedanib over placebo, the key secondary endpoint OS was to be tested next in a fixed sequence of statistical hypotheses; i.e. in (1) patients with adenocarcinoma and <9 months since start of first-line therapy, (2) patients with adenocarcinoma, and (3) all patients. Each of the 3 hypotheses could only be tested at the pre-specified alpha level if the previous null hypothesis in the testing sequence had been rejected. The overall alpha level followed a Lan-DeMets spending function with O'Brien-Fleming shape parameter to preserve an overall 2-sided alpha level of 0.05. Hence, the exact overall alpha level (0.04984) depended on the number of

deaths that had accrued at the interim OS analysis (n = 423 OS events) and the number of deaths accrued by the time of final OS analysis (n = 1121 OS events).

Five (5) analysis data sets were used; these were the screened set (SS), the randomised set (RS), the treated set (TS), the safety set (SFS), and the pharmacokinetic set (PKS).

The RS included all randomised patients, whether patients had received study treatment or not. The efficacy analyses were based on the RS, following the intent-to-treat principle; however, patients not receiving combination therapy (i.e. nintedanib/placebo and docetaxel) were censored to the date of randomisation.

The TS included all randomised patients who were documented to have taken at least 1 dose of study medication (i.e. docetaxel chemotherapy or nintedanib/placebo). Patients were allocated to the treatment groups according to the treatment actually received. Safety analyses for this trial were based on the TS if not indicated otherwise.

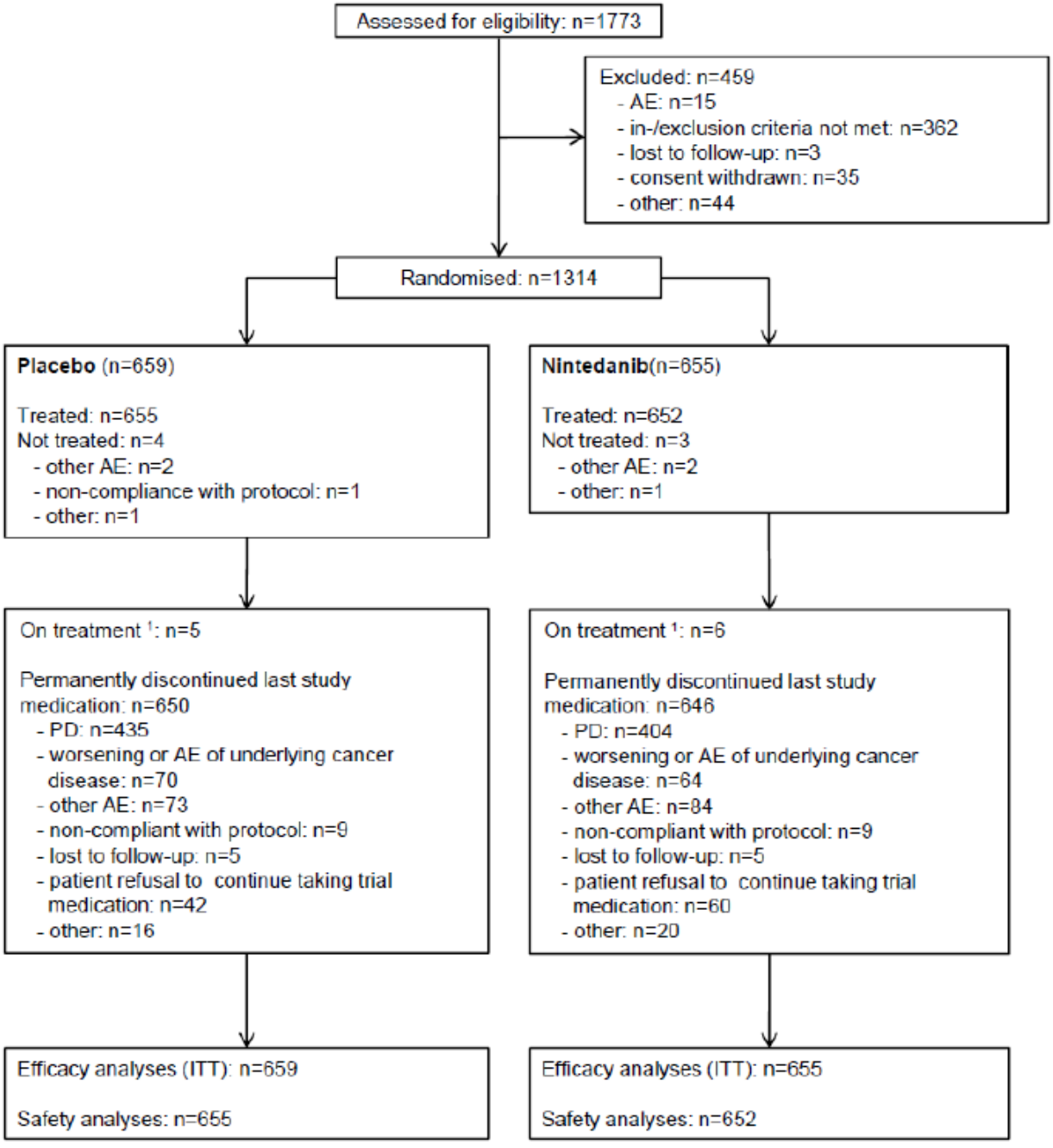
The SFS included all patients who were documented to have received at least 1 dose of investigational treatment (i.e. nintedanib/placebo). Patients were allocated to the treatment groups as actually treated. The exposure to nintedanib/placebo was analysed based on the SFS.

The PKS included all patients in the TS who were documented to have received at least 1 dose of nintedanib and who had at least 1 valid drug plasma concentration available. The PKS was used for the analysis of pharmacokinetic (PK) data.

During the study, the statistical analysis plan was extended by introducing a stepwise validation of the clinical biomarker hypothesis before the database was locked and unblinded for its final OS analysis.

Results

Participant flow



Abbreviation: ITT = Intention-to-treat

[1] At the date of cut-off for final OS analysis

Recruitment

The trial was conducted from 23 December 2008 to 15 February 2013 (cut-off date): 11 patients were still being treated in the trial.

Conduct of the study

Main changes in the Trial Statistical Analysis Plan (TSAP):

The primary efficacy endpoint was PFS based on central independent review, including events that occurred until the cut-off date of the efficacy analyses (defined by the time point of the 713th PFS event as per central review). With the TSAP (signed 8 July 2011), the following endpoints were formally added as secondary efficacy endpoints:

- PFS based on investigator assessment
- PFS based on central independent review, including all randomised patients and events that occurred until the cut-off date of the safety analyses

The TSAP made a number of clarifications regarding the censoring rules for the primary endpoint PFS.

In addition, the TSAP provided clarifications regarding a number of analyses pre-specified in the clinical trial protocol. Importantly, the Brookmeyer and Crowley method was used for summary statistics of the primary endpoint PFS (not the Greenwood variance formula specified in the clinical trial protocol). The TSAP provided definition of the patient subgroups to be investigated regarding the primary efficacy endpoint and selected parameters of disposition, demographics, and safety. The TSAP clarified that dependent on the results of the primary PFS analysis, an additional interim analysis of OS could be performed for regulatory purposes. The alpha spending procedure was a Lan-DeMets spending function with O'Brien-Fleming shape parameter.

Extension of the TSAP prior to un-blinding of the database for the primary PFS analysis

The generation of a biomarker hypothesis from trial 1199.14 led to extension of the TSAP for trial 1199.13 (signed 23 January 2013) prior to locking the trial database by introducing 2 intermediate steps of hierarchical testing for the final OS analysis.

Protocol deviations:

Overall, 24 patients (1.8% of randomised patients) were reported to have at least one important (pre-specified) protocol violation (placebo: 1.7% vs. nintedanib: 2.0%).

Baseline data

Table 14: Demographics in the overall population in study 1199.13 / RS

	Placebo	Nintedanib	Total
All patients, n	659	655	1314
Sex, n (%)			
Female	180 (27.3)	179 (27.3)	359 (27.3)
Male	479 (72.7)	476 (72.7)	955 (72.7)
Age, mean (StD) [years]	59.8 (9.0)	59.7 (9.7)	59.7 (9.3)
Age categories, n (%)			
<65 years	445 (67.5)	455 (69.5)	900 (68.5)
≥65 years	214 (32.5)	200 (30.5)	414 (31.5)
Race, n (%)			
White / Caucasian	530 (80.4)	533 (81.4)	1063 (80.9)
Asian	123 (18.7)	116 (17.7)	239 (18.2)
Black or African American	5 (0.8)	4 (0.6)	9 (0.7)
American Indian or Alaska Native	1 (0.2)	2 (0.3)	3 (0.2)
Race class[1], n (%)			
Asian	124 (18.8)	118 (18.0)	242 (18.4)
non-Asian	535 (81.2)	537 (82.0)	1072 (81.6)
Geographical region, n (%)			
Europe[2]	492 (74.7)	493 (75.3)	985 (75.0)
Asia[3]	156 (23.7)	152 (23.2)	308 (23.4)
Africa[4]	11 (1.7)	10 (1.5)	21 (1.6)
Smoking status, n (%)			
Never smoked	161 (24.4)	165 (25.2)	326 (24.8)
Ex-smoker	354 (53.7)	337 (51.5)	691 (52.6)
Current smoker	144 (21.9)	153 (23.4)	297 (22.6)

[1] As documented on the CRF. 'Asian' includes race categories 'Asian' and 'American Indian / Alaska Native'
[2] Austria, Belarus, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, France, Georgian Republic, Germany, Greece, Israel, Italy, Lithuania, Poland, Portugal, Romania, Russia, Slovakia, Spain, Switzerland, Ukraine, United Kingdom
[3] China, India, Korea
[4] South Africa

In this study 85 patients (12.9 % of the patients with adenocarcinoma histology) were ≥ 70 years of age (median age: 72 years, range: 70 - 80 years).

Table 15: Number of patients according to stratification factors at baseline in the overall population in study 1199.13 / RS

	Placebo n (%)	Nintedanib n (%)	Total n (%)
Patients	659 (100.0)	655 (100.0)	1314 (100.0)
ECOG PS at baseline			
0	189 (28.7)	187 (28.5)	376 (28.6)
1[1]	470 (71.3)	468 (71.5)	938 (71.4)
Prior treatment with bevacizumab[2]			
Yes	23 (3.5)	27 (4.1)	50 (3.8)
No	636 (96.5)	628 (95.9)	1264 (96.2)
Tumour histology[2]			
Squamous cell cancer	279 (42.3)	276 (42.1)	555 (42.2)
Non-squamous cell cancer[3]	380 (57.7)	379 (57.9)	759 (57.8)
Presence of brain metastases at baseline[2]			
Yes	38 (5.8)	38 (5.8)	76 (5.8)
No	621 (94.2)	617 (94.2)	1238 (94.2)

Baseline was the last value prior to the first administration of study treatment. For the ECOG PS, the last value before or at randomisation was used as baseline value.

[1] Including patient no. 135301 in the nintedanib arm who had an ECOG PS of 2 at screening and at randomisation (i.e. at baseline).

[2] As documented on the 'Oncological history' page of the CRF. For patient no. 131904, the histological classification of the primary tumour was unknown. For the stratified randomisation by interactive voice/web-based response system (IVRS/IWRS), the investigator randomly picked a tumour histology; this histology was 'squamous'.

[3] Including all tumour histologies other than 'squamous'.

Table 16: Histological classification in pivotal study 1199.13 / RS

	Placebo	Nintedanib	Total
Patients, n (%)	659 (100.0)	655 (100.0)	1314 (100.0)
Histological classification of primary tumour[1], n (%)			
Adenocarcinoma	336 (51.0)	322 (49.2)	658 (50.1)
Squamous cell carcinoma	278 (42.2)	276 (42.1)	554 (42.2)
Large cell carcinoma	16 (2.4)	25 (3.8)	41 (3.1)
Combination	5 (0.8)	4 (0.6)	9 (0.7)
Other	23 (3.5)	28 (4.3)	51 (3.9)
Missing[2]	1 (0.2)	0	1 (0.1)

Table 17: Oncological history in the adenocarcinoma population in study 1199.13 / RS

	Placebo	Nintedanib	Total
Patients, n (%)	336 (100.0)	322 (100.0)	658 (100.0)
Clinical stage at diagnosis based on UICC/AJCC 6th edition, n (%)	158 (47.0)	154 (47.8)	312 (47.4)
IV	103 (30.7)	86 (26.7)	189 (28.7)
IIIB	22 (6.5)	34 (10.6)	56 (8.5)
<IIIB / IV	33 (9.8)	34 (10.6)	67 (10.2)
Clinical stage at diagnosis based on UICC/AJCC 7th edition, n (%)	178 (53.0)	166 (51.6)	344 (52.3)
IV	134 (39.9)	129 (40.1)	263 (40.0)
IIIB	23 (6.8)	21 (6.5)	44 (6.7)
<IIIB / IV	21 (6.3)	16 (5.0)	37 (5.6)
Clinical stage at diagnosis missing	0	2 (0.6)	2 (0.3)
Time since first histological/cytological diagnosis[1], median [months]	8.71	8.80	8.74
Disease status at screening			
Locally recurrent[2], n (%)	16 (4.8)	22 (6.8)	38 (5.8)
Metastatic[3], n (%)	320 (95.2)	300 (93.2)	620 (94.2)
Patients with metastases present at screening, n (%)	320 (95.2)	300 (93.2)	620 (94.2)
Location of metastatic sites at screening[4], n (%) patients			
Lung ipsilateral	175 (52.1)	163 (50.6)	338 (51.4)
Lung contralateral	144 (42.9)	140 (43.5)	284 (43.2)
Bone	100 (29.8)	92 (28.6)	192 (29.2)
Liver	53 (15.8)	63 (19.6)	116 (17.6)
Adrenal glands	56 (16.7)	42 (13.0)	98 (14.9)
Brain	23 (6.8)	26 (8.1)	49 (7.4)
Other	156 (46.4)	138 (42.9)	294 (44.7)

[1] Time from date of first histological or cytological diagnosis until date of randomisation into the present trial
[2] Based on tickbox 'Local re-occurrence without metastases at screening' on 'Oncological history' page of CRF
[3] Based on tickbox 'Metastases present at screening' on 'Oncological history' page of CRF
[4] Patients may have had metastases at >1 site.

Table 18: Previous first-line therapy for NSCLC in the adenocarcinoma population in study 1199.13 / RS

	Placebo	Nintedanib	Total
	n(%)	n (%)	n (%)
Patients	336 (100.0)	322 (100.0)	658 (100.0)
Patients with any first line therapy	333 (99.1)	318 (98.8)	651 (98.9)
Platinum-based therapy	323 (96.1)	308 (95.7)	631 (95.9)
Non-platinum based therapy	10 (3.0)	10 (3.1)	20 (3.0)
First line including bevacizumab*	21 (6.3)	24 (7.5)	45 (6.8)
Platinum based first line therapy including°	323 (100.0)	308 (100.0)	631 (100.0)
Gemcitabine	92 (28.5)	78 (25.3)	170 (26.9)
Paclitaxel	58 (18.0)	73 (23.7)	131 (20.8)
Vinca alkaloid	63 (19.5)	50 (16.2)	113 (17.9)
Etoposide	37 (11.5)	39 (12.7)	76 (12.0)
Pemetrexed	61 (18.9)	58 (18.8)	119 (18.9)
Other	7 (2.2)	6 (1.9)	13 (2.1)
Vinca alkaloid and etoposide	2 (0.6)	1 (0.3)	3 (0.5)
Vinca alkaloid and gemcitabine	0	1 (0.3)	1 (0.2)
Etoposide and paclitaxel	0	2 (0.6)	2 (0.3)
Pemetrexed and gemcitabine	2 (0.6)	0	2 (0.3)
Vinca alkaloid and paclitaxel	1 (0.3)	0	1 (0.2)
Non-platinum based first line therapy including°	10 (100.0)	10 (100.0)	20 (100.0)
Vinca alkaloid	0	2 (20.0)	2 (10.0)
Pemetrexed	2 (20.0)	3 (30.0)	5 (25.0)
Other	3 (30.0)	2 (20.0)	5 (25.0)
Gemcitabine	1 (10.0)	2 (20.0)	3 (15.0)
Paclitaxel	2 (20.0)	1 (10.0)	3 (15.0)
Vinca alkaloid and paclitaxel	2 (20.0)	0	2 (10.0)

*Derived from coded dictionary terms of the reported compounds.
°Subcategories of platinum-based non-platinum based first-line therapy are mutually exclusive.
Source: [U13-1504, Table 15.1.8: 4]

Numbers analysed

Table 19: Number of patients in data sets

	Placebo n (%)	Nintedanib n (%)	Total n (%)
Screened set (SS)			1773
Randomised set (RS)	659 (100.0)	655 (100.0)	1314 (100.0)
Treated set (TS)	655 (99.4)	652 (99.5)	1307 (99.5)
Safety set (SFS)	650 (98.6)	650 (99.2)	1300 (98.9)
Pharmacokinetic set (PKS)	9 (1.4)	519 (79.2)	528 (40.2)

Outcomes and estimation

- **PFS by ICR**

The PFS results from the primary analysis are presented below.

Table 20: Primary analysis of PFS in the overall population in trial 1199.13, RS

	Placebo	Nintedanib
Patients, n (%)	569 (100.0)	565 (100.0)
Patients with PFS event, n (%)	375 (65.9)	339 (60.0)
PFS [months]		
Median[1]	2.7	3.4
Percentiles (P25, P75)[1]	(1.4, 4.6)	(1.5, 5.7)
Hazard ratio vs. placebo (95% CI)[2]		0.79 (0.68, 0.92)
p-value (2-sided)[2]		0.0019

Abbreviations: P25=25th percentile, P75=75th percentile

[1] Based on unadjusted Kaplan-Meier estimates for each treatment arm
[2] A proportional hazards model stratified by 4 factors (ECOG PS at baseline, prior bevacizumab therapy, tumour histology [squamous vs. non-squamous], presence of brain metastases at baseline) was used to derive the HR, 95% CI, and p-value (corresponding to the stratified log-rank test p-value).
Patient no. 135301 (nintedanib) had an ECOG PS of 2. In the analysis, this patient was treated as having ECOG PS 1.

Table 21: Primary analysis of PFS in the adenocarcinoma population in trial 1199.13, RS

	Placebo	Nintedanib
Patients, n (%)	285 (100.0)	277 (100.0)
Patients with PFS event, n (%)	180 (63.2)	152 (54.9)
PFS [months]		
Median[1]	2.8	4.0
Percentiles (P25, P75)[1]	(1.4, 5.6)	(1.6, 6.8)
Hazard ratio vs. placebo (95% CI)[2]		0.77 (0.62, 0.96)
p-value (2-sided)[2]		0.0193

[1] Based on unadjusted Kaplan-Meier estimates for each treatment arm
[2] A proportional hazards model stratified by 3 factors (ECOG PS at baseline, prior bevacizumab therapy, presence of brain metastases at baseline) was used to derive the HR, 95% CI, and p-value (corresponding to the stratified log-rank test p-value)
Patient no. 135301 (nintedanib) had an ECOG PS of 2. In the analysis, this patient was treated as having ECOG PS 1.

The tables and figure below provide the PFS results from the follow-up analysis.

Table 22: Follow-up analysis of PFS in the overall population in trial 1199.13, RS

	Placebo	Nintedanib
Patients, n (%)	659 (100.0)	655 (100.0)
Patients with PFS event, n (%)	538 (81.6)	519 (79.2)
PFS [months]		
Median[1]	2.7	3.5
Percentiles (P25, P75)[1]	(1.4, 5.5)	(1.5, 5.7)
Hazard ratio vs. placebo (95% CI)[2]		0.85 (0.75, 0.96)
p-value (2-sided)[2]		0.0070

[1] Based on unadjusted Kaplan-Meier estimates for each treatment arm
[2] A proportional hazards model stratified by 4 factors (ECOG PS at baseline, prior bevacizumab therapy, tumour histology [squamous vs. non-squamous], presence of brain metastases at baseline) was used to derive the HR, 95% CI, and p-value (corresponding to the stratified log-rank test p-value).
Patient no. 135301 (nintedanib) had an ECOG PS of 2. In the analysis, this patient was treated as having ECOG PS 1.

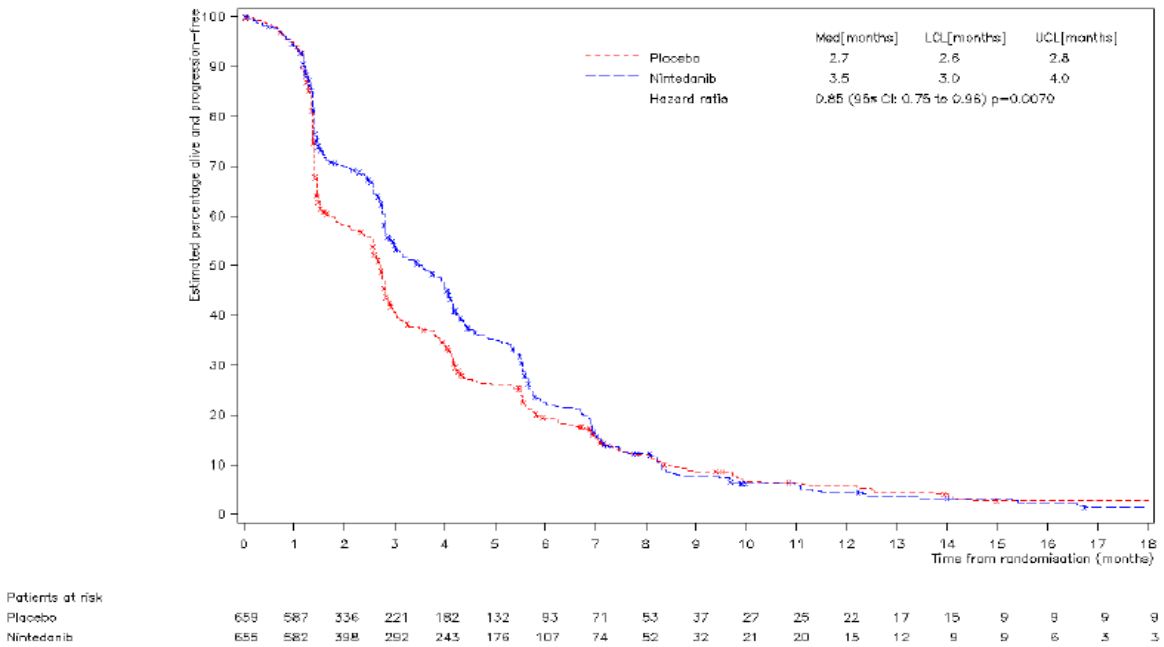


Figure 2: Probability rate of PFS in the overall population in trial 1199.13 / follow-up analysis, RS

Table 23: Follow-up analysis of PFS by tumour histology in trial 1199.13, RS

	Non-squamous		Squamous	
	Placebo	Nintedanib	Placebo	Nintedanib
Patients, n (%)	380 (100.0)	379 (100.0)	279 (100.0)	276 (100.0)
Patients with PFS event, n (%)	304 (80.0)	298 (78.6)	234 (83.9)	221 (80.1)
PFS [months]				
Median[1]	2.8	4.0	2.6	3.0
Percentiles (P25, P75)[1]	(1.4, 5.7)	(1.6, 6.9)	(1.4, 4.1)	(1.4, 5.5)
Hazard ratio vs. placebo (95% CI)[2]		0.85 (0.73, 1.00)		0.83 (0.69, 1.01)
p-value (2-sided)[2]		0.0556		0.0566
Interaction p-value[3]		0.7411		

[1] Based on unadjusted Kaplan-Meier estimates for each treatment arm

[2] A proportional hazards model stratified by 3 factors (ECOG PS at baseline, prior bevacizumab therapy, presence of brain metastases at baseline) was used to derive the HR, 95% CI, and p-value (corresponding to the stratified log-rank test p-value).
Patient no. 135301 (nintedanib) had an ECOG PS of 2. In the analysis, this patient was treated as having ECOG PS 1.

[3] The interaction p-value was derived by fitting a proportional hazards model with and without treatment by tumour histology interaction and comparing the difference in log-likelihoods.

Table 24: Follow-up analysis of PFS in the adenocarcinoma population in trial 1199.13, RS

	Placebo	Nintedanib
Patients, n (%)	336 (100.0)	322 (100.0)
Patients with PFS event, n (%)	267 (79.5)	255 (79.2)
PFS [months]		
Median[1]	2.8	4.2
Percentiles (P25, P75)[1]	(1.4, 5.9)	(2.1, 6.9)
Hazard ratio vs. placebo (95% CI)[2]		0.84 (0.71, 1.00)
p-value (2-sided)[2]		0.0485

[1] Based on unadjusted Kaplan-Meier estimates for each treatment arm

[2] A proportional hazards model stratified by 3 factors (ECOG PS at baseline, prior bevacizumab therapy, presence of brain metastases at baseline) was used to derive the HR, 95% CI, and p-value (corresponding to the stratified log-rank test p-value)

Patient no. 135301 (nintedanib) had an ECOG PS of 2. In the analysis, this patient was treated as having ECOG PS 1.

	Hazard ratio (95%CI)	Events Placebo/Nintedanib	Int. p−value
Overall	**0.85 (0.75,0.96)**	**538/519**	
Sex			**0.9463**
Female	0.85 (0.67,1.09)	143/134	
Male	0.85 (0.73,0.98)	395/385	
Age class			**0.4482**
< 65 years	0.81 (0.70,0.94)	379/369	
>= 65 years	0.94 (0.74,1.19)	159/150	
Race class			**0.7426**
Asian	0.85 (0.63,1.14)	101/90	
Non−asian	0.85 (0.74,0.97)	437/429	
Tumour histology			**0.7247**
Adenocarcinoma	0.84 (0.71,1.00)	267/255	
Other	1.01 (0.64,1.60)	37/43	
Squamous cell carcinoma	0.83 (0.69,1.01)	234/221	
Smoking status			**0.3694**
Currently smokes / ex−smoker	0.88 (0.77,1.01)	411/398	
Never smoked	0.77 (0.59,1.00)	127/121	
ECOG			**0.1976**
0	0.93 (0.74,1.17)	150/141	
1	0.82 (0.71,0.94)	388/378	
Brain metastases			**0.5903**
No	0.85 (0.75,0.97)	509/490	
Yes	0.73 (0.42,1.26)	29/29	
Prior bevacizumab			**0.9707**
No	0.84 (0.75,0.96)	521/497	
Yes	0.86 (0.44,1.67)	17/22	
Time since start of 1st line			**0.0296**
<9 month	0.76 (0.65,0.89)	344/333	
>=9 month	0.96 (0.78,1.18)	190/181	
Best response to 1st line			**0.0915**
CR/PR/SD	0.88 (0.76,1.02)	369/381	
PD	0.72 (0.55,0.95)	113/105	
Baseline sum of longest diameters			**0.0497**
<7.5 cm	0.94 (0.78,1.13)	250/227	
>=7.5 cm	0.74 (0.63,0.88)	287/292	
Stage at diagnosis			**0.4469**
<IIIB/IV	0.84 (0.61,1.16)	85/81	
IIIB	0.94 (0.72,1.22)	117/120	
IV	0.79 (0.68,0.93)	336/317	
Adrenal glands			**0.9865**
No	0.83 (0.72,0.95)	406/388	
Yes	0.85 (0.63,1.14)	103/101	
Liver metastases			**0.1906**
No	0.79 (0.69,0.92)	385/358	
Yes	0.96 (0.74,1.24)	124/131	
Bisphosphonates at baseline			**0.5299**
No	0.85 (0.75,0.96)	513/489	
Yes	0.64 (0.34,1.20)	25/30	
Number of metastatic organs (cen. rev.)			**0.4977**
<= 2 metastatic organs	0.85 (0.69,1.05)	183/179	
> 2 metastatic organs	0.82 (0.70,0.96)	326/310	
Region			**0.3505**
Asia	0.97 (0.75,1.26)	127/120	
Non−Asia	0.82 (0.71,0.94)	411/399	
LDH at baseline			**0.9892**
<= 1	0.84 (0.72,0.99)	335/316	
> 1	0.84 (0.68,1.02)	197/197	

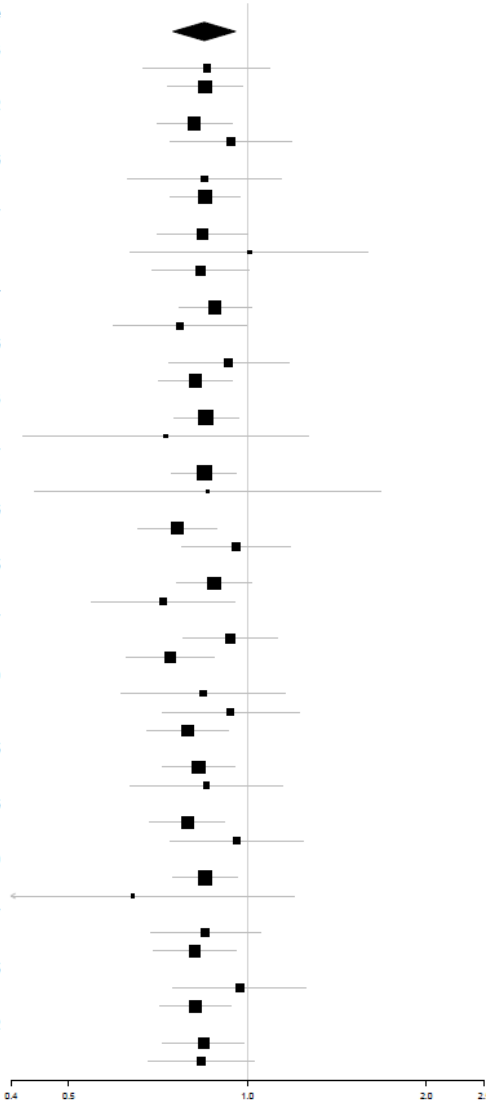


Figure 3: Hazard ratio of PFS by baseline characteristics, based on central independent review, follow-up / RS – all patients

- **PFS by INV**

Table 25: PFS based on investigator assessment, follow-up / RS-all patients

	Placebo	Nintedanib0
Patients, n (%)	659 (100.0)	655 (100.0)
Patients with PFS event, n (%)	563 (85.4)	554 (84.6)
PFS [months]		
Median[1]	3.0	4.2
Percentiles (P25, P75)[1]	(1.4, 5.7)	(2.1, 7.1)
Hazard ratio vs. placebo (95% CI)[2]		0.82 (0.73, 0.93)
p-value (2-sided)		0.0012

[1] Estimated based on unadjusted Kaplan-Meier estimates for each treatment arm.
[2] A proportional hazards model stratified by 4 factors (ECOG PS at baseline, prior bevacizumab treatment, tumour histology (squamous vs. non-squamous), presence of brain metastases at baseline) was used to derive the hazard ratio, 95% CI, and p-value (corresponding to the stratified log-rank test p-value).
Patient no. 135301 (nintedanib) had an ECOG PS of 2. In the analysis, this patient was treated as having ECOG PS 1.

