Clinical Trial Protocol

	Document Number:	**c03853814-03**
EudraCT No.: **EU Trial No:**	2015-005664-41	
BI Trial No.:	1199.238	
BI Investigational Product:	Vargatef®, Nintedanib	
Title:	A Phase I trial to investigate the effect of nintedanib on the pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in patients with non-small cell lung cancer	
Lay Title:	Investigation of the effect of nintedanib on the pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in patients with non-small cell lung cancer	
Clinical Phase:	I	
Trial Clinical Monitor:	Phone: Fax:	
Coordinating Investigator:	Telefon: Fax:	
Status:	Final Protocol (Revised protocol (based on global amendment 2))	
Version and Date:	**Version: 3.0**	**Date: 09 Mar 2017**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Vargatef®	
Name of active ingredient:		Nintedanib	
Protocol date: **17 February 2016**	**Trial number:** **1199.238**		**Revision date:** **09 Mar 2017**

Title of trial:	A Phase I trial to investigate the effect of nintedanib on the pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in patients with non-small cell lung cancer
Coordinating Investigator:	Telefon: Fax:
Trial sites:	Multi-centre
Clinical phase:	I
Objective:	To investigate the effect of multiple oral doses of nintedanib on the single dose kinetics of a combination of ethinylestradiol and levonorgestrel (Microgynon®)
Methodology:	Open-label, two-period, fixed sequence
No. of patients:	Up to approximately 24 patients may be enrolled
total treated:	14 patients who have completed the trial and are evaluable for both treatment periods
each treatment:	14
Diagnosis :	Non-small cell lung cancer (NSCLC) with histology of adenocarcinoma
Main criteria for inclusion:	Patients with NSCLC with histology of adenocarcinoma who are eligible for therapy with nintedanib in accordance with the instructions in the SmPC and who have given informed consent

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Vargatef®	
Name of active ingredient:		Nintedanib	
Protocol date: **17 February 2016**	**Trial number:** **1199.238**		**Revision date:** **09 Mar 2017**

Trial product 1:	Microgynon® tablets
dose:	One tablet containing 30 microgram ethinylestradiol (EE) / 150 microgram levonorgestrel (LE) per tablet in each trial period
mode of administration:	Oral with 240 mL of water
Trial product 2:	Nintedanib soft gelatine capsule (containing 100 mg nintedanib) or Nintedanib soft gelatine capsule (containing 150 mg nintedanib)
dose:	2 x 200 mg per day, dose reduction to 2 x 150 mg if required
mode of administration:	Oral with food and 240 mL of water
Duration of treatment:	Reference (Period 1): 1 tablet Microgynon® will be administered after a standardised breakfast, at the latest 7 days before the first administration of nintedanib Test (Period 2): Microgynon® will be administered together with nintedanib on the pharmacokinetic (PK) day after continuous intake of nintedanib for at least 7 consecutive days On the PK-profile day, 1 tablet of Microgynon® will be given together with the morning dose of nintedanib in the morning after a standardised breakfast. 12 hours later the evening dose of nintedanib will be administered. The PK-profile day should be followed by continuous intake of nintedanib for at least 2 further days Treatment with nintedanib may be continued at the discretion of the investigator according to the label
Endpoints	Primary endpoints: AUC_{0-tz} and C_{max} for ethinylestradiol and levonorgestrel Secondary endpoints: $AUC_{0-\infty}$ for ethinylestradiol and levonorgestrel

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Vargatef®	
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Safety criteria:	Adverse events (AEs) including clinically relevant findings from the physical examination, safety laboratory tests, vital signs
Statistical methods:	Relative exposure of ethinylestradiol and levonorgestrel will be estimated based on the ratios (test to reference treatment) of the geometric means (gMeans) of the primary and secondary endpoints. Additionally, their 2-sided 90% confidence intervals (CIs) will be provided. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale, including effects for 'subject', 'period', and 'treatment'. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Overview

Trial Periods		**Screening Period**	**Period 1**					**Period 2 ****					**End of Trial**
Visit		1	2					3					4
Day		-28	-7#	-6#	-5#	-4#	1	7	8