- **OS**

Table 26: Final analysis of OS in the overall population in trial 1199.13 /

	Placebo	Nintedanib
Patients, n (%)	659 (100.0)	655 (100.0)
Patients with OS event, n (%)	557 (84.5)	564 (86.1)
OS [months]		
Median[1]	9.1	10.1
Percentiles (P25, P75)[1]	(4.8, 17.2)	(5.0, 19.4)
Hazard ratio vs. placebo (95% CI)[2]		0.94 (0.83, 1.05)
p-value (2-sided)[2]		0.2720
Sensitivity analysis including stratification factors		
Hazard ratio vs. placebo (95% CI)[3]		0.92 (0.82, 1.04)
p-value (2-sided)[3]		0.1832
Sensitivity analysis including baseline SLD		
Hazard ratio vs. placebo (95% CI)[3]		0.88 (0.78, 0.99)
p-value (2-sided)[3]		0.0365
Sensitivity analysis including time since start of first-line therapy		
Hazard ratio vs. placebo (95% CI)[3]		0.89 (0.79, 1.01)
p-value (2-sided)[3]		0.0611

[1] Based on unadjusted Kaplan-Meier estimates for each treatment arm
[2] A proportional hazards model stratified by 4 factors (ECOG PS at baseline, prior bevacizumab therapy, tumour histology [squamous vs. non-squamous], presence of brain metastases at baseline) was used to derive the HR, 95% CI, and p-value (corresponding to the stratified log-rank test p-value).
[3] Based on a proportional hazards model with the 4 stratification factors (ECOG PS at baseline, prior bevacizumab therapy, tumour histology [squamous vs. non-squamous], presence of brain metastases at baseline) fitted as covariates
The sensitivity analyses by baseline SLD and time since start of first-line therapy to randomisation were adjusted by the stratification factors and the respective additional covariate. The sensitivity analyses by stratification factors and by baseline SLD were prespecified in the CTP.
Patient no. 135301 (nintedanib) had an ECOG PS of 2. In the analysis, this patient was treated as having ECOG PS 1.

RS

Table 27: Final analysis of OS in the adenocarcinoma population in trial 1199.13/ RS

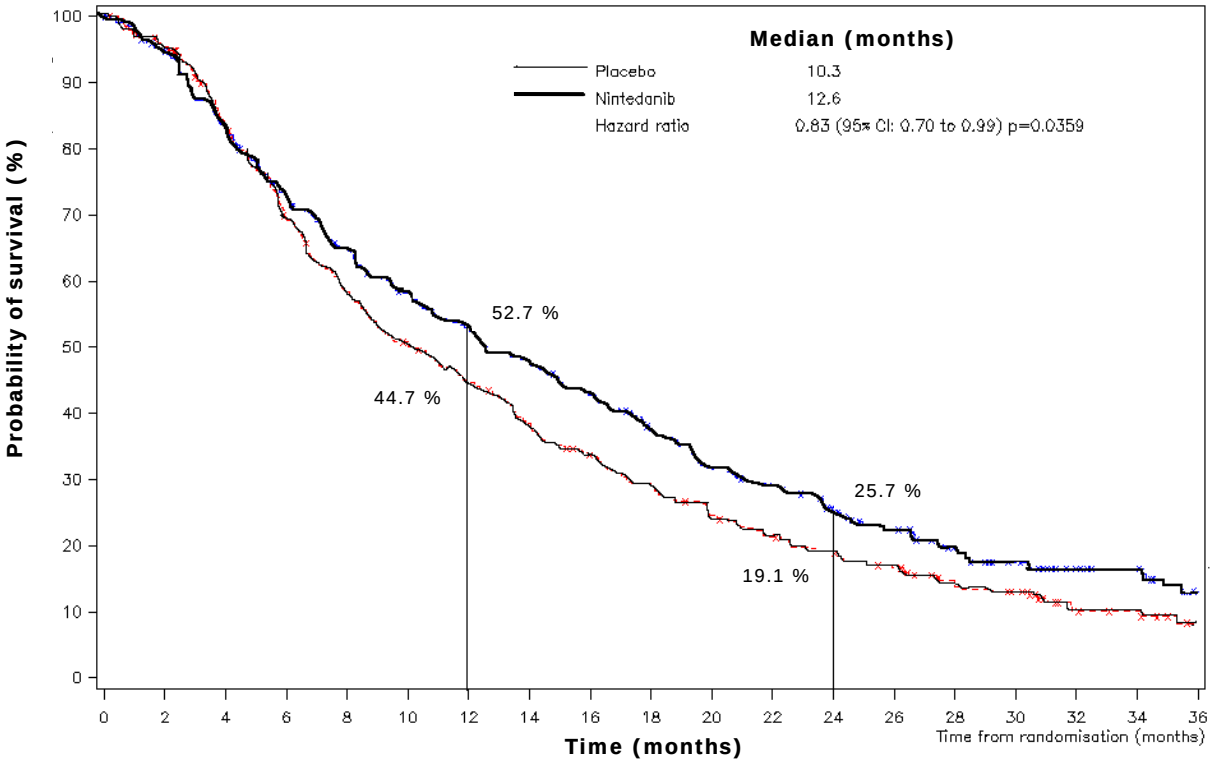
	Placebo	Nintedanib
Patients, n (%)	336 (100.0)	322 (100.0)
Patients with OS event, n (%)	276 (82.1)	259 (80.4)
OS [months]		
Median[1]	10.3	12.6
Percentiles (P25, P75)[1]	(5.5, 19.9)	(5.5, 24.2)
Hazard ratio vs. placebo (95% CI)[2]		0.83 (0.70, 0.99)
p-value (2-sided)[2]		0.0359
Sensitivity analysis including stratification factors		
Hazard ratio vs. placebo (95% CI)[3]		0.83 (0.70, 0.98)
p-value (2-sided)[3]		0.0295
Sensitivity analysis including baseline SLD		
Hazard ratio vs. placebo (95% CI)[3]		0.81 (0.69, 0.97)
p-value (2-sided)[3]		0.0186
Sensitivity analysis including time since start of first-line therapy		
Hazard ratio vs. placebo (95% CI)[3]		0.80 (0.68, 0.95)
p-value (2-sided)[3]		0.0123

[1] Based on unadjusted Kaplan-Meier estimates for each treatment arm

[2] A proportional hazards model stratified by 3 factors (ECOG PS at baseline, presence of brain metastases at baseline, prior bevacizumab therapy) was used to derive the HR, 95% CI, and p-value (corresponding to the stratified log-rank test p-value).

[3] Based on a proportional hazards model with 3 stratification factors (ECOG PS at baseline, prior bevacizumab therapy, presence of brain metastases at baseline) fitted as covariates
The sensitivity analyses by baseline SLD and time since start of first-line therapy to randomisation were adjusted by the stratification factors and the respective additional covariate. The sensitivity analyses by stratification factors and by baseline SLD were prespecified in the CTP.
Patient no. 135301 (nintedanib) had an ECOG PS of 2. In the analysis, this patient was treated as having ECOG PS 1.

Source data: [U13-1504, Table 15.2.10.2: 2, 15.2.10.3: 1, 15.2.10.3: 2, and 15.2.10.3: 3]



No. of patients at

Placebo	336	312	269	219	184	159	139	119	101	88	73	62	55	46	33	29	15	13	7
Nintedanib	322	302	263	230	203	180	163	149	131	113	96	87	72	59	46	36	25	22	10

Figure 4: Probability of overall survival in the adenocarcinoma population in trial 1199.13 / RS

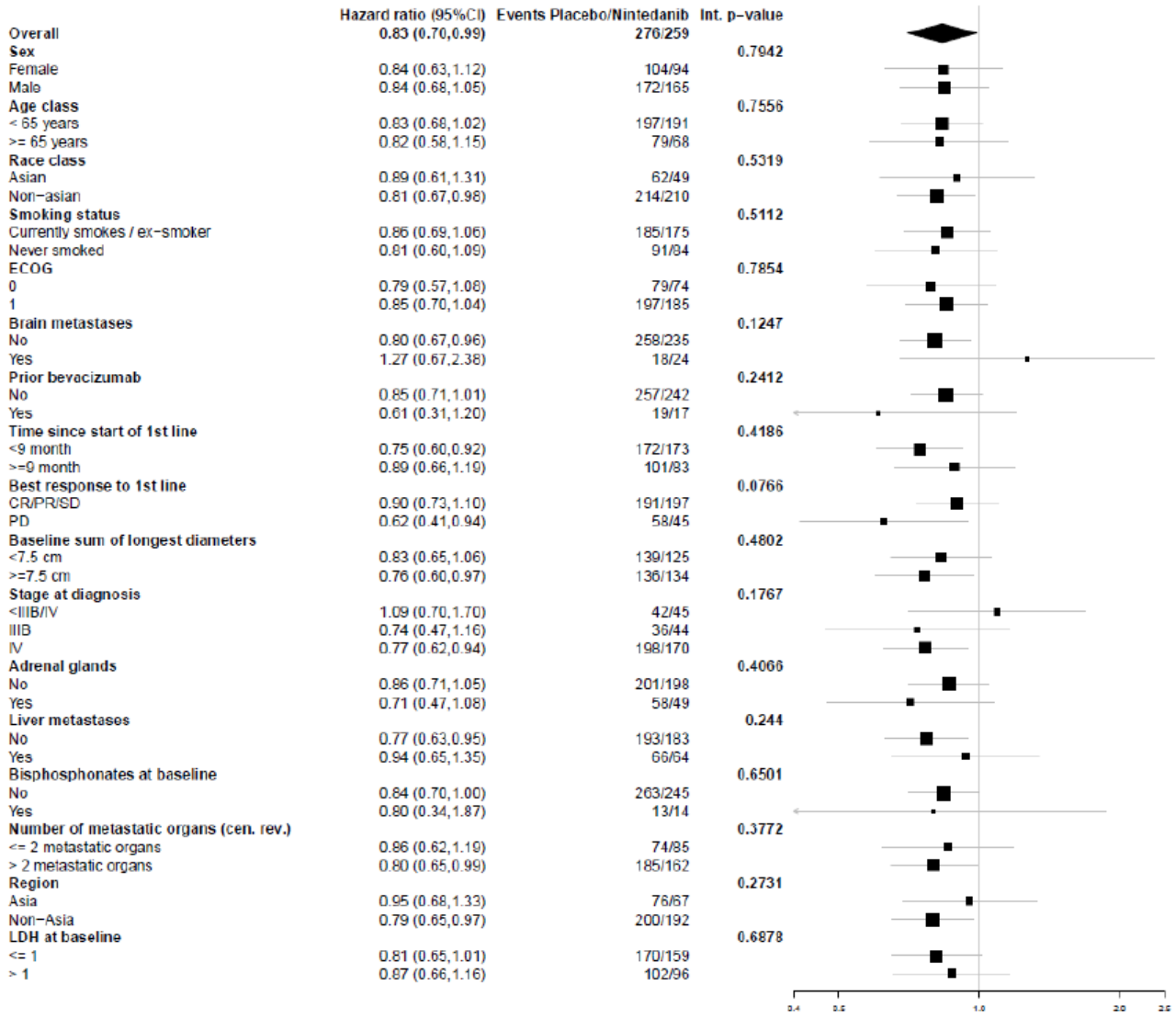


Figure 5: Hazard ratio of OS by baseline characteristics / RS – patients with adenocarcinoma

- **Tumour response by RECIST 1.0**

Table 28: Tumour response and disease control in the adenocarcinoma population in trial 1199.13 / RS

	Placebo	Nintedanib
Patients, n (%)	336 (100.0)	322 (100.0)
Patients with objective tumour response[1], n (%)	12 (3.6)	15 (4.7)
Complete response	0	0
Partial response	12 (3.6)	15 (4.7)
Odds ratio vs. placebo (95% CI)[2]		1.32 (0.61, 2.93)
p-value (2-sided)[2]		0.4770
Unconfirmed complete response / partial response	7 (2.1)	10 (3.1)
Stable disease[3], n (%)	136 (40.5)	179 (55.6)
Patients with disease control[4], n (%)	148 (44.0)	194 (60.2)
Odds ratio vs. placebo (95% CI)[2]		1.93 (1.42, 2.64)
p-value[2]		<0.0001
Duration of disease control, [months]		
Median	6.3	5.7
Percentiles (P25, P75)	(4.2, 9.7)	(4.2, 8.1)
Progressive disease[5], n (%)	147 (43.8)	87 (27.0)
Other[6], n (%)	41 (12.2)	41 (12.7)

[1] Information on time to and duration of objective tumour response can be found in the source table.
[2] Logistic regression model adjusted for ECOG PS at baseline
Patient no. 135301 (nintedanib) had an ECOG PS of 2. In the analysis, this patient was treated as having ECOG PS 1.
[3] SD was assumed if a follow-up imaging indicated SD at least once and at least 6 weeks after randomisation (i.e. at or after Day 43).
[4] A patient was considered to have disease control if he/she had a best objective response of SD or better.
[5] Including patients with SD from a radiological imaging earlier than Day 43 followed by PD
[6] Including patients with SD from a radiological imaging earlier than Day 43 followed by a non-evaluable response

- **Change in tumour size**

Table 29: Best percentage change from baseline in size of target lesions (SLD), based on central independent review, follow-up / RS – patients with adenocarcinoma

	Placebo	Nintedanib
Patients, n (%)	336 (100.0)	322 (100.0)
Patients with baseline and complete post-baseline target lesion assessment, n (%)	286 (85.1)	291 (90.4)
Nintedanib vs. placebo		
Best change from baseline in target lesions, mean [%][1]	-0.99	-7.74
Best change from baseline in target lesions[2], Adjusted mean, (95% CI)[2] [%]	-0.97 (-3.48, 1.55)	-7.76 (-10.25, -5.26)
p-value[2]		0.0002

[1] Not adjusted
[2] ANOVA model adjusted by 3 stratification factors (ECOG PS at baseline, prior bevacizumab treatment, and presence of brain metastases at baseline)
Patient no. 135301 (nintedanib) had an ECOG PS of 2. In the analysis, this patient was treated as having ECOG PS 1.

Ancillary analyses

- **OS subgroup analyses**

Table 30: Analyses of Overall survival (based on cut-off date 15 Feb 2013)

	HR (95% CI)	*p-value*	*OS in median months Placebo vs. nintedanib*
All	0.94 (0.83, 1.05)	0.2720	9.1 vs. 10.1
Adenocarcinoma	0.83 (0.70, 0.99)	0.0359	10.3 vs. 12.6
Non-squamous	0.88 (0.75, 1.03)	0.1133	10.3 vs. 11.5
Adenocarcinoma <9 months since start of first-line	0.75 (0.60, 0.92)	0.0073	7.9 vs. 10.9
Adenocarcinoma with PD as best response to prior therapy	0.62 (0.41, 0.94)	0.0246	6.3 vs. 9.8
Squamous	1.01 (0.85, 1.21)	0.8907	8.7 vs. 8.6
Squamous and baseline sum of longest diameters ≥7.5 cm*	0.82 (0.65, 1.04)	0.0995	6.1 vs. 7.7
Other	1.31 (0.84, 2.03)	0.2269	10.6 vs. 7.8

*Exploratory analysis in patients with squamous cell carcinoma found that the larger the SLD of target lesions at baseline the better the treatment effect, as indicated by a decreasing HR. The estimated HR reached values below 1 at SLD values around 7.5 cm; therefore, an SLD ≥7.5 cm was chosen as cut-point for further in-depth analyses in patients with squamous cell carcinoma.

The Applicant used three methods that all revealed 9 months cut-off since start of first-line therapy in the adenocarcinoma patients as predictive of effect of nintedanib.

An exploratory analysis of OS by T<9 months and T≥9 months showed that the HR was 0.75 (95%CI; 0.60, 0.92) and 0.89 (95%CI; 0.66, 1.19) respectively.

- **OS depending on first-line treatment**

Table 31: Overall survival by any pemetrexed in first-line in the adenocarcinoma population in trial 1199.13 / RS

	No pemetrexed in first line		Pemetrexed in first-line	
Final OS analysis snapshot	**Placebo**	**Nintedanib**	**Placebo**	**Nintedanib**
Patients, n (%)	271 (100.0)	261 (100.0)	65 (100.0)	61 (100.0)
Patients with OS°event, n (%)	220 (81.2)	208 (79.7)	56 (86.2)	51 (83.6)
Median*OS (months)	10.8	13.4	8.0	12.0
HR#(95% CI)	0.83 (0.68, 1.00)		0.79 (0.53, 1.18)	
Interaction between treatment and subgroup variable^	**0.9026**			

° OS = Overall survival.
* Medians are calculated from an unadjusted Kaplan–Meier curve for each treatment arm.
# If HR is below 1 then favours nintedanib. Hazard Ratio and confidence interval obtained from a proportional–hazards model stratified by baseline ECOG PS (0 vs. 1), brain metastases at baseline (yes vs. no) and prior treatment with bevacizumab (yes vs. no).
^ Test of interaction derived by fitting a proportional hazards model with and without treatment by any pemetrexed in first line interaction and comparing the difference in log–likelihoods.
One patient (135301) has a baseline ECOG PS of 2.
Source: [Appendix 1, Table 1.5.2.1]

Table 32: Overall survival by pemetrexed maintenance therapy in first-line in the adenocarcinoma population in trial 1199.13 / RS

	No maintenance pemetrexed in first-line		Maintenance pemetrexed in first-line	
Final OS analysis snapshot	**Placebo**	**Nintedanib**	**Placebo**	**Nintedanib**
Patients, n (%)	322 (100.0)	309 (100.0)	14 (100.0)	13 (100.0)
Patients with OS°event, n (%)	266 (82.6)	250 (80.9)	10 (71.4)	9 (69.2)
Median*OS (months)	10.0	12.6	12.8	18.9
HR#(95% CI)	0.84 (0.70,1.00)		0.78 (0.30,2.07)	
Interaction between treatment and subgroup variable^	**0.7162**			

° OS = Overall survival.
* Medians are calculated from an unadjusted Kaplan–Meier curve for each treatment arm.
# If HR is below 1 then favours nintedanib. Hazard Ratio and confidence interval obtained from a proportional–hazards model stratified by baseline ECOG PS (0 vs. 1), brain metastases at baseline (yes vs. no) and prior treatment with bevacizumab (yes vs. no).
^ Test of interaction derived by fitting a proportional hazards model with and without treatment by taxane in first-line interaction and comparing the difference in log–likelihoods.
One patient (135301) has a baseline ECOG PS of 2.
Source: [Appendix 1, Table 1.5.2.3]

Table 33: Overall survival by taxane-use in first-line in the adenocarcinoma population in trial 1199.13 / RS

	No taxane in first line		Taxane in first-line	
Final OS analysis snapshot	**Placebo**	**Nintedanib**	**Placebo**	**Nintedanib**
Patients, n (%)	271 (100.0)	245 (100.0)	65 (100.0)	77 (100.0)
Patients with OS°event, n (%)	223 (82.3)	200 (81.6)	53 (81.5)	59 (76.6)
Median*OS (months)	10.3	12.2	11.6	15.1
HR#(95% CI)	0.86 (0.71, 1.05)		0.75 (0.51, 1.11)	
Interaction between treatment and subgroup variable^	**0.6135**			

° OS = Overall survival.
* Medians are calculated from an unadjusted Kaplan–Meier curve for each treatment arm.
# If HR is below 1 then favours nintedanib.Hazard Ratio and confidence interval obtained from a proportional–hazards model stratified by baseline ECOG PS (0 vs. 1), brain metastases at baseline (yes vs. no) and prior treatment with bevacizumab (yes vs. no).
^ Test of interaction derived by fitting a proportional hazards model with and without treatment by taxane in first-line interaction and comparing the difference in log–likelihoods.
One patient (135301) has a baseline ECOG PS of 2.
Source: [Appendix 1, Table 1.5.2.5]

- **PFS and OS in patients with local recurrence with or without metastases**

Evaluation of the primary endpoint PFS in the overall study population revealed that there was no interaction between treatment and recurrence with or without metastases at baseline (p=0.5822). Similar results are observed for the adenocarcinoma (primary analysis, p=0.9593) and for the squamous cell carcinoma (primary analysis, p=0.5383) patient populations.

- **Clinical improvement**

Most deterioration events were caused by increase in ECOG performance score. More than half of the patients were censored, mostly due to subsequent anticancer therapy or no event prior to cut-off date. Therefore the applicant was requested to provide time to deterioration of body weight and/or ECOG PS for the adenocarcinoma population in study 1199.13.

Table 34: Time to deterioration of body weight and/or ECOG PS / RS – adenocarcinoma histology

	Placebo	Nintedanib
Patients, n (%)	336 (100.0)	322 (100.0)
Patients with event, n (%)	137 (40.8)	147 (45.7)
Time to deterioration (months)		
Median*	5.7	6.5
Percentiles (P25, P75)	(2.2, 22.5)	(2.1, n.c.)
Hazard ratio vs. placebo (95% CI)†	1.03 (0.81, 1.30)	
p-value	0.8259	

*Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve for each treatment group.
†Hazard ratio, confidence interval, and p-value obtained from a proportional-hazards model stratified by baseline ECOG PS (0 vs. ≥1), brain metastases at baseline (yes vs. no), and prior treatment with bevacizumab (yes vs. no).

There is a slightly longer time to deterioration in the nintedanib arm (not statistically significant). Thus, the addition of nintedanib to docetaxel shows no detrimental effect on time to deterioration of body weight and/or ECOG.

- **QoL**

Focus was on the main HRQoL endpoints, i.e. cough (QLQ-LC13 question 1), dyspnoea (composite of QLQ-LC13 questions 3-5), and pain (composite of QLQ-C30 questions 9 and 19). Compliance with completion of the HRQoL questionnaires was relatively high (>80% in both treatment arms). Analyses were performed in the overall population and in groups based on histology (adenocarcinoma, non-squamous, squamous).

There was no difference in time to deterioration of cough, dyspnoea, and pain between treatment arms. The percentages of patients with worsening, stabilisation, or improvement of cough, dyspnoea, pain and symptom scales/items were similar in both treatment arms.

Overall, the global health status was maintained with nintedanib (HR 0.952; 95% CI 0.827, 1.096). Similar results were found for all histology groups.

In the overall patient population, individual items of QLQ-C30 with a difference between treatment arms were time to deterioration of diarrhoea (HR 1.940; 95% CI 1.665, 2.260), nausea (HR 1.295; 95% CI 1.113, 1.508) and vomiting (HR 1.319: 95% CI 1.106, 1.573) which were shorter in the nintedanib arm. No differences in HRs were found in QLQ-LC13 scores.

As for the overall population, patients with tumours of adenocarcinoma histology had a shorter time to deterioration of diarrhoea, nausea and vomiting. Different from the overall population, time to pain in arm or shoulder was favoured by nintedanib (HR 0.794; 95% CI 0.632, 0.997). Similar results were seen in patients with tumour of non-squamous histology.

However, diarrhoea is more common in the nintedanib arm. This finding is statistically significant, but based on patient-self reported outcome.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 35: Summary of Efficacy for trial 1199.13

Title: Multicentre, randomised, double-blind, Phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard docetaxel therapy compared to placebo plus standard docetaxel therapy in patients with stage IIIB/IV or recurrent non-small cell lung cancer after failure of first line chemotherapy (LUME Lung 1).			
Study identifier	1199.13		
Design	Two-arm, randomised, double-blind, placebo-controlled, parallel-group comparison of nintedanib versus matching placebo		
	Duration of main phase:		23 Dec 2008 – 15 Feb 2013
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority of nintedanib+docetaxel to placebo+docetaxal in patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first line chemotherapy.		
Treatments groups	Nintedanib+docetaxel		Nintedanib 200 mg bid + docetaxel 75 mg/m2 once every 3 weeks, duration: as long as patients tolerated the therapy, 655 patients
	Placebo+docetaxel		Docetaxel 75 mg/m2 once every 3 weeks, duration: as long as patients tolerated the therapy, 659
Endpoints and definitions	Primary endpoint	PFS by ICR	Progression-Free Survival by independent central review. (Follow-up analysis at time point of OS analysis)
	Secondary endpoint	OS	All patients Adenocarcinoma patients Patients with adenocarcinoma T<9 months
	Secondary endpoint	PFS by INV	Progression-Free Survival by investigator
	Secondary endpoint	Tumour response	Tumour response according to modified RECIST criteria version 1.0
	Secondary endpoint	Clinical improvement	Weight and/or ECOG performance score
	Secondary endpoint	QoL	Quality of life measured by: EQ-5D, QLQ-C30 and QLQ-LC13
	Secondary endpoint	PK	Pharmacokinetics of nintedanib and of its metabolites
Database lock	15 Feb 2013		

Results and Analysis

Analysis description	**Final Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Placebo + docetaxel	Nintedanib + docetaxel
	Number of subject	659	655
	PFS, median in months	2.7	3.5

	Percentiles (P25, P75)	1.4; 5.5	1.5; 5.7
	OS, median in months *(adenocarcinoma population)*	10.3 *(N=336)*	12.6 *(N=322)*
	Percentiles (P25, P75)	5.5; 19.9	5.5; 24
	PFS by INV	3.0	4.2
	Percentiles (P25, P75)	1.4; 5.7	2.1; 7.1
	Tumour response (%),	3.6	4.7
	Clinical improvement (time to deterioration, months), 95% CI	5.2 2.1; 19.2	5.9 2.1; 22.7
Effect estimate per comparison	Primary endpoint (PFS by independent central review)	Comparison groups	Placebo+docetaxal vs. Nintedanib+docetaxel
		Hazard ratio	0.85
		95% CI	0.75; 0.96
		P-value	0.0070
	Key secondary Endpoint (OS in the adenocarcinoma, population)	Comparison groups	Placebo+docetaxal vs. Nintedanib+docetaxel
		Hazard ratio	0.83
		95% CI	0.70; 0.99
		P-value	0.0359
	Secondary endpoint (PFS by INV)	Comparison groups	Placebo+docetaxal vs. Nintedanib+docetaxel
		Hazard ratio	0.82
		95% CI	0.73; 0.93
		P-value	0.0012
Notes	OS was tested in hierarchical manner, but only the HR for the adenocarcinoma population is presented in this summary.		

Analysis performed across trials (pooled analyses and meta-analysis)

At the time of the final OS analysis in trial 1199.13, a meta-analysis was performed for PFS, pooling the data for the non-squamous cell carcinoma, adenocarcinoma, and T<9m adenocarcinoma population from trials 1199.13 and 1199.14 (cut-off date 15 Feb 2013), and for OS.

When pooling the data, nintedanib in combination with chemotherapy statistically significantly improved centrally assessed PFS in the adenocarcinoma population (HR 0.84; 95% CI 0.74, 0.95; p=0.0072). The treatment benefit of nintedanib plus chemotherapy on PFS became more pronounced in the pooled dataset of patients with adenocarcinoma who progressed during or shortly after first-line therapy (HR 0.72; 95% CI 0.61, 0.84; p<0.0001). OS was not statistically significant in this analysis.

Clinical studies in special populations

No dedicated clinical studies were conducted in special populations. The below table provide information on the number of patients enrolled in the clinical development programme of nintedanib by age group.

Table 36: Numbers of elderly patients treated across the clinical trial programme (across all indications)

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Efficacy and Safety Studies	968/3194	246/3194	6/3194
Human PK Studies	720/2380	185/2380	2/2380
Human PD Studies	24/96	4/96	1/96
Biopharmaceutical Studies	0/81	0/81	0/81

Supportive study

Study 1199.14 is a double-blind, randomised, placebo-controlled study in patients with non-squamous NSCLC. Despite being halted prematurely, ITT analysis of the primary endpoint PFS assessed by central independent review demonstrated a statistically significant improvement for patients treated with nintedanib plus pemetrexed compared with placebo plus pemetrexed. In line with the observations in trial 1199.13, patients with adenocarcinoma who progressed during or shortly after first-line therapy also derived benefit from treatment with nintedanib and pemetrexed. Altogether, the findings in trial 1199.14 were consistent with the findings in trial 1199.13.

Table 37: Primary analysis of PFS in the overall population in trial 1199.14 / RS

	Placebo	Nintedanib
Patients, n (%)	360 (100.0)	353 (100.0)
Patients with PFS event, n (%)	259 (71.9)	239 (67.7)
PFS [months]		
Median[1]	3.6	4.4
Percentiles (P25, P75)[1]	(1.4, 7.5)	(2.3, 9.5)
Hazard ratio vs. placebo (95% CI)[2]		0.83 (0.70, 0.99)
p-value (2-sided)[2]		0.0435

[1] Based on unadjusted Kaplan-Meier estimates for each treatment arm

[2] A proportional hazards model stratified by 4 factors (ECOG PS at baseline, prior bevacizumab therapy, tumour histology [adeno- vs non-adenocarcinoma], presence of brain metastases at baseline) was used to derive the HR, 95% CI, and p-value (corresponding to the stratified log-rank test p-value).

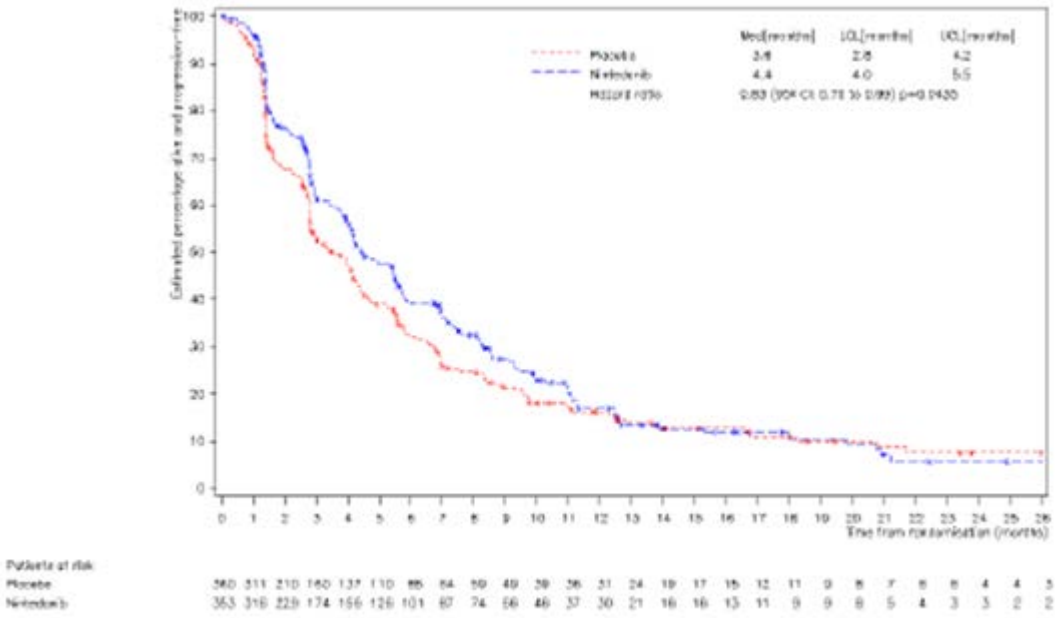


Figure 6: Probability rate of PFS in the overall population in trial 1199.14/ primary analysis, RS

Table 38: Analysis of OS in 1199.14 in the overall, adenocarcinoma, and T<9m adenocarcinoma population / RS

	Overall population		Adenocarcinoma population		T<9m adenocarcinoma population	
	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib
OS analysis cut-off date 15 Feb 2013						
Patients, n (%)	360 (100.0)	353 (100.0)	335 (100.0)	335 (100.0)	203 (100.0)	193 (100.0)
Patients with OS event, n (%)	260 (72.2)	254 (72.0)	241 (71.9)	239 (71.3)	155 (76.4)	143 (74.1)
OS [months]						
Median[1]	12.7	12.0	13.1	12.3	9.3	10.6
Percentiles (P25, P75)[1]	(5.4, 24.0)	(7.0, 24.2)	(5.7, 24.9)	(6.9, 25.6)	(4.4, 18.2)	(6.0, 21.0)
HR vs. placebo (95% CI)[2]		1.01 (0.85, 1.21)		1.00 (0.84, 1.20)		0.87 (0.69, 1.10)
p-value (2-sided)[2]		0.8940		0.9616		0.2555
Sensitivity analysis including baseline SLD						
HR vs. placebo (95% CI)[3]		1.00 (0.84, 1.19)		1.01 (0.84, 1.21)		0.82 (0.65, 1.03)
p-value (2-sided)[3]		0.9674		0.9378		0.0849
Sensitivity analysis including time since start of first-line therapy						
HR vs. placebo (95% CI)[3]		0.99 (0.83, 1.17)		0.99 (0.83, 1.19)		–
p-value (2-sided)[3]		0.8808		0.9109		–
OS analysis cut-off date 18 Jun 2011						
Patients, n (%)	349 (100.0)	351 (100.0)	325 (100.0)	335 (100.0)	194 (100.0)	193 (100.0)
Patients with OS event, n (%)	144 (41.3)	138 (39.3)	135 (41.5)	131 (39.1)	97 (50.0)	84 (43.5)
OS [months]						
Median[1]	12.2	10.9	12.6	11.2	9.1	9.9
Percentiles (P25, P75)[1]	(5.4, 21.8)	(6.8, 22.7)	(5.7, 21.8)	(6.4, 23.8)	(4.2, 16.1)	(5.8, 18.0)
HR vs. placebo (95% CI)[2]		0.92 (0.73, 1.18)		0.93 (0.73, 1.19)		0.86 (0.64, 1.15)
p-value (2-sided)[2]		0.5207		0.5515		0.3029
Sensitivity analysis including baseline SLD						
HR vs. placebo (95% CI)[3]		0.88 (0.70, 1.12)		0.92 (0.72, 1.17)		0.81 (0.60, 1.09)
p-value (2-sided)[3]		0.2994		0.4826		0.1649
Sensitivity analysis including time since start of first-line therapy						
HR vs. placebo (95% CI)[3]		0.90 (0.71, 1.14)		0.92 (0.72, 1.18)		–
p-value (2-sided)[3]		0.3838		0.5181		–

[1] Based on unadjusted Kaplan-Meier estimates for each treatment arm

[2] A proportional hazards model stratified by the factors ECOG PS at baseline, prior bevacizumab therapy, tumour histology (adeno- vs. non-adenocarcinoma; only for the analysis in the overall population), presence of brain metastases at baseline was used to derive the HR, 95% CI, and p-value (corresponding to the stratified log-rank test p-value)

[3] Based on a proportional hazards model with the stratification factors (ECOG PS at baseline, prior bevacizumab therapy, tumour histology [adenocarcinoma vs. non-adenocarcinoma; only for the analysis in the overall population], presence of brain metastases at baseline) and baseline SLD or time since start of first-line therapy to randomisation fitted as covariates

The sensitivity analyses by stratification factors and by baseline SLD were prespecified in the CTP.

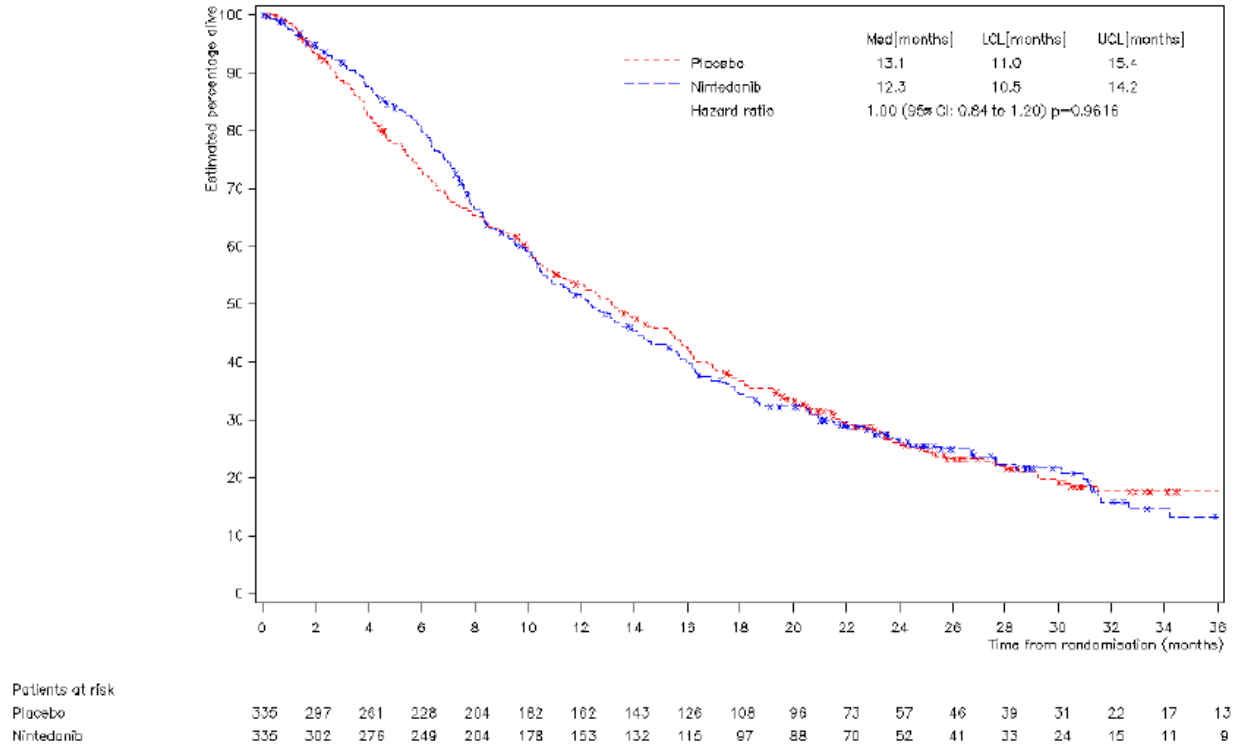


Figure 7: Probability of overall survival - RS

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

One phase III pivotal study (1199.13 (LUME Lung 1)) and one supportive phase III study (1199.14 (LUME Lung 2)) have been submitted in support of this application.

Both studies are well-designed: randomised, double-blinded, parallel-group and placebo-controlled. Study 1199.13 included approximately 650 patients in each treatment arm, patient characteristics were balanced between treatment arms within the overall population and within subgroups according to histology. In the overall population, 72.7 % of the patients were male. The majority of patients were non-Asian (81.6 %), the median age was 60.0 years, the baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (28.6 %) or 1 (71.3 %); one patient had a baseline ECOG performance status of 2.

5.8 % of the patients had stable brain metastasis at study entry and 3.8 % had prior bevacizumab treatment.

Patients with NSCLC with disease stage IIIB and IV were eligible for the studies. In study 1199.13 the effects of nintedanib + docetaxel are investigated compared to placebo+docetaxel and in study 1199.14 the effects of nintedanib + pemetrexed are investigated compared to placebo+docetaxel. Both background treatments (docetaxel and pemetrexed) are well-known and reflect current clinical practice. Analyses of OS for the nintedanib-docetaxel combination in second-line resulted in comparable improvement in OS regardless of whether patients were treated with pemetrexed in first-line or not; i.e. HR for OS was 0.79 for patients previously treated with pemetrexed and 0.83 for patients not previously treated with pemetrexed. No treatment interaction was found between treatment arm and first-line pemetrexed treatment when these groups were compared. Thus, the patients in study 1199.13 do not seem to be undertreated in first-line.

Paclitaxel in combination with platinum is registered for the first-line treatment of NSCLC. Approximately 20% of the patients in study 1199.13 were treated with paclitaxel in first-line. The applicant has performed an analysis of OS in patients with and without paclitaxel in first-line showing an HR for OS in those without paclitaxel in first-line of 0.86, while those treated with paclitaxel in first-line had an HR of 0.75. No significant interaction was found between treatment arm and first-line taxane treatment. The applicant also refers to several studies where docetaxel in second-line has been given after first-line paclitaxel. This includes the registrational study for docetaxel. Thus, the use of docetaxel after paclitaxel in study 1199.13 seems unproblematic

While trial 1199.13 included NSCLC patients irrespective of tumour histology, trial 1199.14 included patients with non-squamous (mostly adenocarcinoma) tumour histology since pemetrexed is indicated for NSCLC with other than predominantly squamous tumour histology. Patients were successfully randomised according to stratification factors identified as important prognostic factors; i.e. tumour histology, ECOG PS, prior bevacizumab treatment and brain metastases. Patients with EGFR-mutation were not excluded from the trials, and only a few were screened for mutation. EGFR mutated patients have a better outcome in terms of PFS and OS compared with patients that are EGFR WT. However, at the time of conduct of study 1199.13 this was not clearly understood by the scientific community. Thus, the Applicant has not systematically collected EGFR status. Nonetheless, there is information regarding EGRF status in 16.9% of the patients. Of those, only 20 patients were positive for EGFR mutations, 12 in the placebo group and 8 in the nintedanib group. The applicant has not conducted any analyses on these small numbers which is understandable and endorsed. The comparison of the PFS and OS results of study 1199.13 with the TITAN[1], TAILOR[2] and DELTA[3] studies revealed that there seems to be no indication of an overrepresentation of patients with EGFR mutations in study 1199.13. Furthermore, there are more Asian patients in placebo group, and bearing in mind that EGFR mutations are more common in Asian patients, there is still a favourable effect in favour of nintedanib. Thus, any impact of a potential imbalance in EGFR mutated patients seems to have little effect on the study results.

Another important mutation is the EML4-ALK fusion oncogene. EGFR mutation and EML4-ALK fusion oncogene are mutually exclusive. The number of patients with EML4-ALK fusion oncogene is relatively low and considered to be around 4-7% in the NSCLC population (Soda et al. 2007, Koivunen et al. 2008). Thus, the number of patient with EML4-ALK fusion oncogene in study 1199.13 is expected to be low. The applicant has not provided any efficacy data on the effect of nintedanib in patients with EML4-ALK fusion oncogene. However, since it is current clinical practice to test for EML4-ALK fusion oncogene in patients with lung cancer, and since these patients are offered more targeted treatment with ALK tyrosine kinase inhibitors such as crizotinib, the effect of nintedanib in these patients is not considered relevant.

The objective of both studies was to demonstrate superiority of nintedanib+docetaxel/pemetrexed over docetaxel or pemetrexed with regard to PFS by independent central review.

On 18 Jun 2011, recruitment into trial 1199.14 was stopped, based on the futility analysis performed by an independent DMC and the study was unblinded. Trial 1199.14 did not pass the futility analysis, which indicated

[1] Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Ciuleanu T et al. The Lancet Oncology - 1 March 2012 (Vol. 13, Issue 3, Pages 300-308)

[2] Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Garassino MC et al. The Lancet Oncology - 1 September 2013 (Vol. 14, Issue 10, Pages 981-988)

[3] Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). Kawaguchi T, et al. JCO JCO.2013.52.4694; published online on May 19, 2014.

that the endpoint PFS based on investigator assessment would likely not be met. The DMC, however, did not identify any safety concerns. Based on the DMC's recommendation, the Applicant halted further recruitment into the trial on 18 Jun 2011. At this time, a total of 713 patients had been enrolled into the trial. For the 183 patients still on treatment on 18 Jun 2011, the treatment code was broken however patients were still followed.

A retrospective analysis of the conditional and predictive power in trial 1199.14 over time, evaluating both PFS by investigator assessment and central assessment, showed that the only time when the conditional power dropped to around 20% was at the predefined time point of the futility analysis. The analyses also showed that the conditional power was generally lower for PFS by investigator assessment than for PFS by central independent review.

Upon review of the results of the primary analysis of trial 1199.14, the DMC issued a statement that is part of the formal record of the study, concluding in retrospect:

"...that the futility calculation, upon which it based its decision to stop the study, was an inadequate estimate of the true futility. This appears to be a result of a discordance between investigator assessments and the central assessments of PFS as well as a statistical aberration at the single time point evaluated. The current data review, which includes the mature and completed data regarding both PFS and OS, with PFS results based upon an independent, central review, demonstrates a strong positive trend favoring the experimental arm in LUME Lung 2."

The statistical analysis plan of study 1199.13 was amended before database lock and un-blinding. Overall survival (OS) was to be tested in hierarchical fashion, where the first intermediate step will be to test the OS effect in adenocarcinoma patients with time since start of first line therapy <9 months (T<9 months), then OS in the adenocarcinoma population, and finally in the overall NSCLC population. A thorough review revealed that tthat the results presented for PFS and OS in the overall population as well as stratified by histology remain unaffected by the choice to amend the TSAP.

The Applicant has given details on the timelines for analyses performed in the search for and validation of a clinical biomarker. All biomarker analysis findings, as well as the interim 1199.13 results at the time-point of the PFS (central review) read-out, were kept confidential behind a fire-wall; nothing was disclosed externally prior to the read-out of the final OS data from 1199.13.

Further to the CHMP request, the applicant has provided a comprehensive research plan aiming at identifying factors predictive for sensitivity as well as resistance to nintedanib in patients with advanced NSCLC. The type and number of soluble plasma marker to be analysed are satisfactory. Furthermore, multiple genes (60) have been identified to have an oncogenic role and possibly play a role in angiogenesis, and the predictive value of these genes will be further investigated. The Applicant is requested to submit data on an annual basis from the tumour biomarker analyses programme which includes testing of samples collected from the LUME-Lung 1 and LUME-Lung 2 for germline genetic variability in angiogenic factors, a single arm study on predictive biomarkers in NSCLC patients eligible for treatment with nintedanib, and implementation of bio-tumour marker testing in all clinical studies in the clinical program for nintedanib (See Annex II).

Efficacy data and additional analyses

Based on the analysis of the primary endpoint (never changed and therefore not affected by the hypothesis generation), study 1199.13 had met the prospectively defined primary endpoint centrally assessed PFS. A statistically significant difference in median PFS is demonstrated with a hazard ratio of 0.85 in the follow-up analysis. These results are supported by PFS by investigator (secondary endpoint), which also demonstrates a

statistically significant HR (0.82). In patients with non-squamous and squamous tumour histology, no detrimental effect on OS was seen, with a HR of 0.94 (95%CI, 0.83; 1.05, p=0.2720) in the overall population and a HR of 0.88 (95%CI, 0.75; 1.03, p=0.1133) in the non-squamous population. However, in the follow-up analysis of PFS, the benefit of nintedanib treatment in patients with tumours of non-squamous and squamous histology did not reach statistical significance, HR 0.85 (95% CI; 0.73, 1.00, p=0.0556) and HR 0.83 (95% CI; 0.69, 1.01, p=0.0566) respectively.

With regard to OS, there is an indication that nintedanib + docetaxel has a clinically relevant and important effect on patients with adenocarcinoma with T<9 months (patients with poor treatment prognosis) and the adenocarcinoma population in general. In the adenocarcinoma population the median OS was 12.6 months in the nintedanib + docetaxel arm compared to 10.3 months in the placebo + docetaxel arm. The difference of 2.3 months in OS in favour of nintedanib is a clinically relevant difference. This should be seen in the context of the clinical setting for patients with NSCLC stage IIIB disease who have a median survival of approximately 10 months, while patients with stage IV disease have a median survival of approximately 6 months. With regard to patients with adenocarcinoma and T<9 months, the median is 10.9 months in the nintedanib + docetaxel arm compared to 7.9 months in the placebo + docetaxel arm. These patients have a more aggressive disease, hence the shorter median OS, but a difference of 3 months in median OS is clinically relevant.

The applicant used three methods that all revealed 9 months cut-off since start of first-line therapy in the adenocarcinoma patients as predictive of effect of nintedanib. In addition, the applicant has presented a clinical plausible rationale for the 9 months cut-off. It is possible though that the OS result in adenocarcinoma patients is driven by patients with less than 9 months since start of first-line treatment. However, an explorative analysis where patients with less than 9 months since start of first-line from treatment are excluded to allow assessment of the efficacy of nintedanib in patients with more than 9 month since start of first-line treatment, showed a benefit in favour of nintedanib regardless of time since start of first-line treatment. Although, the HR was 0.89 in the group of patients with T≥9 months and there was a difference in median OS of 1.9 months, statistical significance was not reached. Nonetheless, there is a strong trend in favour of nintedanib.

The subgroup analyses show consistent results that support the overall OS estimate in the adenocarcinoma population. However, it seems that patients with adenocarcinoma and brain metastases or disease stage <IIIB/IV may have no effect of nintedanib + docetaxel, but the numbers are low, and the 95% CIs are wide and include the overall OS estimate.

Although it cannot be completely excluded that the decision to pursue the adenocarcinoma population was at least in part data driven, the applicant has provided a fair justification for a biological rationale explaining the better efficacy in the adenocarcinoma subgroup and also provided external validation of the findings. Alltogether this justifies the indication encompassing the adenocarcinoma population only.

There was no benefit of treating all patients with squamous tumour histology, HR 1.01 (95% CI 0.85, 1.21; p=0.8907). A post-hoc analysis of treatment effect of nintedanib in patients with squamous tumour with SLD ≥7.5 cm at baseline, indicated that patients with large tumour mass may respond to nintedanib; HR for PFS was 0.71 (95% CI 0.56, 0.91; p=0.0072). The result for the OS analysis in this population was not statistically significant but there was a trend for improvement with a median OS 7.7 months compared to 6.1 months; HR 0.82 (95% CI 0.65, 1.04; p=0.0995).

Patients with recurrent disease are included in the applied indication. According to the CSR, 9.2% of the overall population has locally recurrent disease. Of the total population, 21.7% had previous surgery and 28.8% had radiotherapy while very few had chemotherapy (4%). The applicant has provided an analysis that divide

patients according to whether they had local recurrence with and without metastases at baseline. Patients with re-occurrence of their disease without metastases could be expected to have a more favourable prognosis and perhaps a different response to treatment with nintedanib. According to the analyses presented by the applicant there seems to be no interaction between treatment and recurrence neither in the overall population, nor in the histology subgroups (adenocarcinoma and squamous cell). The numbers of patients are small and no definitive conclusion can be drawn. However, there are no signals giving doubt to whether nintedanib should be given to this patient group.

With regard to tumour response, a clinically relevant difference in disease control was observed in favour of nintedanib. No relevant differences were observed with regard to “clinical improvement” and “QoL”. Most importantly, nintedanib did not have any major detrimental effect on clinical status or QoL.

Nintedanib did not significantly change the time to deterioration of the pre-specified symptoms cough, dyspnoea and pain, but resulted in a significant deterioration in the diarrhoea symptom scale. Nevertheless, the overall treatment benefit of nintedanib was observed without adversely affecting self-reported quality of life.

In study 1199.14, the median OS in patients with adenocarcinoma is 13.1 months vs. 12.3 months in favour of placebo + pemetrexed however the HR is 1.00 (95% CI: 0.84 to 1.20), p=0.9616. Thus, no firm conclusions can be drawn from this study that was prematurely halted. KM-curves clearly show that the difference in median OS, is a chance finding due to technical limitations of KM-curves. This is a well-known limitation of KM-curves, reason why it is important to also focus on the HR, the 95%Cis and the p-value. The curves separate at two months, cross over at 8-9 months and back again at 22-23 months. Thus, based on the above uncertainties and limitations of study 1199.14, any overall interpretation of the results and attempt to conclude would be inappropriate. Nonetheless, in line with the observations in trial 1199.13, patients with adenocarcinoma who progressed during or shortly after first-line therapy also derived benefit from treatment with nintedanib and pemetrexed. Altogether, the findings in trial 1199.14 were consistent with the findings in trial 1199.13 and strengthen the premise that addition of nintedanib to standard chemotherapy improves clinical outcomes in the second-line treatment of patients with NSCLC and tumour histology adenocarcinoma.

From a pharmacokinetic point of view, the Applicant has investigated the potential impact of an imbalance in polymorphisms related to VEGF1-3, FGF 1-3 and PDGF alfa and beta, but no significant difference has been found. In addition, there is no evidence for a difference in EGFR mutation status that could explain the results. The median PFS and OS in Asian patients are consistent with the overall results. There is no indication of any interaction between the non-Asian and Asian subgroups. Thus, it seems that the only reliable explanation is the small number of Asian patients.

2.5.4. Conclusions on the clinical efficacy

The study 1199.13 provides evidence for a clinically relevant and statistically significant difference in PFS in the overall NSCLC population in favour of nintedanib. The efficacy results reported in the adenocarcinoma subpopulation in study 1199.13 indicate a significant effect on OS. These findings are supported by study 1199.14. In conclusion, both studies are supportive of beneficial effects of nintedanib in the adenocarcinoma patient population.

The CHMP considers the following measures necessary to address issues related to efficacy:

In order to investigate suitable bio- tumour markers (including VEGF) to allow identification and selection of a more targeted population of patients most likely to benefit from the treatment of nintedanib, the Applicant will conduct and submit results from a Biomarkers research programme including:

- Collected blood samples from the LUME-Lung 1 and LUME-Lung 2 studies will be assessed for germline genetic variability in angiogenic factors, including VEGF or its downstream receptors.
- Single arm study to examine whether genetic/genomic markers (alone or combined with clinical covariates) could be used to predict overall survival (OS) in NSCLC patients eligible for treatment with nintedanib.
- Data on bio/tumour markers from all clinical studies in the clinical program for nintedanib.

  The applicant will implement collection of material for biomarker investigation and analyses of biomarker data into the study protocol of all new oncology studies planned for nintedanib in the future, wherever clinically appropriate.

Results will be provided as they become available on a yearly basis -Submission of final study report

Q3 2021

2.6. Clinical safety

An integrated analysis of the safety data from 35 completed and ongoing trials was provided. Among 35 studies, a total of 8 nintedanib trials were performed in patients with NSCLC. This comprised 4 phase I trials (1199.5, 1199.18, 1199.28, and 1199.29), one phase I/II trial (1199.82), one phase II trial (1199.10), and 2 phase III trials (1199.13 and 1199.14).

Safety data was presented in different safety analysis sets (SAF).

Table 39: Characteristics of the safety analysis sets (SAFs)

SAF	SAF description	Patients[1] (n)
Studies presented in SAFs		
SAF-1	Nintedanib/placebo plus docetaxel in all patients in trial 1199.13 (short label: all patients 1199.13)	1307
	Nintedanib/placebo plus docetaxel in patients with adenocarcinoma in trial 1199.13 (short label: adenocarcinoma 1199.13)	653
	Nintedanib/placebo plus pemetrexed in patients with adenocarcinoma in trial 1199.14 (short label: adenocarcinoma 1199.14)	661
SAF-2	Nintedanib monotherapy in phase I/II studies; trials 1199.1[2], 1199.3, 1199.9, 1199.10[2], 1199.11[2], 1199.19, 1199.26, 1239.3	376
SAF-3	Nintedanib in cancer patients; trials 1199.1[2], 1199.2, 1199.3, 1199.4[2], 1199.5, 1199.6[2], 1199.9, 1199.10[2], 1199.11[2], 1199.13, 1199.14, 1199.18, 1199.19, 1199.26, 1199.28, 1199.29, 1199.51, 1199.82, 1199.117, 1199.119, 1230.7, 1239.1, 1239.2, 1239.3, 1239.14	1884
SAF-4	Nintedanib in healthy volunteers; trials 1199.17, 1199.20, 1199.21, 1199.75	83

[1] Treated patients; i.e. patients who received at least 1 dose of study medication; cut-off date 15 Feb 2013. As the safety groupings are not mutually exclusive but overlap, patients can be counted in several SAFs and SAF-1 subsets.
[2] Trial 1199.16 is a phase I/II open label extension study. Patients who had completed any of the trials 1199.1, 1199.4, 1199.6, 1199.10, or 1199.11 could be randomised into this extension trial, but were counted only once in SAF-2/SAF-3.

Patient exposure

Table 40: Duration of nintedanib/placebo treatment in phase III trials 1199.13 and 1199.14 (SAF-1), in nintedanib phase I/II monotherapy trials (SAF-2), and in all patients with cancer treated with nintedanib (SAF-3) – Safety set (SFS)

	Adenocarcinoma 1199.13		All patients 1199.13		Adenocarcinoma 1199.14		All patients nintedanib monotherapy		All patients nintedanib
	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Nintedanib ≤200 mg b.i.d.	Nintedanib >200 mg b.i.d.	Nintedanib
Patients, n (%)	331 (100.0)	320 (100.0)	650 (100.0)	650 (100.0)	324 (100.0)	328 (100.0)	174 (100.0)	202 (100.0)	1880 (100.0)
Treatment time [months]									
Mean (StD)	4.70 (5.02)	5.45 (5.29)	4.17 (4.62)	4.78 (4.91)	4.28 (3.97)	5.26 (5.31)	6.2 (6.8)	4.1 (5.7)	5.0 (5.5)
Median	2.97	4.20	2.77	3.38	2.82	3.50	3.5	2.9	3.3
Range (min, max)	(0.07, 31.70)	(0.10, 41.53)	(0.07, 35.63)	(0.03, 41.53)	(0.03, 22.10)	(0.03, 30.80)	(0.1, 31.1)	(0.1, 69.0)	(0.1, 69.0)
Treatment time [months] by category, n (%)									
≤ 1	32 (9.7)	30 (9.4)	68 (10.5)	69 (10.6)	48 (14.8)	39 (11.9)	13 (7.5)	25 (12.4)	221 (11.8)
>1 to ≤2	92 (27.8)	61 (19.1)	193 (29.7)	148 (22.8)	69 (21.3)	65 (19.8)	33 (19.0)	49 (24.3)	405 (21.5)
>2 to ≤4	57 (17.2)	57 (17.8)	147 (22.6)	132 (20.3)	77 (23.8)	70 (21.3)	54 (31.0)	64 (31.7)	430 (22.9)
>4 to ≤6	73 (22.1)	65 (20.3)	123 (18.9)	134 (20.6)	52 (16.0)	61 (18.6)	25 (14.4)	31 (15.3)	333 (17.7)
>6 to ≤9	35 (10.6)	57 (17.8)	55 (8.5)	90 (13.8)	41 (12.7)	35 (10.7)	16 (9.2)	19 (9.4)	229 (12.2)
>9 to ≤12	19 (5.7)	27 (8.4)	32 (4.9)	42 (6.5)	19 (5.9)	24 (7.3)	7 (4.0)	6 (3.0)	116 (6.2)
>12	23 (6.9)	23 (7.2)	32 (4.9)	35 (5.4)	18 (5.6)	34 (10.4)	26 (14.9)	8 (4.0)	146 (7.8)
Dose intensity [%], mean (StD)	93.8 (13.3)	91.2 (15.0)	94.9 (11.5)	92.1 (15.4)	90.1 (16.7)	82.9 (20.3)	97.8 (6.4)	95.1 (10.6)	96.1 (9.8)
Estimated cumulative dose, based on dates[1], mean (StD)	53.9 (57.5)	59.9 (58.1)	48.0 (53.4)	53.1 (54.7)	48.5 (44.4)	54.8 (53.5)	65.9 (77.8)	54.8 (66.2)	53.2 (58.2)

[1] Cumulative dose (g) calculated based on first and last dates of nintedanib/placebo intake (including start and end dates of reduced doses).

Exposure to docetaxel judged by mean docetaxel courses and mean cumulative dose was greater in the nintedanib arm (5.1 courses, 374.91 mg/m^2) than in the placebo arm (4.6 courses, 341.31 mg/m^2) of pivotal trial 1199.13 (all patients). A slightly higher docetaxel exposure was observed in patients with adenocarcinoma histology, i.e. nintedanib arm; 5.7 courses, 421.27 mg/m^2, placebo arm; 5.1 courses, 374.14 mg/m^2.

Table 41: Demographics in phase III trials 1199.13 and 1199.14 (SAF-1), in nintedanib phase I/II monotherapy trials (SAF-2), and in all patients with cancer treated with nintedanib (SAF-3) – Randomised Set (RS)/Treated Set (TS)

	Adenocarcinoma 1199.13		All patients 1199.13		Adenocarcinoma 1199.14		All patients nintedanib monotherapy		All patients nintedanib
	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Nintedanib ≤200 mg b.i.d.	Nintedanib >200 mg b.i.d.	Nintedanib
Patients, n (%)	336 (100.0)	322 (100.0)	659 (100.0)	655 (100.0)	335 (100.0)	335 (100.0)	174 (100.0)	202 (100.0)	1884 (100.0)
Gender, n (%)									
Female	128 (38.1)	119 (37.0)	180 (27.3)	179 (27.3)	143 (42.7)	155 (46.3)	49 (28.2)	63 (31.2)	673 (35.7)
Male	208 (61.9)	203 (63.0)	479 (72.7)	476 (72.7)	192 (57.3)	180 (53.7)	125 (71.8)	139 (68.8)	1211 (64.3)
Age, mean (StD) [years]	58.6 (9.5)	58.5 (10.1)	59.8 (9.0)	59.7 (9.7)	58.6 (11.0)	59.2 (10.3)	62.6 (10.5)	63.7 (9.9)	60.5 (10.1)
Median	59.0	60.0	60.0	60.0	59.0	60.0	63.0	64.0	61.0
(min, max)	(30, 80)	(29, 80)	(26, 80)	(29, 84)	(26, 86)	(21, 84)	(34, 86)	(27, 83)	(21, 86)
Age categories) [years], n (%)									
<65	240 (71.4)	232 (72.0)	445 (67.5)	455 (69.5)	231 (69.0)	231 (69.0)	94 (54.0)	107 (53.0)	1219 (64.7)
≥65	96 (28.6)	90 (28.0)	214 (32.5)	200 (30.5)	104 (31.0)	104 (31.0)	80 (46.0)	95 (47.0)	665 (35.3)
Race									
White / Caucasian	253 (75.3)	253 (78.6)	530 (80.4)	533 (81.4)	206 (61.5)	208 (62.1)	157 (90.2)	189 (93.6)	1486 (78.9)
Black / African American	4 (1.2)	3 (0.9)	5 (0.8)	4 (0.6)	8 (2.4)	11 (3.3)	2 (1.1)	1 (0.5)	25 (1.3)
Asian	78 (23.2)	65 (20.2)	123 (18.7)	116 (17.7)	105 (31.3)	102 (30.4)	15 (8.6)	12 (5.9)	327 (17.4)
American Indian / Alaska Native	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.3)	15 (4.5)	11 (3.3)	–	–	–
Hawaiian / Pacific Islander	0	0	0	0	1 (0.3)	3 (0.9)	–	–	–
Missing	0	0	0	0	0	0	0	0	46 (2.4)
Geographic region									
Asia	96 (28.6)	86 (26.7)	156 (23.7)	152 (23.2)	103 (30.7)	98 (29.3)	15 (8.6)	6 (3.0)	332 (17.6)
Australia / New Zealand	–	–	–	–	16 (4.8)	19 (5.7)	0	0	20 (1.1)
Central / South America	–	–	–	–	69 (20.6)	73 (21.8)	0	0	77 (4.1)
Europe	234 (69.6)	229 (71.1)	492 (74.7)	493 (75.3)	103 (30.7)	96 (28.7)	159 (91.4)	196 (97.0)	1314 (69.7)
North America	–	–	–	–	44 (13.1)	49 (14.6)	0	0	131 (7.0)
South Africa	6 (1.8)	7 (2.2)	11 (1.7)	10 (1.5)	–	–	0	0	10 (0.5)
Body weight, mean (StD) [kg]	70.61 (15.16)	69.89 (14.29)	71.33 (15.31)	70.92 (14.72)	68.46 (14.66)	67.55 (14.04)	–	–	–
Smoking status, n (%)									
Never smoked	115 (34.2)	115 (35.7)	161 (24.4)	165 (25.2)	118 (35.2)	104 (31.0)	–	–	–
Ex-smoker	162 (48.2)	151 (46.9)	354 (53.7)	337 (51.5)	175 (52.2)	183 (54.6)	–	–	–
Current smoker	59 (17.6)	56 (17.4)	144 (21.9)	153 (23.4)	42 (12.5)	48 (14.3)	–	–	–

Abbreviations: – = information not collected or data not summarised

Table 42: Oncological history in phase III trials 1199.13 and 1199.14 (SAF-1) – Randomised Set (RS)

	Adenocarcinoma 1199.13		All patients 1199.13		Adenocarcinoma 1199.14	
	Placebo n (%)	Nintedanib n (%)	Placebo n (%)	Nintedanib n (%)	Placebo n (%)	Nintedanib n (%)
Patients	336 (100.0)	322 (100.0)	659 (100.0)	655 (100.0)	335 (100.0)	335 (100.0)
Disease stage at diagnosis						
<IIIB/IV	54 (16.1)	50 (15.5)	105 (15.9)	105 (16.0)	65 (19.4)	54 (16.1)
IIIB	45 (13.4)	55 (17.1)	146 (22.2)	148 (22.6)	49 (14.6)	73 (21.8)
IV	237 (70.5)	215 (66.8)	408 (61.9)	401 (61.2)	221 (66.0)	208 (62.1)
ECOG performance score[1]						
0	99 (29.5)	96 (29.8)	189 (28.7)	187 (28.5)	132 (39.4)	127 (37.9)
1	237 (70.5)	226 (70.2)	470 (71.3)	468 (71.5)	203 (60.6)	208 (62.1)
Region of primary tumour site						
Left lower lobe	54 (16.1)	60 (18.6)	93 (14.1)	118 (18.0)	51 (15.2)	39 (11.6)
Left upper lobe	93 (27.7)	78 (24.2)	180 (27.3)	181 (27.6)	86 (25.7)	74 (22.1)
Right lower lobe	50 (14.9)	53 (16.5)	96 (14.6)	108 (16.5)	59 (17.6)	70 (20.9)
Right middle lobe	26 (7.7)	27 (8.4)	50 (7.6)	50 (7.6)	26 (7.8)	25 (7.5)
Right upper lobe	112 (33.3)	101 (31.4)	237 (36.0)	188 (28.7)	108 (32.2)	123 (36.7)
Missing	1 (0.3)	3 (0.9)	3 (0.5)	10 (1.5)	5 (1.5)	4 (1.2)
Local re-occurrence without metastases at screening	16 (4.8)	22 (6.8)	54 (8.2)	67 (10.2)	29 (8.7)	43 (12.8)
Metastases present at screening	320 (95.2)	300 (93.2)	605 (91.8)	588 (89.8)	304 (90.7)	290 (86.6)
No. of metastatic sites						
≤2	196 (58.3)	187 (58.1)	399 (60.5)	387 (59.1)	195 (58.2)	180 (53.7)
>2	124 (36.9)	113 (35.1)	206 (31.3)	201 (30.7)	108 (32.2)	110 (32.8)
Location of metastasis						
Adrenal glands	56 (16.7)	42 (13.0)	106 (16.1)	88 (13.4)	44 (13.1)	45 (13.4)
Bone	100 (29.8)	92 (28.6)	159 (24.1)	145 (22.1)	81 (24.2)	86 (25.7)
Brain	23 (6.8)	26 (8.1)	38 (5.8)	38 (5.8)	34 (10.1)	34 (10.1)
Liver	53 (15.8)	63 (19.6)	109 (16.5)	137 (20.9)	54 (16.1)	58 (17.3)
Lung ipsilateral	175 (52.1)	163 (50.6)	317 (48.1)	292 (44.6)	175 (52.2)	156 (46.6)
Lung contralateral	144 (42.9)	140 (43.5)	248 (37.6)	264 (40.3)	139 (41.5)	144 (43.0)
Other	156 (46.4))	138 (42.9)	305 (46.3)	285 (43.5)	129 (38.5)	123 (36.7)
Bevacizumab pre–treatment	21 (6.3)	24 (7.5)	23 (3.5)	27 (4.1)	24 (7.2)	27 (8.1)
First line therapy	333 (99.1)	318 (98.8)	651 (98.8)	646 (98.6)	331 (98.8)	332 (99.1)
Type of first line therapy						
Platinum-based	323 (96.1)	308 (95.7)	636 (96.5)	628 (95.9)	323 (96.4)	323 (96.4)
Non-platinum based	10 (3.0)	10 (3.1)	15 (2.3)	18 (2.7)	8 (2.4)	9 (2.7)
Best response to first line therapy						
Complete response, partial response, or stable disease	236 (70.2)	245 (76.1)	445 (67.5)	476 (72.7)	230 (68.7)	238 (71.0)
Progressive disease	64 (19.0)	53 (16.5)	139 (21.1)	127 (19.4)	75 (22.4)	71 (21.2)
Unknown, not applicable or missing	36 (10.7)	24 (7.5)	75 (11.4)	52 (7.9)	30 (9.0)	26 (7.8)

[1] There was 1 patient with adenocarcinoma in the nintedanib arm of trial 1199.13 with a baseline Eastern Cooperative Oncology Group (ECOG) performance score of 2.

Adverse events

Table 43: Summary of adverse events in phase III trials 1199.13 and 1199.14 (SAF-1), in nintedanib phase I/II monotherapy trials (SAF-2), and in all patients with cancer treated with nintedanib (SAF-3) – TS

	Adenocarcinoma 1199.13		All patients 1199.13		Adenocarcinoma 1199.14		All patients nintedanib monotherapy		All patients nintedanib
	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Nintedanib ≤200 mg b.i.d.	Nintedanib >200 mg b.i.d.	Nintedanib
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients treated	333 (100.0)	320 (100.0)	655 (100.0)	652 (100.0)	332 (100.0)	329 (100.0)	174 (100.0)	202 (100.0)	1884 (100.0)
Patients with any AE	314 (94.3)	308 (96.3)	609 (93.0)	610 (93.6)	313 (94.3)	314 (95.4)	166 (95.4)	200 (99.0)	1813 (96.2)
Patients with any drug-related AE[1]	241 (72.4)	260 (81.3)	446 (68.1)	498 (76.4)	224 (67.5)	273 (83.0)	140 (80.5)	186 (92.1)	1595 (84.7)
Patients with any AE leading to dose reduction of nintedanib/placebo	22 (6.6)	69 (21.6)	41 (6.3)	118 (18.1)	31 (9.3)	109 (33.1)	24 (13.8)	46 (22.8)	410 (21.8)
Patients with any AE leading to permanent discontinuation of last study medication	59 (17.7)	67 (20.9)	142 (21.7)	148 (22.7)	59 (17.8)	54 (16.4)	53 (30.5)	69 (34.2)	460 (24.4)
Patients with other significant AEs[2]	116 (34.8)	161 (50.3)	243 (37.1)	304 (46.6)	111 (33.4)	178 (54.1)	–	–	–
Patients with any SAE	107 (32.1)	111 (34.7)	206 (31.5)	224 (34.4)	104 (31.3)	97 (29.5)	71 (40.8)	85 (42.1)	697 (37.0)
Fatal	32 (9.6)	56 (17.5)	77 (11.8)	107 (16.4)	37 (11.1)	33 (10.0)	36 (20.7)	32 (15.8)	252 (13.4)
Immediately life-threatening	10 (3.0)	11 (3.4)	15 (2.3)	15 (2.3)	5 (1.5)	12 (3.6)	4 (2.3)	2 (1.0)	42 (2.2)
Disability / incapacity	7 (2.1)	0	7 (1.1)	2 (0.3)	3 (0.9)	3 (0.9)	1 (0.6)	2 (1.0)	15 (0.8)
Required hospitalisation	86 (25.8)	86 (26.9)	164 (25.0)	176 (27.0)	93 (28.0)	77 (23.4)	52 (29.9)	65 (32.2)	539 (28.6)
Prolonged hospitalisation	16 (4.8)	20 (6.3)	32 (4.9)	36 (5.5)	12 (3.6)	17 (5.2)	4 (2.3)	5 (2.5)	77 (4.1)
Other	2 (0.6)	1 (0.3)	7 (1.1)	4 (0.6)	3 (0.9)	1 (0.3)	12 (6.9)	10 (5.0)	71 (3.8)
Highest CTCAE grade									
Grade 1	27 (8.1)	16 (5.0)	54 (8.2)	37 (5.7)	33 (9.9)	16 (4.9)	25 (14.4)	22 (10.9)	130 (6.9)
Grade 2	59 (17.7)	49 (15.3)	134 (20.5)	108 (16.6)	102 (30.7)	70 (21.3)	46 (26.4)	56 (27.7)	398 (21.1)
Grade 3	63 (18.9)	64 (20.0)	139 (21.2)	138 (21.2)	114 (34.3)	153 (46.5)	46 (26.4)	81 (40.1)	649 (34.4)
Grade 4	133 (39.9)	123 (38.4)	205 (31.3)	220 (33.7)	27 (8.1)	42 (12.8)	13 (7.5)	9 (4.5)	385 (20.4)
Grade 5	32 (9.6)	56 (17.5)	77 (11.8)	107 (16.4)	37 (11.1)	33 (10.0)	36 (20.7)	32 (15.8)	251 (13.3)

Adverse events were assessed using MedDRA version 15.1.; Abbreviations: – = information not collected or data not summarised

[1] Drug-related refers to relatedness of the AE to any study medication

[2] Other significant AEs are AEs (including serious AEs) leading to dose reduction or permanent discontinuation of last study medication

Table 44: Adverse events in patients with adenocarcinoma in phase III trial 1199.13 (incidence >10% in either treatment arm) – by preferred term and worst CTCAE grade, all treatment courses - on-treatment period, treated set

	Placebo					Nintedanib				
	Any grade n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Patients	333 (100.0)	333 (100.0)	333 (100.0)	333 (100.0)	333 (100.0)	320 (100.0)	320 (100.0)	320 (100.0)	320 (100.0)	320 (100.0)
Patients with AEs	314 (94.3)	86 (25.8)	63 (18.9)	133 (39.9)	32 (9.6)	308 (96.3)	65 (20.3)	64 (20.0)	123 (38.4)	56 (17.5)
Diarrhoea	82 (24.6)	70 (21.0)	11 (3.3)	1 (0.3)	0	139 (43.4)	119 (37.2)	19 (5.9)	1 (0.3)	0
Neutrophil count decreased	135 (40.5)	19 (5.7)	30 (9.0)	86 (25.8)	0	131 (40.9)	15 (4.7)	25 (7.8)	91 (28.4)	0
ALT increased	31 (9.3)	28 (8.4)	3 (0.9)	0	0	121 (37.8)	84 (26.3)	37 (11.6)	0	0
Fatigue	98 (29.4)	83 (24.9)	11 (3.3)	3 (0.9)	0	99 (30.9)	84 (26.3)	13 (4.1)	2 (0.6)	0
AST increased	24 (7.2)	22 (6.6)	2 (0.6)	0	0	97 (30.3)	84 (26.3)	13 (4.1)	0	0
Nausea	59 (17.7)	57 (17.1)	2 (0.6)	0	0	91 (28.4)	88 (27.5)	3 (0.9)	0	0
WBC decreased	94 (28.2)	33 (9.9)	44 (13.2)	17 (5.1)	0	89 (27.8)	26 (8.1)	45 (14.1)	18 (5.6)	0
Decreased appetite	52 (15.6)	47 (14.1)	4 (1.2)	0	1 (0.3)	75 (23.4)	71 (22.2)	3 (0.9)	1 (0.3)	0
Vomiting	41 (12.3)	39 (11.7)	2 (0.6)	0	0	62 (19.4)	58 (18.1)	3 (0.9)	1 (0.3)	0
Alopecia	68 (20.4)	67 (20.1)	0	0	0	56 (17.5)	55 (17.2)	1 (0.3)	0	0
Dyspnoea	52 (15.6)	32 (9.6)	12 (3.6)	1 (0.3)	7 (2.1)	54 (16.9)	39 (12.2)	7 (2.2)	2 (0.6)	6 (1.9)
Neutropenia	51 (15.3)	6 (1.8)	9 (2.7)	36 (10.8)	0	44 (13.8)	6 (1.9)	9 (2.8)	29 (9.1)	0
Cough	63 (18.9)	61 (18.3)	2 (0.6)	0	0	42 (13.1)	39 (12.2)	2 (0.6)	0	1 (0.3)
Pyrexia	47 (14.1)	46 (13.8)	1 (0.3)	0	0	39 (12.2)	37 (11.6)	1 (0.3)	1 (0.3)	0
Stomatitis	26 (7.8)	25 (7.5)	0	1 (0.3)	0	36 (11.3)	32 (10.0)	2 (0.6)	2 (0.6)	0
Haemoglobin decreased	46 (13.8)	39 (11.7)	6 (1.8)	1 (0.3)	0	35 (10.9)	32 (10.0)	3 (0.9)	0	0
Constipation	39 (11.7)	38 (11.4)	1 (0.3)	0	0	22 (6.9)	22 (6.9)	0	0	0

Preferred terms are sorted by frequency in the nintedanib arm.

Table 45: Adverse events in patients with adenocarcinoma in phase III trial 1199.14 (incidence >10% in either treatment arm) – by preferred term and worst CTCAE grade, all treatment courses – on-treatment period, treated set (TS)

	Placebo					Nintedanib				
	Any grade n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Patients	332 (100.0)	332 (100.0)	332 (100.0)	332 (100.0)	332 (100.0)	329 (100.0)	329 (100.0)	329 (100.0)	329 (100.0)	329 (100.0)
Patient with AEs	313 (94.3)	135 (40.7)	114 (34.3)	27 (8.1)	37 (11.1)	314 (95.4)	86 (26.1)	153 (46.5)	42 (12.8)	33 (10.0)
ALT increased	84 (25.3)	58 (17.5)	26 (7.8)	0	0	145 (44.1)	64 (19.5)	81 (24.6)	0	0
AST increased	66 (19.9)	60 (18.1)	6 (1.8)	0	0	126 (38.3)	84 (25.5)	41 (12.5)	1 (0.3)	0
Nausea	109 (32.8)	105 (31.6)	4 (1.2)	0	0	120 (36.5)	110 (33.4)	10 (3.0)	0	0
Diarrhoea	49 (14.8)	45 (13.6)	4 (1.2)	0	0	115 (35.0)	103 (31.3)	11 (3.3)	0	1 (0.3)
Fatigue	118 (35.5)	98 (29.5)	18 (5.4)	2 (0.6)	0	107 (32.5)	86 (26.1)	18 (5.5)	3 (0.9)	0
Decreased appetite	82 (24.7)	76 (22.9)	6 (1.8)	0	0	93 (28.3)	89 (27.1)	4 (1.2)	0	0
Vomiting	66 (19.9)	57 (17.2)	7 (2.1)	2 (0.6)	0	83 (25.2)	77 (23.4)	6 (1.8)	0	0
Neutrophil count decreased	45 (13.6)	22 (6.6)	19 (5.7)	4 (1.2)	0	73 (22.2)	31 (9.4)	28 (8.5)	14 (4.3)	0
WBC decreased	35 (10.5)	18 (5.4)	15 (4.5)	2 (0.6)	0	57 (17.3)	42 (12.8)	15 (4.6)	0	0
Cough	57 (17.2)	49 (14.8)	8 (2.4)	0	0	54 (16.4)	53 (16.1)	1 (0.3)	0	0
Dyspnoea	72 (21.7)	57 (17.2)	7 (2.1)	2 (0.6)	4 (1.2)	52 (15.8)	37 (11.2)	9 (2.7)	2 (0.6)	4 (1.2)
Constipation	56 (16.9)	55 (16.6)	1 (0.3)	0	0	45 (13.7)	44 (13.4)	0	1 (0.3)	0
Abdominal pain	27 (8.1)	25 (7.5)	1 (0.3)	1 (0.3)	0	41 (12.5)	39 (11.9)	2 (0.6)	0	0
Headache	43 (13.0)	42 (12.7)	1 (0.3)	0	0	41 (12.5)	40 (12.2)	1 (0.3)	0	0
Haemoglobin decreased	38 (11.4)	34 (10.2)	3 (0.9)	1 (0.3)	0	38 (11.6)	28 (8.5)	7 (2.1)	3 (0.9)	0
Pyrexia	41 (12.3)	39 (11.7)	2 (0.6)	0	0	34 (10.3)	33 (10.0)	1 (0.3)	0	0
Back pain	34 (10.2)	29 (8.7)	5 (1.5)	0	0	33 (10.0)	32 (9.7)	1 (0.3)	0	0
Dizziness	38 (11.4)	37 (11.1)	1 (0.3)	0	0	30 (9.1)	29 (8.8)	1 (0.3)	0	0

Preferred terms are sorted by frequency in the nintedanib arm.
Source: [U12-2160, Table 15.3.2.4.2.1: 2] and [U12-2160, Appendix 16.1.9.2, Table 7.3.2.1.2]

Adverse Events of Special Interest (AESI)

The analysis of AESIs aimed to provide more information about the potential adverse reactions of nintedanib, potential class effects of VEGFR inhibitors and the general characterisation of the safety profile of combination therapy with docetaxel and nintedanib.

The following AESIs were analysed: Listed AEs as possible adverse drug reactions of nintedanib including AESIs selected based on potential association/complication of AEs; Potential class effects of VEGFR inhibitors; AESIs selected based on potential interaction with concomitant chemotherapy; AESIs selected based on competitor labelling; Cardiac events; Other AEs of interest.

Table 46: Summary of adverse events of special interest in phase III trials 1199.13 and 1199.14 (SAF-1), in nintedanib phase I/II monotherapy trials (SAF-2), and in patients with cancer treated with nintedanib (SAF-3) – TS

Adverse events of special interest as possible adverse drug reactions of nintedanib

	Adenocarcinoma 1199.13		All patients 1199.13		Adenocarcinoma 1199.14		All patients nintedanib monotherapy		All patients nintedanib
	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Nintedanib ≤200 mg b.i.d.	Nintedanib >200 mg b.i.d.	Nintedanib
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients treated	333 (100.0)	320 (100.0)	655 (100.0)	652 (100.0)	332 (100.0)	329 (100.0)	174 (100.0)	202 (100.0)	1884 (100.0)
Patients with any AESI	291 (87.4)	295 (92.2)	560 (85.5)	579 (88.8)	298 (89.8)	304 (92.4)	161 (92.5)	196 (97.0)	1759 (93.4)
Diarrhoea	82 (24.6)	139 (43.4)	143 (21.8)	276 (42.3)	49 (14.8)	115 (35.0)	96 (55.2)	132 (65.3)	1000 (53.1)
Liver-related investigation	49 (14.7)	137 (42.8)	89 (13.6)	219 (33.6)	103 (31.0)	168 (51.1)	29 (16.7)	72 (35.6)	688 (36.5)
Specific liver-related investigation (tailored)	42 (12.6)	130 (40.6)	74 (11.3)	204 (31.3)	95 (28.6)	161 (48.9)	18 (10.3)	61 (30.2)	614 (32.6)
Fatigue	123 (36.9)	127 (39.7)	234 (35.7)	250 (38.3)	140 (42.2)	127 (38.6)	80 (46.0)	86 (42.6)	922 (48.9)
Nausea	59 (17.7)	91 (28.4)	118 (18.0)	158 (24.2)	109 (32.8)	120 (36.5)	93 (53.4)	128 (63.4)	824 (43.7)
Vomiting	41 (12.3)	62 (19.4)	61 (9.3)	110 (16.9)	66 (19.9)	83 (25.2)	65 (37.4)	90 (44.6)	590 (31.3)
Abdominal pain	28 (8.4)	32 (10.0)	59 (9.0)	63 (9.7)	48 (14.5)	52 (15.8)	40 (23.0)	63 (31.2)	399 (21.2)
Dehydration	0	6 (1.9)	3 (0.5)	12 (1.8)	7 (2.1)	12 (3.6)	6 (3.4)	5 (2.5)	77 (4.1)
Hepatic failure	1 (0.3)	3 (0.9)	1 (0.2)	8 (1.2)	2 (0.6)	8 (2.4)	4 (2.3)	12 (5.9)	63 (3.3)
Renal failure	1 (0.3)	3 (0.9)	2 (0.3)	4 (0.6)	8 (2.4)	4 (1.2)	1 (0.6)	3 (1.5)	30 (1.6)

Source: [U13-1504, Table 15.3.2.3: 1, and Table 15.3.2.4.2.3: 1, U12-2160, Table 15.3.2.4.2.3: 1, U13-1507, Appendix 1, Table 6.1.1 and Table 6.1.3]

Adverse events as potential class effects of VEGFR inhibitors

	Adenocarcinoma 1199.13		All patients 1199.13		Adenocarcinoma 1199.14		All patients nintedanib monotherapy		All patients nintedanib
	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Nintedanib ≤200 mg b.i.d.	Nintedanib >200 mg b.i.d.	Nintedanib
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients treated	333 (100.0)	320 (100.0)	655 (100.0)	652 (100.0)	332 (100.0)	329 (100.0)	174 (100.0)	202 (100.0)	1884 (100.0)
Patients with any AESI	291 (87.4)	295 (92.2)	560 (85.5)	579 (88.8)	298 (89.8)	304 (92.4)	161 (92.5)	196 (97.0)	1759 (93.4)
Bleeding events									
Bleeding	37 (11.1)	35 (10.9)	76 (11.6)	92 (14.1)	43 (13.0)	39 (11.9)	24 (13.8)	32 (15.8)	340 (18.0)
Respiratory bleeding	20 (6.0)	15 (4.7)	46 (7.0)	52 (8.0)	25 (7.5)	19 (5.8)	8 (4.6)	7 (3.5)	101 (5.4)
Thromboembolic events									
Thromboembolic events	18 (5.4)	17 (5.3)	30 (4.6)	33 (5.1)	7 (2.1)	10 (3.0)	8 (4.6)	7 (3.5)	93 (4.9)
Venous thromboembolism	4 (1.2)	9 (2.8)	10 (1.5)	18 (2.8)	3 (0.9)	5 (1.5)	3 (1.7)	4 (2.0)	55 (2.9)
Arterial thromboembolism	7 (2.1)	3 (0.9)	9 (1.4)	4 (0.6)	3 (0.9)	4 (1.2)	3 (1.7)	2 (1.0)	16 (0.8)
Perforation events									
Non GI perforation	1 (0.3)	4 (1.3)	1 (0.2)	8 (1.2)	1 (0.3)	1 (0.3)	1 (0.6)	1 (0.5)	15 (0.8)
GI perforation	1 (0.3)	1 (0.3)	3 (0.5)	3 (0.5)	0	1 (0.3)	1 (0.6)	0	12 (0.6)
Hypertension	2 (0.6)	11 (3.4)	6 (0.9)	23 (3.5)	13 (3.9)	14 (4.3)	18 (10.3)	23 (11.4)	128 (6.8)

Abbreviations: GI = gastrointestinal

Adverse events as potential interaction with concomitant chemotherapy

	Adenocarcinoma 1199.13		All patients 1199.13		Adenocarcinoma 1199.14		All patients nintedanib monotherapy		All patients nintedanib
Any grade	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Nintedanib ≤200 mg b.i.d.	Nintedanib >200 mg b.i.d.	Nintedanib
Worst grade ≥3	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients treated	333 (100.0)	320 (100.0)	655 (100.0)	652 (100.0)	332 (100.0)	329 (100.0)	174 (100.0)	202 (100.0)	1884 (100.0)
Patients with any AESI	291 (87.4)	295 (92.2)	560 (85.5)	579 (88.8)	298 (89.8)	304 (92.4)	161 (92.5)	196 (97.0)	1759 (93.4)
Potential interaction with concomitant chemotherapy									
Any grade									
Neutropenia	178 (53.5)	176 (55.0)	323 (49.3)	326 (50.0)	64 (19.3)	99 (30.1)	0	1 (0.5)	584 (31.0)
AESI Worst grade ≥3	155 (46.5)	161 (50.3)	273 (41.7)	292 (44.8)	36 (10.8)	62 (18.8)	0	0	484 (25.7)
Laboratory value grade 3,4 neutrophils	183 (55.8)	194 (61.2)	328 (50.9)	366 (57.0)	66 (20.4)	116 (35.6)	12 (6.9)	1 (0.5)	–
Infection	73 (21.9)	84 (26.3)	152 (23.2)	178 (27.3)	112 (33.7)	94 (28.6)	42 (24.1)	56 (27.7)	593 (31.5)
Peripheral neuropathies	55 (16.5)	61 (19.1)	117 (17.9)	118 (18.1)	50 (15.1)	49 (14.9)	17 (9.8)	29 (14.4)	379 (20.1)
Mucositis	38 (11.4)	53 (16.6)	79 (12.1)	94 (14.4)	37 (11.1)	44 (13.4)	19 (10.9)	23 (11.4)	328 (17.4)
Anaemia	65 (19.5)	51 (15.9)	125 (19.1)	104 (16.0)	61 (18.4)	66 (20.1)	16 (9.2)	12 (5.9)	293 (15.6)
Pneumonia	37 (11.1)	33 (10.3)	73 (11.1)	68 (10.4)	49 (14.8)	31 (9.4)	11 (6.3)	10 (5.0)	162 (8.6)
Febrile neutropenia	15 (4.5)	24 (7.5)	32 (4.9)	48 (7.4)	4 (1.2)	10 (3.0)	0	0	71 (3.8)
Thrombocytopenia	12 (3.6)	16 (5.0)	24 (3.7)	23 (3.5)	20 (6.0)	30 (9.1)	1 (0.6)	1 (0.5)	137 (7.3)
AESI Worst grade ≥3	4 (1.2)	4 (1.3)	6 (0.9)	5 (0.8)	2 (0.6)	9 (2.7)	1 (0.6)	1 (0.5)	44 (2.3)
Laboratory value grade 3,4 platelets	4 (1.2)	4 (1.3)	5 (0.8)	5 (0.8)	3 (0.9)	14 (4.3)	0	1 (0.5)	–
Sepsis	2 (0.6)	4 (1.3)	4 (0.6)	10 (1.5)	3 (0.9)	2 (0.6)	1 (0.6)	0	17 (0.9)

Abbreviations:– = information not collected or data not summarised

Adverse events based on competitor labelling

	Adenocarcinoma 1199.13		All patients 1199.13		Adenocarcinoma 1199.14		All patients nintedanib monotherapy		All patients nintedanib
	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Nintedanib ≤200 mg b.i.d.	Nintedanib >200 mg b.i.d.	Nintedanib
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients treated	333 (100.0)	320 (100.0)	655 (100.0)	652 (100.0)	332 (100.0)	329 (100.0)	174 (100.0)	202 (100.0)	1884 (100.0)
Patients with any AESI	291 (87.4)	295 (92.2)	560 (85.5)	579 (88.8)	298 (89.8)	304 (92.4)	161 (92.5)	196 (97.0)	1759 (93.4)
Cutaneous serious skin reactions	35 (10.5)	50 (15.6)	70 (10.7)	85 (13.0)	32 (9.6)	39 (11.9)	2 (1.1)	10 (5.0)	219 (11.6)
Rash	29 (8.7)	40 (12.5)	53 (8.1)	72 (11.0)	66 (19.9)	64 (19.5)	11 (6.3)	23 (11.4)	366 (19.4)
Hand-foot syndrome	1 (0.3)	1 (0.3)	4 (0.6)	3 (0.5)	2 (0.6)	1 (0.3)	0	0	20 (1.1)
Hypothyroidism	0	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.3)	6 (1.8)	2 (1.1)	0	14 (0.7)
Osteonecrosis	0	1 (0.3)	0	1 (0.2)	1 (0.3)	1 (0.3)	0	0	2 (0.1)
Pulmonary hypertension	0	0	0	1 (0.2)	1 (0.3)	0	0	0	1 (0.1)

Source: [U13-1504, Table 15.3.2.3: 1, and Table 15.3.2.4.2.3: 1; U12-2160, Table 15.3.2.4.2.3: 1, U13-1507, Appendix 1, Table 6.1.1 and Table 6.1.3]

Cardiac events

	Adenocarcinoma 1199.13		All patients 1199.13		Adenocarcinoma 1199.14		All patients nintedanib monotherapy		All patients nintedanib
	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Nintedanib ≤200 mg b.i.d.	Nintedanib >200 mg b.i.d.	Nintedanib
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients treated	333 (100.0)	320 (100.0)	655 (100.0)	652 (100.0)	332 (100.0)	329 (100.0)	174 (100.0)	202 (100.0)	1884 (100.0)
Patients with any AESI	291 (87.4)	295 (92.2)	560 (85.5)	579 (88.8)	298 (89.8)	304 (92.4)	161 (92.5)	196 (97.0)	1759 (93.4)
Cardiac arrhythmias	25 (7.5)	37 (11.6)	57 (8.7)	67 (10.3)	28 (8.4)	26 (7.9)	19 (10.9)	4 (2.0)	154 (8.2)
Cardiac failure	22 (6.6)	25 (7.8)	46 (7.0)	43 (6.6)	40 (12.0)	31 (9.4)	14 (8.0)	9 (4.5)	164 (8.7)
Myocardial infarction	4 (1.2)	4 (1.3)	8 (1.2)	5 (0.8)	9 (2.7)	5 (1.5)	3 (1.7)	3 (1.5)	23 (1.2)
Cardiac arrest	1 (0.3)	2 (0.6)	2 (0.3)	2 (0.3)	2 (0.6)	3 (0.9)	0	0	6 (0.3)
Cardiac failure (tailored)	2 (0.6)	0	5 (0.8)	5 (0.8)	6 (1.8)	3 (0.9)	2 (1.1)	1 (0.5)	16 (0.8)
Sudden death	0	0	0	0	2 (0.6)	1 (0.3)	0	1 (0.5)	2 (0.1)

Source: [U13-1504, Table 15.3.2.3: 1, and Table 15.3.2.4.2.3: 1; U12-2160, Table 15.3.2.4.2.3: 1; U13-1507, Appendix 1, Table 6.1.1 and Table 6.1.3]

Other adverse events

	Adenocarcinoma 1199.13		All patients 1199.13		Adenocarcinoma 1199.14		All patients nintedanib monotherapy		All patients nintedanib
	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Nintedanib ≤200 mg b.i.d.	Nintedanib >200 mg b.i.d.	Nintedanib
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients treated	333 (100.0)	320 (100.0)	655 (100.0)	652 (100.0)	332 (100.0)	329 (100.0)	174 (100.0)	202 (100.0)	1884 (100.0)
Patients with any AESI	291 (87.4)	295 (92.2)	560 (85.5)	579 (88.8)	298 (89.8)	304 (92.4)	161 (92.5)	196 (97.0)	1759 (93.4)
Interstitial lung disease	1 (0.3)	4 (1.3)	5 (0.8)	9 (1.4)	3 (0.9)	1 (0.3)	0	0	16 (0.8)
Photosensitivity conditions	2 (0.6)	1 (0.3)	5 (0.8)	4 (0.6)	0	4 (1.2)	1 (0.6)	1 (0.5)	15 (0.8)
Anaphylactic reaction	1 (0.3)	0	3 (0.5)	1 (0.2)	0	0	0	0	4 (0.2)

Source: [U13-1504, Table 15.3.2.3: 1, and Table 15.3.2.4.2.3: 1, U12-2160, Table 15.3.2.4.2.3: 1, U13-1507, Appendix 1, Table 6.1.1 and Table 6.1.3]

The most commonly reported AESIs occurring in more than 30% of patients with adenocarcinoma in trial 1199.13 treated with nintedanib in combination with docetaxel were neutropenia (SSC), diarrhoea (SSC), fatigue (SSC), and liver-related investigation (SMQ).

Differences between the nintedanib and placebo arms of ≥5% of patients with adenocarcinoma were observed for: diarrhoea, liver related investigations, specific liver related investigation, nausea (SSC), vomiting (SSC), mucositis (SMQ: 16.6% nintedanib; 11.4% placebo), and cutaneous serious skin reactions (SSC: 15.6% nintedanib; 10.5% placebo).

Diarrhoea

The SSC diarrhoea was defined by the MedDRA PT 'diarrhoea'.

Table 47: Incidence and clinical consequences of the SSC diarrhoea in phase III trials 1199.13 and 1199.14 (SAF-1) – TS

	Adenocarcinoma 1199.13		All patients 1199.13		Adenocarcinoma 1199.14	
	Placebo n (%)	Nintedanib n (%)	Placebo n (%)	Nintedanib n (%)	Placebo n (%)	Nintedanib n (%)
Patients	333 (100.0)	320 (100.0)	655 (100.0)	652 (100.0)	332 (100.0)	329 (100.0)
Patients with diarrhoea	82 (24.6)	139 (43.4)	143 (21.8)	276 (42.3)	49 (14.8)	115 (35.0)
Considered drug-related	53 (15.9)	109 (34.1)	99 (15.1)	217 (33.3)	26 (7.8)	84 (25.5)
Serious	7 (2.1)	6 (1.9)	13 (2.0)	16 (2.5)	1 (0.3)	3 (0.9)
Worst CTCAE grade						
Grade 1	46 (13.8)	62 (19.4)	75 (11.5)	135 (20.7)	34 (10.2)	69 (21.0)
Grade 2	24 (7.2)	57 (17.8)	51 (7.8)	98 (15.0)	11 (3.3)	34 (10.3)
Grade 3	11 (3.3)	19 (5.9)	16 (2.4)	39 (6.0)	4 (1.2)	11 (3.3)
Grade 4	1 (0.3)	1 (0.3)	1 (0.2)	3 (0.5)	0	0
Grade 5	0	0	0	1 (0.2)	0	1 (0.3)
Outcome of diarrhoea						
Recovered	79 (23.7)	134 (41.9)	139 (21.2)	264 (40.5)	46 (13.9)	110 (33.4)
Not yet recovered	2 (0.6)	5 (1.6)	3 (0.5)	7 (1.1)	2 (0.6)	1 (0.3)
Sequelae	0	0	0	0	0	0
Fatal	0	0	0	1 (0.2)	0	1 (0.3)
Unknown	1 (0.3)	0	1 (0.2)	4 (0.6)	1 (0.3)	3 (0.9)
Clinical consequences						
Permanent discontinuation of last study medication	1 (0.3)	3 (0.9)	1 (0.2)	8 (1.2)	1 (0.3)	1 (0.3)
Dose reduction of nintedanib or placebo	11 (3.3)	26 (8.1)	16 (2.4)	47 (7.2)	0	14 (4.3)
Therapy required	39 (11.7)	96 (30.0)	77 (11.8)	184 (28.2)	20 (6.0)	69 (21.0)

Percentages were calculated based on the number of patients in the treatment arm of the analysis set.

Age ≥65 years, female, ECOG performance score >0 at baseline, body weight <50 kg at baseline, and geographic region Asia were defined before data analysis as potential risk factors for diarrhoea. The number of patients with diarrhoea of worst grade ≥3 was low (20 patients nintedanib; 12 patients placebo), and the 95% CIs were very wide and overlapping for the risk and complementary groups. No risk factors were identified in patients with adenocarcinoma in trial 1199.13.

In patients experiencing diarrhoea in the overall population (study 1199.13), the median time to the first onset of diarrhoea of any CTCAE grade was comparable between the study treatment groups: 10 days for placebo (5, 47 days; P25% 75%) versus 13 days for nintedanib (5, 47 days; P25% 75%). Results were consistent for the adenocarcinoma. In all patients, median time to the first onset of diarrhoea of grade ≥3 was 6 days for placebo (4, 25 days; P25% 75%) versus 28 days for nintedanib (7, 86 days; P25% 75%). A similar trend was seen for the adenocarcinoma population of study 1199.13 with diarrhoea of grade ≥3.

The median duration of diarrhoea (all severity grades) was prolonged in the nintedanib arm as compared to the placebo arm in both the overall population (placebo: 6 days versus nintedanib: 12 days) and the adenocarcinoma population (placebo: 5 days versus nintedanib: 16.5 days). A similar trend was seen for both populations with diarrhoea of grade ≥3.

Diarrhoea was generally manageable with supportive care, dose interruption, and dose reduction, and led to treatment discontinuation only in a few patients. In the majority of cases, the patient recovered, however, in one case the outcome of the diarrhoea was fatal in the nintedanib arm. Very few events led to permanent discontinuation.

Liver enzyme elevations

Table 48: Incidence and clinical consequences of the SMQ liver-related investigation in phase III trials 1199.13 and 1199.14 (SAF-1), in nintedanib phase I/II monotherapy trials (SAF-2), and in patients with cancer treated with nintedanib (SAF-3) – TS

	Adenocarcinoma 1199.13		All patients 1199.13		Adenocarcinoma 1199.14		All patients nintedanib monotherapy		All patients nintedanib
	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Nintedanib ≤200 mg b.i.d.	Nintedanib >200 mg b.i.d.	Nintedanib
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients	333 (100.0)	320 (100.0)	655 (100.0)	652 (100.0)	332 (100.0)	329 (100.0)	174 (100.0)	202 (100.0)	1884 (100.0)
Patients with liver-related investigation	49 (14.7)	137 (42.8)	89 (13.6)	219 (33.6)	103 (31.0)	168 (51.1)	29 (16.7)	72 (35.6)	688 (36.5)
Considered drug-related	31 (9.3)	108 (33.8)	59 (9.0)	174 (26.7)	75 (22.6)	144 (43.8)	15 (8.6)	63 (31.2)	567 (30.1)
Serious	1 (0.3)	3 (0.9)	1 (0.2)	5 (0.8)	1 (0.3)	2 (0.6)	3 (1.7)	17 (8.4)	37 (2.0)
Worst CTCAE grade									
Grade 1	30 (9.0)	27 (8.4)	46 (7.0)	48 (7.4)	34 (10.2)	20 (6.1)	1 (0.6)	8 (4.0)	127 (6.7)
Grade 2	13 (3.9)	61 (19.1)	31 (4.7)	101 (15.5)	39 (11.7)	51 (15.5)	8 (4.6)	15 (7.4)	219 (11.6)
Grade 3	6 (1.8)	48 (15.0)	12 (1.8)	68 (10.4)	30 (9.0)	96 (29.2)	19 (10.9)	46 (22.8)	329 (17.5)
Grade 4	0	1 (0.3)	0	2 (0.3)	0	1 (0.3)	1 (0.6)	3 (1.5)	11 (0.6)
Grade 5	0	0	0	0	0	0	0	0	2 (0.1)
Outcome of liver-related investigation									
Recovered	37 (11.1)	107 (33.4)	68 (10.4)	168 (25.8)	86 (25.9)	135 (41.0)	18 (10.3)	58 (28.7)	511 (27.1)
Not yet recovered	10 (3.0)	21 (6.6)	17 (2.6)	32 (4.9)	7 (2.1)	20 (6.1)	8 (4.6)	11 (5.4)	123 (6.5)
Sequelae	0	1 (0.3)	0	3 (0.5)	0	0	0	0	3 (0.2)
Fatal	0	0	0	0	0	0	0	0	2 (0.1)
Unknown	2 (0.6)	8 (2.5)	4 (0.6)	16 (2.5)	10 (3.0)	13 (4.0)	3 (1.7)	3 (1.5)	49 (2.6)
Clinical consequences									
Permanent discontinuation of last study medication	2 (0.6)	7 (2.2)	4 (0.6)	11 (1.7)	8 (2.4)	14 (4.3)	3 (1.7)	13 (6.4)	63 (3.3)
Dose reduction of nintedanib or placebo	2 (0.6)	32 (10.0)	4 (0.6)	50 (7.7)	10 (3.0)	70 (21.3)	8 (4.6)	24 (11.9)	202 (10.7)
Therapy required	16 (4.8)	65 (20.3)	31 (4.7)	100 (15.3)	17 (5.1)	25 (7.6)	12 (6.9)	9 (4.5)	177 (9.4)

Percentages were calculated based on the number of patients in the treatment arm of the analysis set.
Source: [U13-1504, Appendix 16.1.9.2, Table 7.2.3.18, and Table 7.3.2.3.17; U12-2160, Appendix 16.1.9.2, Table 7.3.2.3.17, U13-1507, Appendix 1, Table 6.2.1.1 and Table 6.2.2.1]

In the overall population (study 1199.13), the median time to the first onset of the liver enzyme elevation (AST and/or ALT any CTCAE grade based on laboratory measurements) was similar between the study groups: 16 days placebo (8, 43 days; P25% 75%) vs 14 days nintedanib (8, 29 days; P25% 75%). This implied that half of the patients that developed a 'liver enzyme elevation' in the nintedanib arm had the first event within the first 14 days after first administration of study medication. Similar results were observed for patients with adenocarcinoma (all severity grades) (study 1199.13).

Median time to first onset of grade ≥3 liver enzyme elevations was 21 days (14, 45 days; P25% 75%) in all patients experiencing this event in the nintedanib arm and 26 days (15, 45 days; P25% 75%) in the adenocarcinoma patients experiencing this event in the nintedanib arm.

These increases were reversible in the majority of cases. The median duration of liver enzyme elevation of any grade based on laboratory values was 15 days (grade ≥3, was 8 days) for both all patients as well as adenocarcinoma patients. Most of the patients recovered and only few events led to permanent discontinuation. Most events occurred within the first 3 months of treatment.

Nausea and Vomiting

The SSC nausea was defined by the MedDRA preferred terms 'nausea' and 'retching'. In the overall population (all severity grades, study 1199.13), more patients had nausea in the nintedanib than in the placebo treatment group (placebo 18.0% vs nintedanib 24.2%). Consistent with this, more patients in the adenocarcinoma population experienced nausea in the nintedanib than in the placebo treatment group (placebo 17.7% vs nintedanib 28.4%).

In the overall population (all severity grades), the median time to the first onset of nausea was greater for patients experiencing the event in the nintedanib than in the placebo treatment group: 13 days placebo (4, 34 days; P25% 75%) vs 21 days nintedanib (4, 64 days; P25% 75%). The corresponding results for the adenocarcinoma population (all severity grades, study 1199.13) showed that the time to first onset for patients experiencing the event in the placebo and nintedanib groups were similar; 20 days placebo (5, 51 days; P25% 75%) vs 22 days nintedanib (3, 62 days; P25% 75%). Median time to first onset regarding nausea of grade ≥3 was not considered due to the small sample size. Median duration of nausea was about 3 weeks (overall and adenocarcinoma population; all grades and grade ≥3). For the duration of nausea with CTCAE grade ≥3, the worst CTCAE grade was collected.

The SSC vomiting was defined by the MedDRA preferred terms 'vomiting' and 'regurgitation'. However, there were no 'regurgitation' AEs reported. In the overall population (all severity grades, study 1199.13), more patients had vomiting in the nintedanib arm than in the placebo treatment group (nintedanib 16.9% vs. placebo 9.3%). Consistent with this, more patients in the adenocarcinoma population experienced vomiting in the nintedanib than in the placebo treatment group (nintedanib 19.4% vs placebo 12.3%). There was almost no difference between the nintedanib and placebo treatment groups for the time to first onset of AEs within the SSC vomiting. In the overall population (all severity grades, study 1199.13), the median time to the first onset of vomiting was similar for patients experiencing vomiting in the placebo and nintedanib treatment groups: 25 days placebo (7, 49 days; P25% 75%) vs 23 days nintedanib (5, 59 days; P25% 75%). Numbers on median time to first onset regarding grade ≥3 vomiting were not considered due to the small sample size both in the overall and the adenocarcinoma populations. Median duration of vomiting was about 1 week (overall and adenocarcinoma population; all grades and grade ≥3). It is noted that for the duration of vomiting with CTCAE grade ≥3, the worst CTCAE grade was collected.

Hepatic failure

In pivotal trial 1199.13 (all patients) hepatic failure was more common in the nintedanib arm [n=8 (1.2%), grade ≥3: n=5 (0.8%)] than in the placebo arm [n=1 (0.2%), grade ≥3: no cases]. Hepatic failure was also more frequent in the nintedanib arm (n=8, 2.4%) than in the placebo arm (n=4, 1.2%) of trial 1199.14 (adenocarcinoma). AEs within the SMQ hepatic failure were reported in 2.3% of patients on nintedanib monotherapy ≤200 mg b.i.d., 5.9% of patients on nintedanib monotherapy >200 mg b.i.d.,and 3.3% of patients with cancer treated with nintedanib.

The majority of the reported AEs classified as hepatic failure, did not correspond with hepatocellular drug-induced liver injury (DILI). Only one patient (in study 1199.14) has been identified to possible have DILI. In this case ALT and AST increased and bilirubin was marginally increased. Treatment with nintedanib was interrupted. Liver parameters returned to normal. When re-challenged the ALT and AST increased again, but bilirubin was normal or minimally elevated. This patient did not have liver metastases or any other condition that could have introduced bias. However, the patient did not show clinical signs of jaundice. The patient continued treatment until day 268.

Bleeding

The MedDRA SMQ 'bleeding' was used. In the overall population (all severity grades, study 1199.13), there was a slight imbalance of patients between the treatment arms developing a bleeding event (placebo 11.6% vs nintedanib 14.1%). This was due to more patients with low grade bleeding in the nintedanib arm as compared to the placebo arm in the squamous cell cancer population (10.8% vs 17.1%). In the adenocarcinoma population bleeding events were rather balanced between the treatment groups (placebo 11.1% vs nintedanib 10.9%). The majority of bleeding events were considered of mild to moderate severity (e.g. epistaxis) and almost all patients recovered from the bleeding events. There was almost no difference between the nintedanib and placebo treatment groups for the time to first onset of bleeding. In the overall population (all severity grades), the median time to the first onset of bleeding was the same for patients developing a bleeding event in the two treatment groups: 28 days placebo (11, 86 days; P25% 75%) vs 28 days nintedanib (8, 73 days; P25% 75%). The corresponding results for the adenocarcinoma population (all severity grades) were consistent with the overall population: 27 days placebo (13, 98 days; P25% 75%) vs 25 days nintedanib (8, 70 days; P25% 75%). The median duration of bleeding, was 10.5 days (overall population, and 5 days for the adenocarcinoma population, all severity grades).

The most commonly reported bleeding event in study 1199.13 was epistaxis (reported by 2.7% of patients in the placebo arm and 4.9% in the nintedanib arm); epistaxis was mainly of grade 1 or 2. The majority of fatal bleeding events were tumour-associated. There were no imbalances of respiratory or fatal bleedings for adenocarcinoma patients (respiratory bleeding: 6.0% vs 4.7%; fatal bleeding: 0.6% vs 0.9%) and no intracerebral bleeding was reported.

Thromboembolic events

The overall rate of patients with AEs within the SMQ thromboembolic events was low. In patients with adenocarcinoma in trial 1199.13, there was no difference between the treatment arms in the overall rate of patients with thromboembolic events (5.3% nintedanib; 5.4% placebo, grade ≥3 2.5% vs. 3.3%). AEs within the AESI arterial thromboembolism were reported in 0.9% of patients in the nintedanib arm and 2.1% of patients in the placebo arm (0.9% grade ≥3 in each arm); AEs within the SMQ venous thromboembolism were reported in 2.8% of patients (0.9% grade ≥3) in the nintedanib arm, and 1.2% of patients (0.6% grade ≥3) in the placebo arm. The imbalance was mainly due to deep vein thrombosis and there was no difference of pulmonary embolism between the treatment arms.

There was no meaningful difference in the rate of patients with AEs within the SMQ thromboembolic events between the treatment arms of all patients in trial 1199.13, or patients with adenocarcinoma in trial 1199.14. There was no indication of a difference between the dose groups in the frequency of patients with thromboembolic events in nintedanib monotherapy phase I/II trials. The overall frequency of patients with thromboembolic events was 4.9% of patients with cancer treated with nintedanib (including 2.9% of patients with AEs within the SMQ venous thromboembolism, and 0.8% of patients with AEs within the AESI term arterial thromboembolism).

The number of patients with grade 5 thromboembolic events in SAF-1 was small and balanced across treatment arms. In the 1199.13 adenocarcinoma population there was 1 (0.3%) patient on placebo and 3 (0.9%) patients on nintedanib who developed a fatal thromboembolic event. In all patients in 1199.13 there were 4 (0.6%) patients on placebo and 5 (0.8%) patients on nintedanib. In the 1199.14 adenocarcinoma population there were no patients on placebo and 1 (0.3%) patient on nintedanib who had a fatal thromboembolic event.

Perforation (gastro-intestinal and non-gastro intestinal)

In patients with adenocarcinoma in trial 1199.13, the frequency of patients with AEs within the SSC gastrointestinal perforation (0.3% in each treatment arm) and in the SSC non-gastrointestinal perforation (1.3% nintedanib; 0.3% placebo) was low. The reported AEs in the SSC non-gastrointestinal perforation did not include any perforation, however 4 patients in the nintedanib arm, and 1 patient in the placebo arm experienced an abscess located in the lung or chest wall. Some of the abscesses were associated with tumour-related conditions or with myelosupression. The reported abscesses were not regarded as precursors or consequences of a perforation.

Sepsis

Sepsis was more frequent in the nintedanib arm (1.5%, n=10) than in the placebo arm (0.6%, n=4) of pivotal trial 1199.13 (all patients, study1199.13). 7/10 AEs of sepsis in the nintedanib arm, and 1/4 AEs of sepsis in the placebo arm were fatal. 3/7 patients with fatal sepsis in the nintedanib arm also had neutropenia.

The proportion of patients in the adenocarcinoma population for which sepsis was reported was: placebo 0.6% (2/333) vs nintedanib 1.3% (4/320). Concerning SAF-2 (nintedanib monotherapy), sepsis was only registered in 1 patient (0.6%) with a starting dose ≤200 mg b.i.d. and not in any patients with a starting dose >200 mg b.i.d.

In the overall population (all severity grades), the median time to the first onset for patients developing sepsis was: 59 days placebo (49, 68 days; P25% 75%) vs 49 days nintedanib (29,52 days; P25% 75%)]. These results were consistent for the adenocarcinoma population (all severity grades). The median duration of sepsis in the nintedanib arm was 3.5 days in the overall population and 4.5 days in the adenocarcinoma population. The median time for onset of sepsis was cycle 3 or 4 of chemotherapy administration.

Six of the 11 drug-related fatal events in the nintedanib arm were due to sepsis (n=3), septic shock (n=2) or neutropenic infection (n=1). The drug-related fatal AEs of sepsis, septic shock and neutropenic infection occurred in patients with advanced second-line metastatic NSCLC in the context of concomitant docetaxel use, a known myelotoxic agent. Two patients had concomitant neutropenia and in two additional patients neutropenia might have played a role. Apart from the relationship to neutropenia (and concomitant docetaxel use) no other modifiable risk factor was identified (see also section on serious adverse events/deaths).

Neutropenia

Table 49: Patients with neutropenia (based on AEs within the SSC or laboratory values), febrile neutropenia (SSC), infection (SSC), or sepsis (SSC) in the treatment period / TS – all patients (Study 1199.13)

	Placebo		Nintedanib	
Number of patients	655	(100.0)	652	(100.0)
Any neutropenia (AE within SSC)	323	(49.3)	326	(50.0)
Any neutropenia (laboratory value)	447	(68.2)	483	(74.1)
Neutropenia of CTCAE grade ≥3 (AE within SSC)	273	(41.7)	292	(44.8)
Neutropenia of CTCAE grade 3,4 (laboratory value)	328	(50.1)	366	(56.1)
Neutropenia of CTCAE grade ≥4 (AE within SSC)	194	(29.6)	220	(33.7)
Neutropenia of CTCAE grade 4 (laboratory value)	218	(33.3)	260	(39.9)
Febrile neutropenia (AE within SSC)	32	(4.9)	48	(7.4)
Infection of CTCAE grade ≥3 (AE within SSC)	41	(6.3)	45	(6.9)
Infection of CTCAE grade 4,5 (AE within SSC)	14	(2.1)	18	(2.8)
Sepsis (AE within SSC)	4	(0.6)	10	(1.5)
Pneumonia (AE within SSC)	73	(11.1)	68	(10.4)

Source data: Appendix 16.1.9.1, Table 7.1.3.34

Three patients (0.5%) in the placebo arm experienced a CTCAE grade 4 AE of infection compared to five patients (0.8%) in the nintedanib arm. All patients with a CTCAE grade 4 infection recovered except for three patients in the nintedanib arm that had an unknown outcome. Of the three patients with an unknown outcome two patients experienced a fatal AE of respiratory failure and the third patient experienced a fatal AE of neutropenic infection. The fatal events were temporally related to the grade 4 infection AEs. Seventeen patients (2.6%) in the placebo arm compared to 29 patients (4.4%) in the nintedanib arm experienced a CTCAE grade 4 AE of febrile neutropenia. All patients with a CTCAE grade 4 AE of febrile neutropenia recovered.

Overall, of the 178 patients with an AE within the infections and infestations SOC in the nintedanib arm, five patients had a CTCAE grade 4 AE. The AEs of infection resolved in two patients. In the remaining three patients, the outcome of the grade 4 infections was unknown but the patients developed concomitant fatal AEs of respiratory failure and neutropenic infection.

Cutaneous adverse reactions

There were no grade 5 events of cutaneous serious skin reactions or rash in the nintedanib arm of study 1199.13.

Adverse events within the special MedDRA query (SMQ) cutaneous serious skin reactions occurred in 10.7% of the patients treated with placebo and 13.0% of the patients treated with nintedanib. Stomatitis was the most reported preferred term (PT) and accounted for the majority of events in the SMQ cutaneous serious skin reactions (placebo 8.7% vs. nintedanib 9.7%). There were no grade 5 events in the SMQ cutaneous serious skin reactions and few patients had grade 3 or 4 events in the SMQ cutaneous serious skin reactions (placebo 0.5% vs. nintedanib 0.8%); all represented events of stomatitis (including an event on placebo with a PT of mouth ulceration).

Cutaneous serious skin reactions not associated with stomatitis in the nintedanib group were primarily attributable to reports of exfoliative rash. All cases of exfoliative rash were of grade 1 or 2. None of the patients experienced Stevens Johnson Syndrome or Toxic Epidermal Necrolysis.

Adverse events within the special search category of rash occurred in 8.1% of the patients treated with placebo and 11.0% of the patients treated with nintedanib. The vast majority of patients had events of grade 1 or 2 in severity in both arms. The PTs rash, dermatitis acneiform, exfoliative rash, erythema, skin ulcer and dermatitis were the most reported events in both arms and were all of grade 1 or 2 in severity.

Mucositis

The special search category (SSC) of mucositis overlapped with the SMQ cutaneous serious skin reactions as both included the term stomatitis. Similar to what was seen with the SMQ cutaneous serious skin reactions, stomatitis was responsible for the majority of events in the SMQ mucositis.

In study 1199.13, AEs in the SSC mucositis were slightly more frequent in the nintedanib arm than in the placebo arm (AEs of any grade and CTCAE grade ≥3) with a slightly more pronounced difference between the treatment arms in patients with adenocarcinoma. No obvious risk factors for the development of mucositis could be identified in study 1199.13. Stomatitis was the most frequently reported AE in the SSC mucositis and is a known adverse drug reaction of docetaxel and of other angiogenesis inhibitors.

Peripheral neuropathy

In the overall population of study 1199.13, AEs in the SSC peripheral neuropathy were balanced between the treatment arms; however, in patients with adenocarcinoma they were slightly more frequent in the nintedanib arm than in the placebo arm (AEs of any grade and of CTCAE grade ≥3). Peripheral neuropathy is a known adverse drug reaction of docetaxel and also of other angiogenesis inhibitors. AEs in the SSC peripheral neuropathy were also reported in patients who received nintedanib monotherapy; however, some of these patients may have had pre-existing neuropathy from prior anti-cancer therapy. In study 1199.13 (overall population and patients with adenocarcinoma) no risk factor for the development of peripheral neuropathy under treatment with nintedanib in combination with docetaxel could be identified.

Hypertension

The overall frequency of patients with AEs within the SMQ hypertension was lower than expected from other VEGFR inhibitors but was more frequent in the nintedanib arm than in the placebo arm in patients with adenocarcinoma in trial 1199.13 (3.4% nintedanib; 0.6% placebo). The AEs were mostly of grade 1 or 2.

Cardiac events

Cardiac failure

Regarding pivotal trial 1199.13 (all patients), the most common PT in both treatment arms was oedema peripheral (5.5% vs. 6.4%).

Cardiac arrhythmias

In pivotal trial 1199.13 (all patients) cardiac arrhythmias were more common in the nintedanib arm (10.3%) than in the placebo arm (8.7%). In the adenocarcinoma patients, cardiac arrhythmias were also more common in the nintedanib arm (11.6%) than in the placebo arm (7.5%). However, in spite of higher frequency of cardiac arrhythmias in nintedanib treated patients, other cardiac events occurred at comparable rates in both treatment arms. The most common PT within the SMQ cardiac arrhythmias in trial 1199.13 (all patients) were atrial fibrillation (nintedanib arm: 2.3% vs. placebo arm: 1.4%), sinus tachycardia (1.7% vs. 1.2%) and tachycardia (1.2% vs. 0.8%). ECG was performed at screening, start of each treatment cycle (before treatment) and at end of treatment (EOT).

No QT prolongation was observed for nintedanib in the clinical trial program. Potential QT interval prolongation was assessed in phase II trial 1199.26 (patients with renal cell carcinoma receiving nintedanib monotherapy). No QT prolongation was identified during 15 days of exposure to nintedanib.

Immunological events

In the pivotal trial 1199.13, concomitant chemotherapy consisted of docetaxel which is known to cause very common immunological adverse events such hypersensitivity (grade 3 and 4 AE 5.3%). In study 1199.13, overall incidence of patients with anaphylactic reactions was comparable between the nintedanib group and the placebo group in both the overall population (nintedanib: 0.2% vs. placebo: 0.5%) and the adenocarcinoma population (nintedanib 0% vs. placebo 0.3%).

The overall frequency of patients with preferred terms from the system organ class immune system disorders was numerically lower in the nintedanib group as compared to the placebo group. This was applicable for both the overall population (nintedanib 1.8% vs. placebo 2.3) and the adenocarcinoma population (nintedanib 2.5% vs. placebo 3.3%). The vast majority of the immunological events were non-life-threatening. There were only single cases of grade 4 severity and there were no fatal cases.

Pneumonitis and reduction in LVEF

The overall percentage of patients with interstitial lung disease (ILD) in the 1199.13 trial was low and below the threshold of ILD incidence reported in NSCLC patients treated with chemotherapy. Although LVEF was not routinely measured in the 1199.13 trial, the two preferred terms “ejection fraction decreased” and “low cardiac output syndrome”, which are considered indicative for reduced LVEF were not reported for nintedanib-treated patients in this trial. Similarly low findings of ILD or ejection fraction decreased were observed in the overall population of cancer patients exposed to nintedanib (SAF-3).

Overdose

The most frequent AEs reported at higher doses of nintedanib (>200 mg b.i.d.) were effects on the gastrointestinal system (diarrhoea, nausea, abdominal pain) and liver-related investigation. In most cases, AEs were reversible upon dose reduction or discontinuation of nintedanib treatment, and administration of appropriate concomitant medication. In summary, nintedanib doses >200 mg increased the frequencies of the most common AEs which were also observed at doses ≤200 mg b.i.d.; no additional nintedanib-related AEs were identified in the high-dose group.

The highest dose of nintedanib applied in systematic phase I trials was 450 mg q.d. The BI safety database of nintedanib was searched for any cases of accidental overdose and for any AEs associated with a nintedanib overdose. Overall, 2 patients were treated erroneously with doses higher than the recommended dose of 200 mg b.i.d (overdose of maximum 600 mg bid up to eight days). AE occurred consistent with the known safety profile of nintedanib, i.e. increased liver enzymes and gastrointestinal symptoms. All patients recovered from these AEs.

Adverse drug reactions

Adverse drug reactions were identified comparing treatment with nintedanib plus docetaxel against placebo plus docetaxel in patients with locally advanced, or metastatic based on the global, double-blind randomised pivotal phase 3 trial 1199.13 (LUME-Lung 1). Criteria taken into account were (1) relative increase in adverse event frequency over control arm, (2) consistent trend across clinical studies, (3) known class effects, (4) compatible

temporal association, (5) positive dose-response relationship, and (6) biological plausibility (adverse mechanism).

Adverse drug reactions are presented in the table below.

Table 50: Adverse event crude incidences (all grades) in study 1199.13 (adenocarcinoma population) - treated set

	Nintedanib	
ADS Term	N	(%)
Number of patients	320	(100.0)
Neutropenia	176	(55.0)
Diarrhoea	139	(43.4)
ALT increased	124	(38.8)
AST increases	100	(31.3)
Nausea	91	(28.4)
Vomiting	62	(19.4)
Decreased appetite	75	(23.4)
Peripheral neuropathies	61	(19.1)
Mucositis	53	(16.6)
Rash	40	(12.5)
ALKP increased	32	(10.0)
Febrile neutropenia	24	(7.5)
Bleeding	35	(10.9)
Hyperbilirubinaemia	20	(6.3)
Abdominal pain	32	(10.0)
Electrolyte imbalance	46	(14.4)
Abscesses	4	(1.3)
Hypertension	11	(3.4)
Dehydration	6	(1.9)
Sepsis	4	(1.3)
Venous thromboembolism	9	(2.8)
GI perforation	1	(0.3)

Serious adverse event / deaths / other significant events

Serious adverse events

Table 51: Serious adverse events in patients with adenocarcinoma in phase III trials 1199.13 (incidence > 1% in either treatment arm) – by preferred term and worst CTCAE grade, all treatment courses

	Placebo					Nintedanib				
	Any grade n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Patients	333 (100.0)	333 (100.0)	333 (100.0)	333 (100.0)	333 (100.0)	320 (100.0)	320 (100.0)	320 (100.0)	320 (100.0)	320 (100.0)
Patients with SAEs	107 (32.1)	14 (4.2)	33 (9.9)	27 (8.1)	32 (9.6)	111 (34.7)	11 (3.4)	19 (5.9)	25 (7.8)	56 (17.5)
Febrile neutropenia	6 (1.8)	0	2 (0.6)	4 (1.2)	0	18 (5.6)	0	4 (1.3)	14 (4.4)	0
Malignant neoplasm progression	8 (2.4)	0	0	0	7 (2.1)	12 (3.8)	0	0	0	12 (3.8)
Dyspnoea	18 (5.4)	2 (0.6)	9 (2.7)	0	7 (2.1)	9 (2.8)	1 (0.3)	0	2 (0.6)	6 (1.9)
Pneumonia	12 (3.6)	6 (1.8)	5 (1.5)	0	1 (0.3)	9 (2.8)	2 (0.6)	4 (1.3)	1 (0.3)	2 (0.6)
Diarrhoea	7 (2.1)	1 (0.3)	5 (1.5)	1 (0.3)	0	6 (1.9)	1 (0.3)	4 (1.3)	1 (0.3)	0
General physical health deterioration	5 (1.5)	1 (0.3)	1 (0.3)	0	3 (0.9)	6 (1.9)	0	1 (0.3)	0	5 (1.6)
Neutropenia	11 (3.3)	0	1 (0.3)	10 (3.0)	0	6 (1.9)	1 (0.3)	0	5 (1.6)	0
Asthenia	2 (0.6)	1 (0.3)	0	0	1 (0.3)	5 (1.6)	1 (0.3)	3 (0.9)	0	1 (0.3)
Respiratory failure	1 (0.3)	0	0	0	1 (0.3)	5 (1.6)	0	0	0	5 (1.6)
Vomiting	4 (1.2)	2 (0.6)	2 (0.6)	0	0	5 (1.6)	3 (0.9)	1 (0.3)	1 (0.3)	0
Atrial fibrillation	0	0	0	0	0	4 (1.3)	1 (0.3)	1 (0.3)	2 (0.6)	0
Chest pain	6 (1.8)	1 (0.3)	3 (0.9)	2 (0.6)	0	4 (1.3)	1 (0.3)	1 (0.3)	0	2 (0.6)
Pleural effusion	6 (1.8)	2 (0.6)	3 (0.9)	0	1 (0.3)	4 (1.3)	0	2 (0.6)	1 (0.3)	1 (0.3)
Sepsis	1 (0.3)	0	1 (0.3)	0	0	4 (1.3)	0	0	1 (0.3)	3 (0.9)
Pyrexia	4 (1.2)	4 (1.2)	0	0	0	2 (0.6)	2 (0.6)	0	0	0

Preferred terms are sorted by frequency in the nintedanib arm.
Source: [U13-1504, Table 15.3.2.4.2.1: 4] and [U13-1504, Appendix 16.1.9.2, Table 7.3.2.1.4]

Table 52: Serious adverse events in all patients in phase III trial 1199.13 (incidence >1% in either treatment arm) – by preferred term and worst CTCAE grade, all treatment courses – on-treatment period, treated set

	Placebo					Nintedanib				
	Any grade n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Patients	655 (100.0)	655 (100.0)	655 (100.0)	655 (100.0)	655 (100.0)	652 (100.0)	652 (100.0)	652 (100.0)	652 (100.0)	652 (100.0)
Patients with SAEs	206 (31.5)	31 (4.7)	58 (8.9)	39 (6.0)	77 (11.8)	224 (34.4)	20 (3.1)	48 (7.4)	49 (7.5)	107 (16.4)
Febrile neutropenia	19 (2.9)	1 (0.2)	7 (1.1)	11 (1.7)	0	30 (4.6)	0	6 (0.9)	24 (3.7)	0
Malignant neoplasm progression	17 (2.6)	1 (0.2)	0	0	15 (2.3)	25 (3.8)	0	0	0	25 (3.8)
Dyspnoea	30 (4.6)	5 (0.8)	12 (1.8)	1 (0.2)	12 (1.8)	24 (3.7)	2 (0.3)	4 (0.6)	3 (0.5)	15 (2.3)
Neutropenia	21 (3.2)	0	3 (0.5)	18 (2.7)	0	21 (3.2)	1 (0.2)	5 (0.8)	15 (2.3)	0
Pneumonia	26 (4.0)	8 (1.2)	10 (1.5)	0	8 (1.2)	17 (2.6)	3 (0.5)	9 (1.4)	2 (0.3)	3 (0.5)
Diarrhoea	13 (2.0)	4 (0.6)	8 (1.2)	1 (0.2)	0	16 (2.5)	4 (0.6)	9 (1.4)	2 (0.3)	1 (0.2)
General physical health deterioration	8 (1.2)	1 (0.2)	1 (0.2)	0	6 (0.9)	11 (1.7)	1 (0.2)	2 (0.3)	0	8 (1.2)
Pleural effusion	8 (1.2)	2 (0.3)	4 (0.6)	0	2 (0.3)	8 (1.2)	1 (0.2)	4 (0.6)	1 (0.2)	2 (0.3)
Respiratory failure	2 (0.3)	0	0	0	2 (0.3)	8 (1.2)	0	0	0	8 (1.2)
Vomiting	7 (1.1)	4 (0.6)	3 (0.5)	0	0	8 (1.2)	5 (0.8)	2 (0.3)	1 (0.2)	0
Asthenia	4 (0.6)	1 (0.2)	2 (0.3)	0	1 (0.2)	7 (1.1)	2 (0.3)	3 (0.5)	0	2 (0.3)
Chest pain	8 (1.2)	1 (0.2)	5 (0.8)	2 (0.3)	0	7 (1.1)	1 (0.2)	1 (0.2)	3 (0.5)	2 (0.3)
Fatigue	1 (0.2)	0	1 (0.2)	0	0	7 (1.1)	1 (0.2)	4 (0.6)	1 (0.2)	1 (0.2)
Pyrexia	9 (1.4)	8 (1.2)	1 (0.2)	0	0	7 (1.1)	5 (0.8)	1 (0.2)	1 (0.2)	0
Sepsis	3 (0.5)	1 (0.2)	1 (0.2)	0	1 (0.2)	7 (1.1)	0	1 (0.2)	1 (0.2)	5 (0.8)
Haemoptysis	7 (1.1)	4 (0.6)	0	1 (0.2)	2 (0.3)	6 (0.9)	1 (0.2)	1 (0.2)	0	4 (0.6)

Preferred terms are sorted by frequency in the nintedanib arm.
Source: [U13-1504, Table 15.3.2.1: 4] and [U13-1504, Appendix 16.1.9.2, Table 7.2.1.8]

Deaths

Table 53: Summary of exposure – treated set (1199.13, all patients and adenocarcinoma)

	Duration of nintedanib / placebo intake [months]*				Number of docetaxcel courses			
	All patients		Adenocarcinoma patients		All patients		Adenocarcinoma patients	
	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib
All patients Mean (SD)	650 4.2 (4.6)	650 4.8 (4.9)	331 4.7 (5.0)	320 5.5 (5.3)	655 4.6 (4.0)	652 5.1 (4.2)	333 5.1 (4.5)	320 5.7 (4.7)
All deaths Mean (SD)	557 3.6 (3.3)	564 4.0 (3.4)	276 3.9 (3.5)	259 4.5 (3.7)	562 4.3 (3.3)	565 4.7 (3.3)	278 4.6 (3.6)	259 5.1 (3.4)
PD-deaths Mean (SD)	456 3.7 (3.4)	454 4.2 (3.3)	228 3.9 (3.6)	207 4.5 (3.4)	457 4.4 (3.4)	455 4.8 (3.4)	228 4.6 (3.7)	207 5.1 (3.4)
Non-PD deaths Mean (SD)	101 3.0 (2.7)	110 3.5 (3.8)	48 3.7 (3.1)	52 4.4 (4.8)	105 3.7 (2.7)	110 4.2 (2.9)	50 4.4 (3.1)	52 5.1 (3.4)

*2 patients did not receive nintedanib and 5 patients did not receive placebo. These patients are not included.
Source data: [U13-1504, Tables 15.3.1: 1, 15.3.1: 3, 15.3.2.4.1: 1, 15.3.2.4.1: 3]; [Appendix 1, Tables 3.1.3 - 3.1.8]; [Appendix 1, Tables 3.2.3 - 3.2.8]

The main analysis of AEs leading to death was restricted to those fatal AEs with an onset date or worsening during study treatment or up to 28 days after permanent discontinuation of last study medication.

Table 54: Adverse events leading to death in patients with adenocarcinoma in phase III trials 1199.13 (incidence >1 patient overall) – by preferred term

	Placebo n (%)	Nintedanib n (%)
Patients	333 (100.0)	320 (100.0)
Patients with AEs leading to death	32 (9.6)	56 (17.5)
Malignant neoplasm progression	7 (2.1)	12 (3.8)
Dyspnoea	7 (2.1)	6 (1.9)
General physical health deterioration	3 (0.9)	5 (1.6)
Respiratory failure	1 (0.3)	5 (1.6)
Sepsis	0	3 (0.9)
Chest pain	0	2 (0.6)
Metastases to meninges	0	2 (0.6)
Multi-organ failure	0	2 (0.6)
Pneumonia	1 (0.3)	2 (0.6)
Asthenia	1 (0.3)	1 (0.3)
Haemoptysis	1 (0.3)	1 (0.3)
Intracranial pressure increased	1 (0.3)	1 (0.3)
Metastases to central nervous system	1 (0.3)	1 (0.3)
Pleural effusion	1 (0.3)	1 (0.3)
Pulmonary haemorrhage	1 (0.3)	1 (0.3)
Patients with fatal AE attributed to progression of disease	24 (7.2)	36 (11.3)
Patients with fatal AE not attributed to progression of disease	8 (2.4)	20 (6.3)

Preferred terms are sorted by frequency in the nintedanib arm

A Kaplan-Meier analysis of the patients who experienced AEs leading to death on treatment showed a trend for an overall survival improvement in the nintedanib arm (hazard ratio 0.75, 95% CI: 0.47, 1.22, median overall survival 3.6 months nintedanib; 2.5 months placebo).

More patients in the nintedanib than in the placebo arm died because of an AE which was not attributed to PD (placebo: 8 out of 32 patients, 25.0%; nintedanib: 20 out of 56 patients, 35.7%). After adjustment for exposure, the incidence rate ratio of nintedanib vs. placebo for fatal AEs was 2.29 (95% CI 1.01, 5.21) in the adenocarcinoma population and 1.18 (95%CI 0.86, 1.62) in overall patient population.

Table 55: Adverse events leading to death in at least 2 patients in either treatment group and attributed to PD – all patients (study 1199.13)

	Placebo		Nintedanib	
Preferred term	N	(%)	N	(%)
Number of patients	655	(100.0)	652	(100.0)
Total with fatal events attributed to PD	52	(7.9)	72	(11.0)
Malignant neoplasm progression	15	(2.3)	25	(3.8)
Dyspnoea	10	(1.5)	14	(2.1)
General physical health deterioration	5	(0.8)	8	(1.2)
Respiratory failure	2	(0.3)	4	(0.6)
Haemoptysis	2	(0.3)	3	(0.5)
Metastases to meninges	0		3	(0.5)
Pulmonary haemorrhage	2	(0.3)	3	(0.5)
Acute respiratory failure	0		2	(0.3)
Pleural effusion	2	(0.3)	2	(0.3)
Intracranial pressure increased	2	(0.3)	1	(0.2)

Preferred terms sorted by frequency of patients in the nintedanib arm

Table 56: Adverse events leading to death in at least 2 patients in either treatment group and not attributed to PD – all patients (study 1199.13)

	Placebo		Nintedanib	
Preferred term	N	(%)	N	(%)
Number of patients	655	(100.0)	652	(100.0)
Total with fatal events not attributed to PD	25	(3.8)	35	(5.4)
Sepsis	1	(0.2)	5	(0.8)
Respiratory failure	0		4	(0.6)
Pneumonia	7	(1.1)	2	(0.3)
Death	1	(0.2)	2	(0.3)
Lower respiratory tract infection	0		2	(0.3)
Septic shock	0		2	(0.3)
Dyspnoea	2	(0.3)	1	(0.2)
Haemorrhage	2	(0.3)	1	(0.2)
Pulmonary embolism	3	(0.5)	0	

Preferred terms sorted by frequency of patients in the nintedanib arm

Non-PD deaths during treatment or ≤90 days post-treatment and >90 days post-treatment for both all patients and adenocarcinoma patient in study 1199.13 are summarised below.

Table 57: Deaths without attribution to PD (using death date) - treated set (all patients and adenocarcinoma)

	All patients			Adenocarcinoma		
	Placebo N (%)	Nintedanib N (%)	Relative risk Exposure adjusted rate* (95% CI)	Placebo N (%)	Nintedanib N (%)	Relative risk Exposure adjusted rate* (95% CI)
Number of patients	655 (100.0)	652 (100.0)		333 (100.0)	320 (100.0)	
Total deaths	105 (16.0)	110 (16.9)	1.05 (0.82, 1.34) 0.91 (0.70, 1.19)	50 (15.0)	52 (16.3)	1.08 (0.76, 1.55) 0.93 (0.63, 1.37)
Deaths during treatment	6 (0.9)	5 (0.8)	0.84 (0.26, 2.73) 0.73 (0.22, 2.38)	2 (0.6)	2 (0.6)	1.04 (0.15, 7.34) 0.89 (0.13, 6.33)
Deaths during treatment +28 days	24 (3.7)	35 (5.4)	1.47 (0.88, 2.43) 1.27 (0.76, 2.14)	8 (2.4)	19 (5.9)	2.47 (1.10, 5.57) 2.12 (0.93, 4.84)
Deaths >28 days post-treatment	81 (12.4)	75 (11.5)	0.93 (0.69, 1.25) 0.81 (0.59, 1.11)	42 (12.6)	33 (10.3)	0.82 (0.53, 1.26) 0.70 (0.44, 1.11)
Deaths during treatment +90 days	50 (7.6)	57 (8.7)	1.15 (0.80, 1.65) 0.99 (0.68, 1.45)	19 (5.7)	32 (10.0)	1.75 (1.01, 3.03) 1.50 (0.85, 2.65)
Deaths >90 days post-treatment	55 (8.4)	53 (8.1)	0.97 (0.67, 1.39) 0.84 (0.58, 1.23)	31 (9.3)	20 (6.3)	0.67 (0.39, 1.15) 0.58 (0.33, 1.01)

*Exposure adjustment rate was adjusted by the exposure time (time from start of treatment until last day of study medication)
Source: [Appendix 1, Table 3.1.2]; [Appendix 1, Table 3.2.2]

When the observation time was extended to during treatment +90 days, 19 (5.7%) placebo patients and 32 (10.0%) nintedanib patients had a non-PD death (adenocarcinoma population). Thus, 11 additional deaths on placebo and 13 additional deaths on nintedanib were observed beyond 28 days but ≤90 days post-treatment. These additional deaths were collected as outcome measures in the CRF as they occurred after the end of the residual effect period of 28 days. A review of these deaths revealed no further safety signals. The 11 additional deaths that occurred on placebo were deaths of 'unknown cause'. The 13 additional deaths that occurred on nintedanib included 8 deaths of 'unknown cause', 2 due to AEs (interstitial lung disease [described as induced by erlotinib] and ischaemic stroke), and 3 deaths due to 'other reason' (an event of 'gangrene of feet', an event of 'natural cause' and an event of 'respiratory failure').

The result of the review of all non-PD deaths during treatment or ≤90 days post-treatment and >90 days post-treatment for both all patients and adenocarcinoma patient in study 1199.13 did not reveal any new risks or pattern suggestive of delayed toxicity which could have compromised the survival benefit for patients treated with nintedanib.

A time at risk adjusted analysis that captured all deaths of entire observation period was also performed.

Table 58: Time at risk adjusted analysis of all deaths and incidence rate ratio – treated set (all patients and adenocarcinoma)

	Placebo			Nintedanib			Nintedanib vs placebo
	N (%) with event	Time at risk* (pt-yrs)	Rate/ 100 pt-yrs	N (%) with event	Time at risk* (pt-yrs)	Rate/ 100 pt-yrs	Incidence rate ratio (95% CI)
All patients							
Number of patients	655 (100.0)			652 (100.0)			
Patients died	562 (85.8)	638.4	88.03	565 (86.7)	693.0	81.53	0.93 (0.82, 1.04)
Patients died due to PD	457 (69.8)	638.4	71.58	455 (69.8)	693.0	65.66	0.92 (0.81, 1.04)
Patients died not due to PD	105 (16.0)	638.4	16.45	110 (16.9)	693.0	15.87	0.97 (0.74, 1.26)
Adenocarcinoma patients							
Number of patients	330 (100.0)			320 (100.0)			
Patients died	278 (83.5)	349.3	79.59	259 (80.9)	391.3	66.20	0.83 (0.70, 0.99)
Patients died due to PD	228 (68.5)	349.3	65.27	207 (64.7)	391.3	52.91	0.81 (0.67, 0.98)
Patients died not due to PD	50 (15.0)	349.3	14.31	52 (16.3)	391.3	13.29	0.93 (0.63, 1.37)

*Time at risk is time to death or time to be known alive for patients who did not died
Source: [Appendix 1, Table 3.1.1]; [Appendix 1, Table 3.2.1]

Respiratory Failure

In all patients in 1199.13 there were 4 fatal non-PD events of respiratory failure in the nintedanib arm and none in the placebo arm. The events of respiratory failure had different underlying etiologies. All events of respiratory failure had a short clinical course of 24 hours from time of onset to death. A review of the individual case narratives revealed no discernible pattern in terms of clinical picture, time to onset of the events, age, baseline medical conditions, or concomitant medications. In addition all 4 events of fatal respiratory failure were determined to be unrelated to the study drug by the investigator.

Sepsis

An imbalance in the events of fatal sepsis/septic shock was observed with 7 patients in the nintedanib arm versus 1 patient in the placebo arm. A review of the patients with fatal non-PD sepsis/septic shock revealed that 3 of the patients experienced concomitant neutropenia. Neutropenia might have played a role in 2 additional patients. Otherwise the review of the events of sepsis/ septic shock revealed no discernible pattern in terms of age, gender, race, or time to onset. Overall, in 2 of the 7 cases, insufficient information was provided to support the diagnosis of sepsis. Furthermore 2 cases occurred after only 3-5 days of treatment with nintedanib.

Myelotoxicity (including neutropenia, febrile neutropenia, and sepsis) is a known side effect of treatment with docetaxel. In the pivotal study 1199.13 there was an increase in neutropenia based on laboratory values (all grades: placebo: 68.2% vs. nintedanib: 74.1%; grade 3 and 4: 50.1% vs. 56.1%) when combining nintedanib with docetaxel compared with combining placebo with docetaxel. The percentage of patients with AEs within the special search category (SSC) febrile neutropenia was also greater in the nintedanib arm when compared to the placebo arm (placebo: 4.9% vs. nintedanib: 7.4%).

Laboratory findings

Blood samples for the assessment of haematology, biochemistry, and coagulation parameters were to be collected at all scheduled visits. At unscheduled visits, blood samples were only to be collected if additional tests were deemed necessary.

Urine samples were to be collected at screening, at the first visit of each treatment course, and at EOT, or if deemed necessary.

Liver parameters

The proportion of patients with elevated AST, ALT, ALKP, or total bilirubin was higher in the nintedanib arm (approximately 1.6 to 2 fold, all grades combined) than in the placebo arm. The elevations in these liver parameters were mostly of CTCAE grade 1 or 2 and were reversible in the majority of patients by the time of the data cut-off. These findings were consistent with the analyses for the AESI liver-related investigation.

Haematology parameters

Low white blood cell, platelet, or neutrophil counts were slightly more frequent in the nintedanib arm (up to approximately 1.3 fold for low platelet count, all grades combined) than in the placebo arm. These changes were reversible in the majority of patients. In line with the laboratory evaluations, the analyses for the AESIs showed slight increases in the proportion of patients reported with infection in the nintedanib arm.

Thyroid parameters

Treatment with nintedanib did not result in notable changes in thyroid laboratory parameters.

Coagulation other biochemistry parameters

In the nintedanib arm, the frequency of abnormal aPTT (approximately 1.3 fold; mostly of CTCAE grade 1 or 2) or electrolyte imbalances (up to approximately 1.6 fold for hypernatraemia, all grades combined) was slightly higher than in the placebo arm. These changes were reversible in the majority of patients.

Table 59: Coagulation and other biochemistry parameters in patients with adenocarcinoma in pivotal phase III trial 1199.13 by worst CTCAE grade on treatment - TS

	Placebo				Nintedanib			
	N[1]	Any grade[2] n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	N[1]	Any grade[2] n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)
Coagulation								
aPTT	317	85 (26.8)	81 (25.6)	4 (1.3)	311	105 (33.8)	99 (31.8)	6 (1.9)
PT-INR[3]	323	91 (28.2)	89 (27.6)	2 (0.6)	315	83 (26.3)	80 (25.4)	3 (1.0)
Other biochemistry								
Hypernatraemia	328	28 (8.5)	24 (7.3)	4 (1.2)	317	44 (13.9)	39 (12.3)	5 (1.6)
Hyponatraemia	328	149 (45.4)	113 (34.5)	36 (11.0)	317	155 (48.9)	108 (34.1)	47 (14.8)
Hyperkalaemia	328	76 (23.2)	65 (19.8)	11 (3.4)	317	83 (26.2)	68 (21.5)	15 (4.7)
Hypokalaemia	328	70 (21.3)	61 (18.6)	9 (2.7)	317	89 (28.1)	70 (22.1)	19 (6.0)
Hypermagnesaemia	325	49 (15.1)	33 (10.2)	16 (4.9)	314	49 (15.6)	35 (11.1)	14 (4.5)
Hypomagnesaemia	325	124 (38.2)	113 (34.8)	11 (3.4)	314	134 (42.7)	129 (41.1)	5 (1.6)
Creatinine	328	74 (22.6)	74 (22.6)	0	317	64 (20.2)	64 (20.2)	0

[1] Patients with at least one post-baseline value
[2] Including CTCAE grades 1 to 4
[3] For PT-INR, CTCAE grade 4 is not defined; all patients counted in the category "grade 3/4" had an PT-INR of grade 3

Very few patients experienced hyperphosphatemia.

Urinalysis

Urinalysis was performed by dipstick test. The parameters urine protein, pH, nitrite, glucose, RBC, and WBC were assessed according to worst value on treatment and transitions during the course of the study. No meaningful difference was seen between the two treatment arms in pivotal study 1199.13 (all patients).

Safety in special populations

Age

The proportion of patients ≥ 65 years old was balanced across treatment arms in both the overall and the adenocarcinoma populations of 1199.13 (overall population: placebo 32.4% vs. nintedanib 30.7%; adenocarcinoma population: placebo 28.2% vs. nintedanib 28.1%). The proportion of patients experiencing AEs was balanced across age groups in both treatment arms in the overall and adenocarcinoma populations.

Patients ≥65 years old experienced more events in the SSC cardiac arrhythmias when compared to patients <65 years old regardless of randomization to placebo or nintedanib. This was seen in both the overall (placebo: <65 years: 7.4% vs. ≥65 years: 11.3%, nintedanib: <65 years 7.3% vs. ≥65 years: 17.0%) and adenocarcinoma populations (placebo: <65 years: 5.9% vs. ≥65 years: 11.7%, nintedanib: <65 years: 7.8% vs. ≥65 years: 21.1%).

While patients ≥65 years old experienced more events in the sensitive SSC cardiac failure when compared to patients <65 years old in the both arms [in the overall population (placebo: < 65 years: 5.6% vs. ≥65 years: 9.9%, nintedanib: <65 years: 5.5% vs. ≥65 years: 9.0%) and in the nintedanib arm of the adenocarcinoma population (placebo: <65 years: 6.7% vs. ≥65 years: 6.4%, nintedanib: <65 years: 5.7% vs. ≥65 years: 13.3%)], there was no imbalance in the more specific SSC of cardiac failure tailored [in the overall population (placebo: < 65 years: 0.5% vs. ≥65 years: 1.4%, nintedanib: <65 years: 0.7% vs. ≥65 years: 1.0%) and in the nintedanib arm of the adenocarcinoma population (placebo: <65 years: 0 vs. ≥65 years: 2.1%, nintedanib: <65 years: 0 vs. ≥65 years: 0)].

Table 60: Frequency of patients with ADRs which may be of special concern in the elderly – on treatment period, treated set (SAF 3)

MedDRA Terms	Age <65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)
Patients	1219 (100)	520 (100)	143 (100)	2 (100)
Total ADRs	1016 (83.3)	449 (86.3)	129 (90.2)	1 (50.0)
Serious ADRs – Total	134 (11.0)	77 (14.8)	34 (23.8)	1 (50.0)
- Fatal	8 (0.7)	8 (1.5)	2 (1.4)	0
- Hospitalization/prolong existing hospitalization	122 (10.0)	69 (13.3)	27 (18.9)	0
- Life-threatening	9 (0.7)	7 (1.3)	5 (3.5)	0
- Disability/incapacity	2 (0.2)	1 (0.2)	1 (0.7)	0
- Other (medically significant)	10 (0.8)	6 (1.2)	5 (3.5)	1 (50.0)
AE leading to drop-out*	124 (10.2)	97 (18.7)	20 (14.0)	1 (50.0)
Psychiatric disorders (SOC)*	34 (2.8)	17 (3.3)	3 (2.1)	0
Nervous system disorders (SOC)*	251 (20.6)	112 (21.5)	43 (30.1)	0
Accidents and injuries (SMQ)*	4 (0.3)	5 (1.0)	0	0

Cardiac disorders (SOC)*	24 (2.0)	19 (3.7)	6 (4.2)	0
Vascular disorders (SOC)*	69 (5.7)	45 (8.7)	14 (9.8)	0
Cerebrovascular disorders (SMQ)*	3 (0.2)	0	1 (0.7)	0
Infections and infestations (SOC)*	99 (8.1)	43 (8.3)	13 (9.1)	0
Quality of life decreased (PT)*	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	38 (3.1)	19 (3.7)	11 (7.7)	0

* Only drug related adverse events are counted; Source data: [Appendix 1, Table 25.2.1.1]

Overall safety profile was similar across age groups in both treatment arms in both the overall and adenocarcinoma populations.

Gender

The proportion of female patients was balanced across treatment arms in both the overall and the adenocarcinoma populations of 1199.13 (overall population: placebo 27.0% vs. nintedanib 27.5%; adenocarcinoma population: placebo 37.8% vs. nintedanib 37.2%). The proportion of patients experiencing AEs was balanced across both genders in both treatment arms in the overall and adenocarcinoma populations.

Females in the nintedanib arm, in both the overall and adenocarcinoma populations, were more likely to experience adverse events belonging to the SSC of liver related investigations (overall population: male 26.4% vs. female 52.5%; adenocarcinoma population: male 32.3% vs. female 60.5%) and tailored liver related investigations (overall population: male 24.3% vs. female 49.7%; adenocarcinoma population: male 30.8% vs. female 57.1%) when compared to males. Otherwise the overall safety profile was similar across gender in both treatment arms in both the overall and adenocarcinoma populations.

Race

The proportion of Asian patients was balanced across treatment arms in both the overall and the adenocarcinoma populations of 1199.13 (overall population: placebo 18.9% vs. nintedanib 18.1%; adenocarcinoma population: placebo 23.7% vs. nintedanib 20.6%). The proportion of Asian patients with AEs in the nintedanib arm was similar across arms in the adenocarcinoma (placebo 88.6% vs. nintedanib 97.0%) and overall populations (placebo 91.1% vs. nintedanib 94.1%).

Asian patients in both the placebo and nintedanib arms experienced more events in the SSC of liver related investigations in the overall population (placebo: Non-Asians 11.3% vs. Asians 23.4%, nintedanib: Non-Asians 27.3% vs. Asians 61.9%) and the adenocarcinoma populations (placebo: Non-Asians 10.6% vs. Asians 27.8%, nintedanib: Non-Asians 34.6% vs. Asians 74.2%) when compared to Non-Asians. A similar finding was observed with AEs in the SSC of tailored liver related investigations. Otherwise the overall safety profile was similar among Asians and Non-Asians in both treatment arms in the overall and adenocarcinoma populations.

Weight

The majority of patients in 1199.13 weighed 50 kg to <90 kg. The number of patients weighing <50 kg was small but balanced across treatment arms in both the overall [placebo 34 patients (5.2%) vs. nintedanib 32 patients (4.9%)] and adenocarcinoma [placebo 20 patients (6.0%) vs. nintedanib 17 patients (5.3%)] populations. The number of patients weighing ≥90 kg was small but balanced across treatment arms in both the overall [placebo 75 patients (11.5%) vs. nintedanib 72 patients (11.0%)] and adenocarcinoma [placebo 34 patients (10.2%) vs. nintedanib 31 patients (9.7%)] populations. Overall the proportion of patients with AEs in all weight groups across treatment arms was balanced in the overall and adenocarcinoma populations. The safety profile across patients in the 50 to <70 kg and the 70 to <90 kg weight categories was comparable. The number of patients in the <50 kg and >90 kg weight categories was too small to allow for a meaningful safety analysis across these weight categories.

Body Surface Area (BSA)

There was a small proportion of patients with a BSA <1.5 m^2 in both the overall and the adenocarcinoma populations of 1199.13 (overall population: placebo 7.2% vs. nintedanib 6.0%; adenocarcinoma population: placebo 8.4% vs. nintedanib 7.5%). The number of patients with a BSA <1.5m2 was too small to allow for a meaningful safety analysis across weight categories.

ECOG Performance Score (PS)

ECOG performance score was a stratification factor in study 1199.13. The majority of patients in the trial had an ECOG PS of 1. The proportion of patients with an ECOG PS of 0 and 1 was balanced across treatment arms in both the overall and the adenocarcinoma populations of 1199.13 (ECOG PS of 0: overall population: placebo 28.4% vs. nintedanib 28.7%; adenocarcinoma population: placebo 28.8% vs. nintedanib 30.0%).

No significant difference in the AE profile was observed among patients with an ECOG PS of 0 or 1 among treatment arms in both the overall and adenocarcinoma populations of 1199.13. Although patients with a baseline ECOG PS of 1 in the nintedanib arm experienced slightly more events in the SSC of liver related investigations in the overall population (ECOG PS of 0: 27.3% vs. ECOG PS of 1: 36.1%) and the adenocarcinoma populations (ECOG PS of 0: 35.4% vs. ECOG PS of 1: 46.0%) when compared to patients with baseline ECOG PS of 0. A similar finding was observed with AEs in the SSC of tailored liver related investigations.

Brain Metastasis

Brain metastasis was a stratification factor in study 1199.13 and only patients with non-active brain metastasis were allowed into the trial. The majority of patients in the trial did not have brain metastasis. The proportion of patients with brain metastasis was small and balanced across treatment arms in both the overall and the adenocarcinoma populations of 1199.13 (overall population: placebo 5.8% vs. nintedanib 5.8%; adenocarcinoma population: placebo 6.9% vs. nintedanib 8.1%).

No significant difference in the AE profile was observed among patients with and without brain metastasis among treatment arms in both the overall and adenocarcinoma populations of 1199.13. A few patients with brain metastasis in the nintedanib arm experienced events of bleeding (overall population: placebo 4 patients vs. nintedanib 2 patients; adenocarcinoma population: placebo 2 patients vs. nintedanib 2 patients). All events of bleeding were respiratory in nature and there were no events of CNS bleeding.

Hepatic impairment

A small number of patients with baseline hepatic impairment were included in 1199.13 (overall population: placebo 14.4% vs. nintedanib 10.7%; adenocarcinoma population: placebo 13.2% vs. nintedanib 10.9%). There were slightly more patients with hepatic impairment in the placebo arm than in the nintedanib arm. All patients with hepatic impairment had mild hepatic impairment (ULN< AST and/or ALT ≤2.5 x ULN and/or ULN< total bilirubin ≤1.5 x ULN) except for 2 patients in the nintedanib arm that had moderate hepatic impairment (2.5 x ULN <AST and/or ALT≤5 x ULN and/or 1.5 x ULN < total bilirubin ≤3 x ULN).

Overall patients with normal hepatic function and those with mild hepatic impairment experienced a comparable number of AEs in the overall and adenocarcinoma across both treatment arms. Patients with mild hepatic impairment in both the placebo and nintedanib arms experienced more events in the SSC of liver related investigations in the overall population (placebo: normal hepatic function 12.0% vs. mild hepatic impairment 24.2%, nintedanib: normal hepatic function 32.1% vs. mild hepatic impairment 44.1%) and the adenocarcinoma populations (placebo: normal hepatic function 13.9% vs. mild hepatic impairment 20.5%, nintedanib: normal hepatic function 40.7% vs. mild hepatic impairment 57.6%) when compared to patients with baseline normal hepatic function. A similar finding was observed with AEs in the SSC of tailored liver related investigations.

Renal Impairment

Only four patients with baseline renal impairment (creatinine level ≥1.5 x ULN) were treated in 1199.13 (3 patients were in the placebo arm and 1 patient was in the nintedanib arm). Therefore no conclusions could be made regarding the safety profile of these patients.

Geographical Region

Patients in 1199.13 were categorised into two major geographic regions; Asia and non-Asia. The majority of patients were from Non-Asia [placebo (76.3%) and nintedanib (76.7%)]. The proportion of patients from Asia and non-Asia was balanced across treatment arms. The proportion of patients with AEs was comparable across both geographical regions (Asia and non-Asia) and treatment arms in both the overall and adenocarcinoma populations. Patients from Asia in both the placebo and nintedanib arms experienced more events in the SSC of liver related investigations in both the overall population (placebo: Non-Asia 10.8% vs. Asia 22.6%, nintedanib: Non-Asia 27.4% vs. Asia 53.9%) and the adenocarcinoma populations (placebo: Non-Asia 10.1% vs. Asia 26.3%, nintedanib: Non-Asia 35.0% vs. Asia 64.0%) than patients from Europe. A similar finding was observed with AEs in the SSC of tailored liver related investigations.

Smoking Status

The majority of patients in 1199.13 were current smokers/ ex-smokers in both the overall and adenocarcinoma populations (current smokers/ex-smokers: overall population: placebo 75.6% vs. nintedanib 74.7%; adenocarcinoma population: placebo 65.8% vs. nintedanib 64.1%). The remaining patients were never smokers.

The proportion of patients experiencing AEs was comparable in never smokers and current/ex-smokers across treatment arms in both the overall and adenocarcinoma populations. Never smokers in the nintedanib arm were more likely to experience adverse events belonging to the SSC of liver related investigations in the overall (current smoker/ex-smoker 26.3% vs. never smoked 55.2%) and adenocarcinoma populations (current smoker/ex-smoker 30.7% vs. never smoked 64.3%) than patients in the placebo arm. A similar finding was observed with AEs in the SSC of tailored liver related investigations.

Adverse events in patients with squamous cell carcinoma and "other" histologies (pivotal trial 1199.13)

Squamous cell carcinoma

AEs of any grade (nintedanib arm: 90.5% vs. placebo arm: 90.6%) and grade ≥3 AEs (66.5% vs. 58.6%) occurred at slightly lower frequencies in patients with squamous cell carcinoma than in "all" patients (93.6% vs. 93.0% and 71.3% vs. 64.3%). Overall, the most commonly reported AEs were the same in patient with squamous cell carcinoma as in patients with adenocarcinoma and "all" patients. However, liver-related investigations were less common in patients with squamous cell carcinoma (22.9% vs. 11.9%) than in all patients in the trial (33.6% vs. 13.6%), and bleeding was more frequent in the patients with squamous cell carcinoma (17.1% vs. 10.8%) than in "all" patients in the trial (14.1% vs. 11.6%). Moreover, coagulation abnormalities were also slightly more frequent in the patients with squamous cell carcinoma [increased activated partial thromboplastin time (aPTT) (37.4% vs. 29%) and increased international normalised ratio (INR) (36.2% vs. 34.6%)], than in all patients in the trial [aPTT (35% vs. 27.8%) and increased INR (31.5% vs. 31.1%)].

In patients with squamous cell carcinoma SAEs (nintedanib arm: 32.7% vs. placebo arm: 32.0%) occurred at similar rates as in all patients in pivotal trial 1199.13. Concerning fatal events, comparable frequencies between the two treatment arms were observed in patients with squamous cell carcinoma (13.5% vs. 14.7%), which differed from all patients in the trial where fatal events were more frequent in the nintedanib arm than in the placebo arm (16.4% vs. 11.8%). Discontinuations were slightly more common in the placebo arm (26.6%) than in the nintedanib arm (23.3%) in patients with squamous cell carcinoma, which is slightly different to all patients in the trial where comparable frequencies were observed (22.7% vs. 21.7%).

Although bleeding was more common in patients with squamous cell carcinoma, the overall safety profile for patients with SCC appears to be comparable to all patients in the trial.

"Other" histologies

Due to the small number of patients with "other" histologies in pivotal trial 1199.13 (nintedanib arm: 57, placebo arm: 45) it is not feasible to draw firm conclusions concerning the frequencies of different AEs.Both AEs of any grade (nintedanib arm: 93.0% vs. placebo arm: 97.7%) and grade ≥3 AEs (68.4% vs. 68.2%) occurred at similar frequencies as in all patients in the trial. In contrary to all patients where SAEs were moderately more common in the nintedanib arm (34.4%) than in the placebo arm (31.5%), a substantially higher frequency of SAEs were observed in the nintedanib arm (40.4%) than in the placebo arm (22.7%) of patients harbouring "other" histologies. Similarly, fatal events were more frequent in patients with "other" histologies (26.4% vs. 9.1%) than in all patients in the trial (16.4% vs. 11.8%). Moreover, discontinuations occurred at comparable frequencies between the nintedanib arm (22.7%) and placebo arm (21.7%) in all patients in the trial. In contrary, discontinuations were more common in the nintedanib arm (29.8%) than in the placebo arm (20.5%) of patients with "other" histologies. Increased frequencies of SAEs, fatal events and discontinuations were observed in patients with "other" histologies.

Safety related to drug-drug interactions and other interactions

The phase I dose escalation trial 1199.4 investigated escalating doses of nintedanib in combination with docetaxel in patients with prostate cancer. There was no indication of a clinically relevant pharmacokinetic interaction between nintedanib (doses ranged from 100 mg b.i.d. to 250 mg b.i.d.) and docetaxel (single dose of 75 mg/m²). The AE profile was similar to that in the phase I nintedanib monotherapy dose escalation studies, except for the chemotherapy-related side effects. There was no indication that nintedanib exacerbated side effects commonly seen with docetaxel.

The combination of escalating doses of nintedanib with pemetrexed was investigated in patients with NSCLC in the phase I dose escalation trials 1199.18 and 1199.28 (in Japanese patients). No clinically relevant pharmacokinetic interaction between nintedanib and pemetrexed was observed. The nintedanib doses ranged from 100 mg b.i.d. to 200 mg b.i.d. (1199.28) and 250 mg b.i.d. (1199.18); pemetrexed was administered at 500 mg/m^2 in both studies. No adverse drug reactions in addition to the individual safety profiles of nintedanib and pemetrexed were identified.

Trials 1199.5 and 1199.6 investigated the combination of nintedanib with carboplatin and paclitaxel and trial 1199.51 the combination with mFOLFOX6 (oxaliplatin, 5-fluorouracil, and leucovorin). No clinically relevant pharmacokinetic alterations were observed. These studies revealed that 200 mg b.i.d. of nintedanib could be safely combined with standard doses of the chemotherapies. The AE profile was similar to that in phase I nintedanib monotherapy dose escalation studies, except for the chemotherapy-related toxicities.

Discontinuation due to adverse events

Dose reductions

Table 61: Adverse events leading to dose reduction of nintedanib or placebo in all patients in phase III trial 1199.13 (>1% in either treatment group) – by preferred term and worst CTCAE grade, all treatment courses –TS

	Placebo n (%)	Nintedanib n (%)
Patients	655 (100.0)	652 (100.0)
Patients with AEs leading to dose reduction of nintedanib/placebo	41 (6.3)	118 (18.1)
Diarrhoea	16 (2.4)	47 (7.2)
ALT increased	3 (0.5)	38 (5.8)
AST increased	0	21 (3.2)
Vomiting	5 (0.8)	10 (1.5)
Fatigue	6 (0.9)	8 (1.2)
Nausea	7 (1.1)	5 (0.8)

Preferred terms are sorted by frequency in the nintedanib arm

Table 62: Adverse events leading to dose reduction of nintedanib or placebo in patients with adenocarcinoma in phase III trial 1199.13 (>1% in either treatment group) – by preferred term and worst CTCAE grade, all treatment courses –TS

	Placebo n (%)	Nintedanib n (%)
Patients	333 (100.0)	320 (100.0)
Patients with AEs leading to dose reduction of nintedanib/placebo	22 (6.6)	69 (21.6)
Diarrhoea	11 (3.3)	26 (8.1)
ALT increased	2 (0.6)	25 (7.8)
AST increased	0	12 (3.8)
Vomiting	2 (0.6)	7 (2.2)
Nausea	1 (0.3)	4 (1.3)

Preferred terms are sorted by frequency in the nintedanib arm

In study 1199.14, dose reductions of nintedanib/placebo were more common in the nintedanib arm (33.2%) than in the placebo arm (9.6%). More patients in the nintedanib arm (34.3%) than in the placebo arm (11.1%) also had at least 1 dose reduction of pemetrexed.

Discontinuations

The analysis of AEs leading to permanent discontinuation of the last study medication included patients who discontinued treatment with combination therapy and did not continue with monotherapy, patients who discontinued monotherapy with nintedanib/placebo (after having earlier discontinued the cytostatic component of the combination therapy), and patients who discontinued monotherapy with cytostatic (after having earlier discontinued the nintedanib/placebo component). Patients with AEs leading to discontinuation of one component of the study medication (nintedanib/placebo or cytostatic) were not included in the analysis if they continued to take the other component of the study medication.

Table 63: Adverse events leading to permanent discontinuation of last study medication in all patients in phase III trial 1199.13 (incidence >1% in either treatment arm) – by preferred term and worst CTCAE grade, all treatment courses - TS

	Placebo			Nintedanib		
	Any grade n (%)	Grade 1/2 n (%)	Grade 3/4/5 n (%)	Any grade n (%)	Grade 1/2 n (%)	Grade 3/4/5 n (%)
Patients	655 (100.0)	655 (100.0)	655 (100.0)	652 (100.0)	652 (100.0)	652 (100.0)
Patients with AEs leading to permanent discontinuation of last study medication	142 (21.7)	43 (6.6)	99 (15.1)	148 (22.7)	33 (5.1)	115 (17.6)
Malignant neoplasm progression	8 (1.2)	1 (0.2)	7 (1.1)	14 (2.1)	0	14 (2.1)
Dyspnoea	20 (3.1)	5 (0.8)	15 (2.3)	11 (1.7)	3 (0.5)	8 (1.2)
Fatigue	9 (1.4)	4 (0.6)	5 (0.8)	10 (1.5)	6 (0.9)	4 (0.6)
ALT increased	2 (0.3)	1 (0.2)	1 (0.2)	8 (1.2)	5 (0.8)	3 (0.5)
Diarrhoea	1 (0.2)	1 (0.2)	0	8 (1.2)	1 (0.2)	7 (1.1)
General physical health deterioration	6 (0.9)	1 (0.2)	5 (0.8)	7 (1.1)	0	7 (1.1)
Pneumonia	9 (1.4)	1 (0.2)	8 (1.2)	4 (0.6)	1 (0.2)	3 (0.5)

Preferred terms are sorted by frequency in the nintedanib arm

Table 64: Adverse events leading to permanent discontinuation of last study medication in patients with adenocarcinoma in phase III trial 1199.13 (incidence >1% in either treatment arm) – by preferred term and worst CTCAE grade, all treatment courses - TS

	Placebo			Nintedanib		
	Any grade n (%)	Grade 1/2 n (%)	Grade 3/4/5 n (%)	Any grade n (%)	Grade 1/2 n (%)	Grade 3/4/5 n (%)
Patients	333 (100.0)	333 (100.0)	333 (100.0)	320 (100.0)	320 (100.0)	320 (100.0)
Patients with AEs leading to permanent discontinuation of last study medication	59 (17.7)	16 (4.8)	43 (12.9)	67 (20.9)	10 (3.1)	57 (17.8)
ALT increased	0	0	0	5 (1.6)	2 (0.6)	3 (0.9)
Malignant neoplasm progression	5 (1.5)	1 (0.3)	4 (1.2)	5 (1.6)	0	5 (1.6)
AST increased	1 (0.3)	1 (0.3)	0	4 (1.3)	2 (0.6)	2 (0.6)
Dyspnoea	11 (3.3)	2 (0.6)	9 (2.7)	4 (1.3)	0	4 (1.3)
Hypersensitivity	4 (1.2)	1 (0.3)	3 (0.9)	1 (0.3)	0	1 (0.3)

Preferred terms are sorted by frequency in the nintedanib arm

In patients with adenocarcinoma histology in trial 1199.14, discontinuations occurred at comparable frequencies in both study arms (nintedanib 16.4%, placebo: 17.8%).

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

Patient exposure

Safety data from 35 completed trials were pooled into four safety analysis sets (SAFs), SAF-1 to 4 which is considered meaningful. This provides the basis for a robust assessment of the safety profile of nintedanib.

Safety assessment was primarily based on pivotal trial 1199.13 which compared treatment with nintedanib/docetaxel (n=652) to placebo/docetaxel (n=655). Patients were exposed to nintedanib in a sufficient timeframe when considering the nature of their disease.

Regarding exposure to nintedanib/placebo in pivotal trial 1199.13 (all patients), mean duration of nintedanib/placebo treatment was 4.78 months in the nintedanib arm and 4.17 months in the placebo arm. For patients with adenocarcinoma a slightly longer treatment time was observed in both the nintedanib arm (5.45 months) and placebo arm (4.70 months). Exposure to docetaxel, judged by mean docetaxel courses and cumulative dose was greater in the nintedanib arm than in the placebo arm of pivotal trial 1199.13 (all patients). Moreover, higher docetaxel exposure was observed in patients with adenocarcinoma histology. However, these differences observed in exposure are unlikely to have a major impact on the AEs reported in the two treatment arms. Moreover, the higher exposure to docetaxel observed in the nintedanib arm of pivotal trial 1199.13 indicated that co-administration of nintedanib/docetaxel may be performed without reducing concomitant docetaxel treatment, suggesting tolerability of the concomitant treatment.

Adverse events

In general, there were more AEs reported in the nintedanib arm, which is expected. Patients in the placebo arm had a higher frequency of Grade 1/2 AEs, while patients in the nintedanib arm were more likely to experience Grade 3/4/5 AEs, where the most common AEs were: liver enzyme elevations, decreased WBC and neutrophils, diarrhoea, vomiting, nausea and neutropenia. The decreased levels of WBC and neutrophils led to slightly more infections in the nintedanib arm. Slightly more cases of sepsis were also observed in the nintedanib arm. With regard to the Grade 1/2 more patients experienced, diarrhoea, ALT elevations, AST elevations, nausea, decreased appetite, and vomiting in the nintedanib in combination with docetaxel arm.

In relation to Adverse Events of Special Interest (AESI) the Applicant has investigated this issue from several viewpoints: AESI related to bevacizumab (only VEGF inhibitor approved for the treatment of NSCLC), AESI related to VEGF inhibitors in general, and AESI related to docetaxel. Overall, there were some AESI that occurred more frequently than others: diarrhoea, nausea, vomiting and liver-related AEs.

Diarrhoea was the most frequently reported gastro-intestinal adverse reaction and appeared in close temporary relationship with the administration of chemotherapy (docetaxel). Diarrhoea was more frequent in the nintedanib arm (42.3%) than in the placebo arm (21.8%) of pivotal trial 1199.13 (all patients) and was also the most common reason for dose reductions in the trial. The majority of patients experienced diarrhoea of mild to moderate severity. In the adenocarcinoma population, diarrhoea occurred in 43.4 % (≥ grade 3: 6.3 %) of in the nintedanib arm. Nevertheless, as the majority of patients had recovered by the time of data cut-off (nintedanib arm: 264/276), placebo arm: 139/143), diarrhoea appears to be manageable with dose reductions and supportive treatments. Therefore, diarrhoea should be treated at first signs with adequate hydration and anti-diarrhoeal medicinal products, for example loperamide, and may require interruption, dose reduction or discontinuation of therapy with nintedanib. The dose reduction scheme (i.e. after treatment interruption and recovery to grade 1 or baseline, dose reduction from 200 mg twice daily to 150 mg twice daily and if a 2nd dose reduction is necessary, from 150 mg twice daily to 100 mg twice daily) in case of diarrhoea ≥ grade 2 for more than 7 consecutive days despite anti-diarrhoeal treatment or diarrhoea ≥grade 3 despite anti-diarrhoeal treatment, is regarded to provide adequate guidance in order to control diarrhoea and associated complications (see SmPC sections 4.2, 4.4 and 4.8).

Nausea and vomiting, mostly of mild to moderate severity, were frequently reported gastrointestinal adverse reactions. They were also more common in the nintedanib arm than in the placebo arm of pivotal trial 1199.13. However, the level of grade ≥3 was low. The development of nausea or vomiting was temporarily associated within each cycle with the administration of chemotherapy. These adverse reactions were managed with supportive care, interruption, dose reduction or discontinuation of therapy. Supportive care for nausea and vomiting may include medicinal products with anti-emetic properties, e.g. glucocorticoids, anti-histamines or 5-HT3 receptor antagonists and adequate hydration. In the event of dehydration, administration of electrolytes and fluids is required. Plasma levels of electrolytes should be monitored, if relevant gastrointestinal adverse events occur. In addition, interruption, dose reduction or discontinuation of therapy with nintedanib may be required despite appropriate supportive care. The same dose reduction scheme as for diarrhoea (see above and section 4.2 of SmPC) is recommended in case of vomiting ≥ grade 2 and/or nausea ≥ grade 3 despite anti-emetic treatment. This dose adjustment scheme should also be followed in case of other non-haematological or haematological adverse reaction of ≥ grade 3.

Administration of nintedanib was associated with an elevation of liver enzymes (ALT, AST, ALKP) or bilirubin, with a potentially higher risk for female patients. These increases were reversible in the majority of cases.

Liver-related adverse reactions occurred in 42.8 % of nintedanib-treated patients. Approximately one third of these patients had liver-related adverse reactions of ≥grade 3 severity. In patients with increased liver parameters, the use of the established stepwise dose reduction scheme was the appropriate measure and discontinuation of treatment was only necessary in 2.2 % of patients.

Transaminase, ALKP and bilirubin levels should be investigated before the initiation of the combination treatment with nintedanib plus docetaxel. Based on the data presented, the values should be monitored as clinically indicated or periodically during treatment, i.e. in the combination phase with docetaxel at the beginning of each treatment cycle and monthly in case nintedanib is continued as monotherapy after discontinuation of docetaxel (see SmPC section 4.4). Treatment interruptions followed by dose adjustment serve as the initial measure for the management of liver enzyme elevations. Alternative causes of the liver enzyme elevations should be investigated and respective action should be taken as necessary. The SmPC (Section 4.2) includes a specific dose reduction scheme to minimise the potential consequences of liver enzyme elevations while maintaining the efficacy of nintedanib treatment. If elevation of AST and/or ALT values to >5 x the upper limit of normal (ULN) or elevation of AST and/or ALT values to >2.5 x ULN in conjunction with total bilirubin elevation to ≥1.5 x ULN occur, treatment with nintedanib should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy (i.e. recovery of transaminase-values to ≤2.5 x ULN in conjunction with bilirubin to normal). The nintedanib dose should then be reduced from 200 mg twice daily to 150 mg twice daily or from 150 mg twice daily to 100 mg twice daily if a 2nd dose adjustement is considered necessary. In case of specific elevations of liver values (elevation of AST and/or ALT values to >3 x ULN in conjunction with total bilirubin ≥2 x ULN and ALKP <2 x ULN) treatment with nintedanib should be interrupted. Unless there is an alternative cause established, nintedanib should be permanently discontinued.

There were slightly higher frequency of AEs identified by the sensitive SMQ hepatic failure in the nintedanib arm than in the placebo arm. It appeared that the incidence of AEs associated with hepatic failure may, to some degree, be dose dependent (SAF-2). Patients receiving ≤200 mg nintedanib b.i.d. had lower risk of this AE. A thorough case-by-case assessment of the brief case narratives for patients with hepatic failure did not reveal any potential safety signal with regard to hepatic failure. While there is no doubt that nintedanib can cause increase in liver enzymes, there seems to be no solid evidence for DILI. Section 4.4 of the SmPC adequately emphasizes the importance of supervision of liver enzymes. Hepatic failure has also been included in the RMP as an important potential risk.

There was also a slightly higher frequency of AEs identified by a sensitive search for non-GI perforations in the nintedanib arm than in the placebo arm. However, a case-by-case review did not reveal an increased risk of non-gastrointestinal perforations. Overall, the frequency of gastrointestinal perforation was low and comparable between the treatment arms in the study 1199.13. However, based on the mechanism of action patients treated with nintedanib may have an increased risk of gastrointestinal perforations. Particular caution should be exercised when treating patients with previous abdominal surgery or a recent history of a hollow organ perforation. Nintedanib should therefore only be initiated at least 4 weeks after major surgery. Therapy with nintedanib should be permanently discontinued in patients who develop gastrointestinal perforation (see SmPC section 4.4).

With regard to AESI for docetaxel, there was no indication that nintedanib leads to an increase in neutropenia (AE) although a higher frequency of neutropenia of CTCAE grade ≥3 was observed in patients treated with nintedanib in combination with docetaxel as compared to treatment with docetaxel alone. Sepsis and febrile neutropenia were reported as subsequent complications of neutropenia. The rates of sepsis (1.3 %) and febrile neutropenia (7.5 %) were increased under treatment with nintedanib as compared to the placebo arm. Therefore, it is important that the patient's blood counts are monitored during therapy, in particular during the combination treatment with docetaxel. Frequent monitoring of complete blood counts should be performed at the beginning of each treatment cycle and around the nadir for patients receiving treatment with nintedanib in combination with docetaxel, and as clinically indicated after the administration of the last combination cycle (see SmPC section 4.4).

Peripheral neuropathy is also known to occur with docetaxel treatment. Peripheral neuropathy was reported in 16.5 % of patients in the placebo arm and in 19.1 % of patients in the nintedanib arm.

VEGFR inhibition might be associated with an increased risk of bleeding. In the study 1199.13 (all patients) bleeding was more common in the nintedanib arm (14.1%, grade ≥3: 2.3%) than in the placebo arm (11.6%, grade ≥3: 1.8%) which is in contrast to the patients with adenocarcinoma where frequencies were comparable (10.9% vs. 11.1%). The difference in frequency was driven by a higher incidence of bleeding in the patients with squamous cell carcinoma (17.1% vs. 10.8%). Moreover, bleeding has also been observed in other nintedanib trials indicating that nintedanib may increase the frequency of bleeding events also in other tumour histologies than squamous cell carcinoma.

Patients with recent pulmonary bleeding (> 2.5 ml of red blood) as well as patients with centrally located tumours with radiographic evidence of local invasion of major blood vessels or radiographic evidence of cavitary or necrotic tumours have been excluded from clinical trials. Therefore it is not recommended to treat these patients with nintedanib. There are no data available for patients with inherited predisposition to bleeding or for patients receiving a full dose of anticoagulative treatment prior to start of treatment with nintedanib. In patients on chronic low dose therapy with low molecular weight heparins or acetylsalicylic acid, no increased frequency of bleeding was observed. Patients who developed thromboembolic events during treatment and who required anticoagulant treatment were allowed to continue nintedanib and did not show an increased frequency of bleeding events. Patients taking concomitant anticoagulation, such as warfarin or phenprocoumon should be monitored regularly for changes in prothrombin time, international normalized ratio (INR), or clinical bleeding episodes (see SmPC section 4.4).

No increased frequency of cerebral bleeding in patients with adequately pre-treated brain metastases which were stable for ≥ 4 weeks before start of treatment with nintedanib was observed. However, such patients should be closely monitored for signs and symptoms of cerebral bleeding. Patients with active brain metastasis were excluded from clinical trials and are not recommended for treatment with nintedanib (see SmPC section 4.4).

Patients treated with Vargatef have an increased risk of venous thromboembolism including deep vein thrombosis. Therefore, patients should be closely monitored for thromboembolic events. Nintedanib should be discontinued in patients with life-threatening venous thromboembolic reactions (see SmPC section 4.4).

The frequency of arterial thromboembolic events was comparable between the two treatment arms in the phase 3 study 1199.13. Patients with a recent history of myocardial infarction or stroke were excluded from this study. However, an increased frequency of arterial thromboembolic events was observed in patients with idiopathic pulmonary fibrosis (IPF) treated with nintedanib monotherapy (data not shown). Therefore, caution should be used when treating patients with a higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischaemia (see SmPC section 4.4).

Based on the mechanism of action nintedanib may impair wound healing. No increased frequency of impaired wound healing was observed in trial 1199.13. No dedicated studies investigating the effect of nintedanib on wound healing were performed. Treatment with nintedanib should therefore only be initiated or - in case of perioperative interruption - resumed based on clinical judgement of adequate wound healing (see SmPC section 4.4).

The Applicant has not conducted a thorough QTc study of nintedanib in combination with docetaxel, but an analysis across all studies did not reveal any arrhythmogenic potential of nintedanib which is reassuring. However, since QT-prolongation is a recognised class effect of previous TKIs (Shah et al, 2013), caution should be exercised when administering nintedanib in patients who may develop QTc prolongation (see SmPC section 4.4). Cardiac failure and QT prolongation have also been included in the RMP as important potential risks based on findings with some approved TKIs.

Hypertension is considered an important potential class effect of VEGFR inhibitors and can lead to discontinuation of treatment, hospitalisation, and can be fatal or life-threatening. However, the overall frequency of patients with AEs within the SMQ ‘hypertension’ was low and lower than expected from other VEGFR inhibitors. The AEs were mostly of mild to moderate severity and there were neither life-threatening nor hypertension AEs with a fatal outcome. In line with the above, the frequency of patients who started new antihypertensive treatment during the on-treatment period was low (2.1% of the patients in the nintedanib arm vs 0.6% of the patients in the placebo arm in all treated patients. In line with other VEGFR inhibitors hypertension was included in the RMP as important potential identified risk.

In the two reported cases of overdose, AE occurred consistent with the known safety profile of nintedanib. There is no specific antidote or treatment for nintedanib overdose. In case of overdose, treatment should be interrupted and general supportive measures initiated as appropriate.

Dietary soya-products are known to cause allergic reactions including severe anaphylaxis in person with soya allergy. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations. Therefore, and due to the composition of Vargatef (see quality section), Vargatef is contraindicated in patients with hypersensitivity to nintedanib, peanut or soya, or to any of the excipients (see SmPC section 4.3).

Vargatef has also minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines during treatment with Vargatef (see SmPC section 4.7)

With regards to serious adverse events, SAEs were slightly more common in the nintedanib arm (34.4%) than in the placebo arm (31.5%) in trial 1199.13 (all patients). The majority of SAEs in both treatment arms appeared to be related to myelosuppression (i.e. febrile neutropenia, neutropenia, pyrexia and sepsis) and disease related symptoms (e.g. malignant neoplasm progression, dyspnoea, pneumonia, general physical health deterioration). The signs of myelosuppression may be seen in relation with the high level of grade ≥3 TEAEs pertaining to myelosuppression. More SAEs were also reported in the nintedanib arm (any grade; 34.7, grade ≥3; 31.3%) than in the placebo arm (any grade; 32.1, grade ≥3; 27.6%) in patients with adenocarcinoma. The frequencies of different SAEs were comparable to the frequencies of SAEs observed in all patients.

There was a higher incidence of AEs leading to death in the nintedanib arm. Time-to-death was similar for these patients when comparing the two treatment arms. Thus, it was that the add-on of nintedanib did not lead to earlier AEs leading to deaths. In the overall population in study 1199.13 the majority of AEs leading to death were due PD. In the placebo arm 25 AEs leading to death were not attributed to PD compared to 35 in the nintedanib arm. The higher exposure to study treatment and the longer time since first histological/cytological classification diagnosis in the nintedanib arm may be the only reasonable explanations for the difference in fatal AEs. The adjusted incidence rate ratio of nintedanib versus placebo for fatal AEs was 1.18 (95%CI 0.86, 1.62) in the adenocarcinoma population. However the analysis of fatal AEs was based on patients who died on treatment during administration of study drug + 28 days. The Applicant argued that such an analysis may be more specific to detect study treatment related differences between the two arms. This may be correct for some fatal AEs, but not necessarily for all fatal AEs since some will develop over a longer period of time. Consequently, the Applicant provided data that summarise non-PD deaths during treatment or ≤ 90 days post-treatment and >90 days post-treatment for all patients and adenocarcinoma patients in study 1199.13. The difference in non-PD deaths in the adenocarcinoma population was still present at +90 days. However, the time at risk adjusted analysis showed that the incidence rate ratio was comparable for all non-PD related deaths in the adenocarcinoma patient population (0.93 (95% CI: 0.63, 1.37)) which is reassuring.

With regard to deaths due to non-PD related AEs, there were slightly more cases of sepsis and respiratory failure in the nintedanib arm. Based on a review of the case reports, there did not appear to be an association between nintedanib treatment and respiratory failure. With regard to sepsis, a considerable number of patients had concomitant neutropenia. Myelotoxicity is a known AE of treatment with docetaxel. Thus, patients being treated with nintedanib and docetaxel have a higher risk of sepsis. This has been adequately addressed in the SmPC and RMP.

With regard to Asian patients, the number of patients with fatal non-PD deaths was comparable between the placebo and nintedanib group, but more than half of fatal respiratory and sepsis related non-PD deaths occurred in Asian patients. However, a review of the individual cases revealed no discernible clinical pattern. It is recognised that the numbers were very low, and that any interpretation of data should be made with caution. The fatal respiratory events had different underlying etiologies. Overall, there is no indication of any geographical pattern and the SAEs seem to be scattered all over Asia.

Since nintedanib is an add-on to docetaxel, it leads to more AEs and thereby potentially to more permanent discontinuations. In the adenocarcinoma population in study 1199.13 there were slightly more AEs leading to permanent discontinuation in the nintedanib arm in the adenocarcinoma population. These were mainly caused by liver enzyme increase. However, the differences were not considered to be substantial and did not lead to any major concerns. In the overall population in study 1199.13, the overall incidence of AEs leading to permanent discontinuations was considered similar. Some differences were observed, e.g. there were more cases of diarrhoea and malignant neoplasm progression. These events are adequately addressed in the SmPC and RMP.

There were a higher number of patients being treated with nintedanib subject to AEs leading to dose reductions. The main AEs were liver enzyme increase, vomiting, diarrhoea and nausea, which are adequately addressed in the relevant sections of the SmPC.

Special population

The safety of nintedanib in children aged 0-18 years has not been established and no data are available. In elderly patients (≥ 65 years), no overall differences in safety were observed.

No safety data are available in subpopulations with co-morbid CNS conditions such as dementia, depression, brain metastasis, or with co-morbid conditions such as arthritis and osteoporosis. Since these are common comorbidities in elderly cancer patients which may impact survival, treatment with Vargatef in these subpopulations has been included in the RMP under missing information.

Safety data for Black and African American patients are also limited.

The safety of nintedanib has not been studied in patients with severe renal impairment (<30 ml/min creatinine clearance) nor in patients with hepatic impairment classified as Child Pugh B and C. Therefore, treatment of patients with hepatic impairment and treatment of patients with renal impairment have been included as missing information in the RMP. In addition, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with Vargatef is not recommended.
Although the number of patients weighing <50 kg was rather small and safety data should be interpreted with caution, SAEs appeared to be more common in these patients compared to patients with a weight ≥ 50 kg. The higher frequency of SAEs observed in patients <50 kg is covered in the RMP. Close monitoring is recommended in patients weighing < 50 kg.

No safety data were provided on the use of Vargatef in pregnant women but pre-clinical studies in animals have shown reproductive toxicity of this active substance (see section on non-clinical aspects). Therefore, pregnancy testing should be conducted at least prior to treatment with Vargatef. Female patients should be advised to notify their doctor or pharmacist if they become pregnant during therapy with Vargatef.

Nintedanib exposure increased linearly with patient age, was inversely correlated to weight, and was generally higher in patients of Asian race (see clinical aspects, pharmacokinetics). This may result in a higher risk of developing liver enzyme elevations. Close monitoring is recommended in patients with several of these risk factors.

2.6.2. Conclusions on the clinical safety

The addition of nintedanib to docetaxel led to more adverse events which were expected. The higher incidence of neutrophil count decreased and neutropenia led to slightly more infections in the nintedanib arm which was expected due to the myelotoxic effects of docetaxel and the longer exposure to study treatment in the nintedanib arm.

Based on a thorough review of the deaths up to 90 days post-treatment and a risk adjusted analysis there is no indication of a relevant increase in of non-PD deaths due to nintedanib. The majority of the reported adverse events are considered manageable with dose reductions, supportive treatments and treatment interruptions. The most frequently reported adverse drug reactions (ADRs) specific for nintedanib were diarrhoea, increased liver enzyme values (ALT and AST) and vomiting.

As initial measure for the management of adverse reactions (see SmPC sections 4.2, 4.4 and 4.8) treatment with nintedanib should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy (to grade 1 or baseline). Nintedanib treatment may be resumed at a reduced dose. Dose adjustments in 100 mg steps per day (i.e. a 50 mg reduction per dosing) based on individual safety and tolerability are recommended. In case of further persistence of the adverse reaction(s), i.e. if a patient does not tolerate 100 mg twice daily, treatment with Vargatef should be permanently discontinued.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

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

PRAC Advice

The PRAC considered that the risk management system version 1.3 could be acceptable with revisions as described in the attached PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice with changes to the safety concerns and the pharmacovigilance plan.

The CHMP considered that final data from the on-going trials investigating hepatic impairment (1199.37, 1199.39 and 1199.120) will contribute in addressing the missing information on patients with moderate and severe hepatic impairment and addressing the possible influence of hepatic impairment on the PK of nintedanib. In addition, as the potential *in vitro* inhibitory effect of nintedanib on the kidney transporters OAT1 and OAT3 has not been investigated yet in accordance with the *Guideline on the investigation of drug interactions,* this issue is considered as missing information and the subject of a study in the pharmacovigilance plan.

The MAH implemented the changes requested in the RMP by PRAC and CHMP. The CHMP endorsed the Risk Management Plan version 1.4 with the following content.

Safety concerns

Summary of safety concerns	
Important identified risks	Diarrhoea Liver enzyme elevations and hyperbilirubinaemia Neutropenia Sepsis Venous thromboembolism Perforation (gastro-intestinal and non-gastro-intestinal) Bleeding Hypertension
Important potential risks	Arterial thromboembolism Treatment in pregnant women and teratogenicity Hepatic failure Cardiac failure QT prolongation
Missing information	Treatment of breastfeeding women Treatment of patients with hepatic impairment Treatment of patients with renal impairment Treatment of patients with healing wounds Treatment of subpopulations with co-morbid CNS conditions such as dementia, depression, brain metastasis, or with co-morbid conditions such as arthritis and osteoporosis Treatment of patients weighing < 50 kg *In vitro* inhibitory potential on OAT1 and OAT3

Pharmacovigilance plans

Table 65: Ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan

Activity/Study title (category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
1199.37: A multicentre, open label, phase I/ randomised phase II study to evaluate safety, pharmacokinetics and	Phase I: maximum tolerated dose (MTD) in patients with mild and moderate liver impairment and recommended dose for	Treatment of patients with hepatic impairment	Started	The final CTR including the PK analyses of patients of Group 1 and 2* is expected in Q1 2015.

efficacy of BIBF 1120 in comparison with Sorafenib for advanced hepatocellular carcinoma patients (category 3)	phase II Phase II: efficacy and safety of nintedanib as compared to sorafenib in patients with HCC			
1199.39: A multicenter, open label,phase I/ randomized phase II study to evaluate safety, pharmacokinetics and efficacy of BIBF 1120 in comparison with sorafenib for advanced hepatocellular carcinoma patients in Asia (category 3)	Phase I: MTD in patients with mild and moderate liver impairment and recommended dose for phase II Phase II: efficacy and safety of nintedanib as compared to sorafenib in patients with HCC	Treatment of patients with hepatic impairment	Started	The final CTR including the PK data for the patients of Group 1 and 2* will be available by Q1 2015.
1199.120: An open label, dose escalation phase I study to evaluate the safety and tolerability of continuous twice-daily oral treatment of nintedanib in Japanese patients with hepatocellular carcinoma (category 3)	To evaluate MTD in Japanese HCC and to recommend dose of nintedanib for further trials in two groups of patients according to liver function To evaluate PK of nintedanib and to explore a correlation of PK with degree of liver impairment	Treatment of patients with hepatic impairment	Started	Final data including PK data for the patients of Group 1 and 2* is expected for Q4 2015. The final CTR is projected for Q1 2016.
PK1407T: *In vitro* evaluation of the interaction of nintedanib with human OAT transporters (category 3)	To determine the interaction potential of BIBF 1120 toward OAT1 and OAT3	*In vitro* inhibitory potential on OAT1 and OAT3	Started	The final CTR is expected by end of 2014

* Group I included patients with AST and ALT ≤ 2xULN and Child Pugh A (score 5-6) at baseline. Group II included patients with AST or ALT >2xULN to ≤ 5xULN or Child Pugh B (score 7 only) at baseline.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Diarrhoea	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Sections 4.2, 4.4, 4.8, 5.1, and 5.3).	None.
Liver enzyme elevations	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC	None.

and hyperbilirubinaemia	Sections 4.2, 4.4, 4.8, 4.9, 5.2, and 5.3).	
Neutropenia	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Sections 4.2, 4.4, and 4.8).	None.
Sepsis	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Sections 4.2, 4.4, and 4.8).	None.
Venous thromboembolism	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Sections 4.2, 4.4, and 4.8).	None.
Perforation (gastro-intestinal and non-gastro-intestinal)	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Sections 4.4 and 4.8).	None.
Bleeding	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Sections 4.2, 4.4, and 4.8).	None.
Hypertension	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Section 4.8)	None
Important potential risks		
Arterial thromboembolism	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Section 4.4).	None.
Treatment in pregnant women and teratogenicity	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Sections 4.3, 4.6, and 5.3).	None.
Hepatic failure	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Sections 4.2, 4.4, 4.8, 4.9, 5.2, and 5.3).	None.
Cardiac failure	Routine risk minimisation by routine pharmacovigilance	None
QT prolongation	Routine risk minimisation by routine pharmacovigilance and means of labelling (SmPC Sections 4.4 and 5.1).	None
Missing information		
Treatment in breastfeeding women	Routine risk minimisation by routine pharmacovigilance and appropriate labelling (SmPC Sections 4.6 and 5.3).	None.

Treatment of patients with hepatic impairment	Routine risk minimisation by routine pharmacovigilance and appropriate labelling (SmPC Sections 4.2, 4.4, and 5.2).	
Treatment of patients with renal impairment	Routine risk minimisation by routine pharmacovigilance and appropriate labelling (SmPC Sections 4.2 and 5.2).	None.
Treatment of patients with healing wounds	Routine risk minimisation by routine pharmacovigilance and appropriate labelling (SmPC Section 4.4).	None.
Treatment of subpopulations with co-morbid CNS conditions such as dementia, depression, brain metastasis, or with co-morbid conditions such as arthritis and osteoporosis	Routine risk minimisation by routine pharmacovigilance and appropriate labelling (SmPC Section 4.4).	None.
Treatment of patients weighing < 50 kg	Routine risk minimisation by routine pharmacovigilance and appropriate labelling (SmPC Sections 4.4 and 5.2).	None.
In vitro inhibitory potential on OAT1 and OAT3	Routine risk minimisation by routine pharmacovigilance.	None

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The benefits with the addition of nintedanib to docetaxel were: an increase in progression – free survival (PFS) of 1.4 months (4.2 months in the nintedanib plus docetaxel arm as compared to 2.8 months in docetaxel plus placebo arm), also expressed as a reduction in the risk of progression or death by 16 % (hazard ratio [HR] 0.84; 95 % confidence interval [CI]: 0.71; 1.00, *p*=0.0485) and an increase in Overall survival (OS) by 2.3 months (OS was 12.6 months in the nintedanib plus docetaxel arm as compared to 10.3 months in the docetaxel plus placebo arm).

The data show a clinically relevant PFS gain by independent central review in favour of the nintedanib arm as demonstrated by a hazard ratio of 0.85 (95%CI: 0.75; 0.96, p=0.0070) in the overall patient population. While the OS in the overall population did not show a statistically significant difference, there is evidence towards an improvement in OS of nintedanib+docetaxel in the adenocarcinoma population with HR of 0.83 (95%CI, 0.70; 0.99, p=0.0359) with no dentrimental effect on QoL. These results are supported by PFS by investigator (secondary endpoint), which also demonstrates a statistically significant HR (0.82). Statistically significant improvements in PFS were also seen for the strata of patients with adenocarcinoma histology; HR 0.84 (95% CI 0.71, 1.00). There seems to be a consistent treatment effect across the majority of subgroups, both for PFS and OS, with regard to the adenocarcinoma population.

Uncertainty in the knowledge about the beneficial effects

Nintedanib is a multi-targeted therapy, and response to treatment would be expected to be linked to expression of molecular markers. Tumour marker analysis had been identified as crucial by the CHMP SAWP; suitable bio-/tumour markers (including VEGF) to allow identification and selection of a more targeted population of patients most likely to benefit from the treatment of nintedanib, will be investigated as part of a Biomarkers research programme and results will be provided as a post-authorisation condition (See Annex II,).

The subgroup of patients with a disease stage < IIIB/IV and the subgroup with brain metastases did not seem to benefit from nintedanib. However, the numbers are low and the point estimate is associated with a very wide confidence interval, and no further data can be requested.

Risks

Unfavourable effects

Patients in the nintedanib arm were more likely to experience Grade 3/4/5 adverse events than in the placebo arm. Of these, the most common AEs were: liver enzyme elevations, nausea, vomiting, decreased WBC and neutrophils, diarrhoea, and neutropenia.

Some adverse events of specific interest also occurred more frequently than others in the nintedanib arm: diarrhoea, nausea and liver-related adverse events. There were slightly more patients identified with the SMQ hepatic failure and non-gastro-intestinal perforations in the nintedanib versus the placebo arm. In addition, there is some evidence that nintedanib in combination with docetaxel leads to a higher incidence of neutropenia, although only slight differences in infections and febrile neutropenia were observed. With regard to serious adverse events, there were some slight differences in the incidences of Grade 3/4/5 SAEs neutropenia and malignant neoplasm progression.

More cases of sepsis and fatal sepsis were observed in the nintedanib arm. Sepsis and febrile neutropenia have been reported as subsequent complications of neutropenia. The rates of sepsis (1.3 %) and febrile neutropenia (7.5 %) were increased under treatment with nintedanib as compared to the placebo arm.

Differences were observed on the safety of nintedanib in special populations (gender, never-smokers etc.). Females appeared to be more likely to experience adverse events belonging to the SMQ of liver related investigations. Also, never-smokers were more likely to experience neutropenia, adverse events under the SMQ liver related investigations and specific liver related investigations.

Overall, these adverse events are adequately addressed in the SmPC and in the RMP. Overall, the majority of the reported adverse events are considered manageable with dose reductions, supportive treatments and treatment interruptions.

There was also a higher incidence of adverse events leading to non-PD deaths in the nintedanib arm. However, based on a thorough review of these deaths up to 90 days post-treatment and a risk adjusted analysis showing an incidence rate ratio of 0.93 (95% CI: 0-63, 1.37) there is no indication of a relevant increase in non-PD deaths due to nintedanib.

Uncertainty in the knowledge about the unfavourable effects

The safety of nintedanib in special populations is not entirely clear. Further safety data will be collected post-marketing as reflected in the risk management plan.

In particular, no safety data are available in the following populations: children aged 0-18 years, patients with co-morbid CNS conditions, patients with severe renal impairment, patients with hepatic impairment classified as Child Pugh B and C, patients weighing <50 kg, patients with healing wounds, as well as pregnant and breastfeeding women. In addition, safety data for Black and African American patients are limited. Information on special populations has adequately reflected in the different sections of the SmPC as a risk minimisation measure.

Benefit-risk balance

Importance of favourable and unfavourable effects

The slowing of disease progression and prolonging life is of utmost importance in a population of patients with NSCLC and in cancer patients in general. The risk of death due to infections and sepsis is manageable.

Benefit-risk balance

Overall, based on the results of the pivotal study 1199.13 and supportive study 1199.14 it can be concluded that the benefit-risk balance of nintedanib in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy is positive.

Discussion on the benefit-risk balance

Available data showed a clinically relevant difference in PFS.

Delaying progression of disease is of importance to the patients. Furthermore, a clinically relevant OS improvement was observed in patients with adenocarcinoma with T<9 months and the adenocarcinoma population in general. In the context of patients with NSCLC stage IIIB and IV disease with a median survival of approximately 10 months and 6 months respectively, an improvement of 2.3 months in OS in favour of nintedanib in the subgroup of patients with adenocarcinoma histology is considered clinically relevant. With regard to patients with adenocarcinoma and T<9 months, the OS difference is even more pronounced (3 months in favour of nintedanib).

The addition of nintedanib to docetaxel did not result in any unexpected safety signals and no detrimental effect on HRQoL could be observed, other than an increased risk of diarrhoea, which did not have any substantial effect on QoL.

Both background treatments (docetaxel and pemetrexed) in studies 1199.13 and 1199.14 are well-known and reflect current clinical practice. Analyses of OS for the nintedanib-docetaxel combination in second-line resulted in comparable improvement in OS regardless of whether patients were treated with pemetrexed in first-line or not. No treatment interaction was found between treatment arm and first-line pemetrexed treatment when these groups were compared.

Overall, the risks of nintedanib in combination with docetaxel in the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy, are in general manageable by dose adjustments and out-weighted by the benefits consisted of clinically relevant PFS in the overall population, which is accompanied by an increase in OS.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Vargatef in combination with docetaxel in the treatment of of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy, 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 restricted 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.

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to investigate suitable bio-/tumour markers (including VEGF) to allow identification and selection of a more targeted population of patients most likely to benefit from the treatment of nintedanib, the Applicant will conduct and submit results from a Biomarkers research programme including:	Results will be provided on a yearly basis.
1. Collected blood samples from the LUME-Lung 1 and LUME-Lung 2 studies will be assessed for germline genetic variability in angiogenic factors, including VEGF or its downstream receptors.	Submission of final study report of the single-arm study: Q3 2021
2. Single arm study to examine whether genetic/genomic markers (alone or combined with clinical covariates) could be used to predict overall survival (OS) in NSCLC patients eligible for treatment with nintedanib.	
3. Data on bio-/tumour markers from all clinical studies in the clinical program for nintedanib. The applicant will implement collection of material for biomarker investigation and analyses of biomarker data into the study protocol of all new oncology studies planned for nintedanib in the future, wherever clinically appropriate.	

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.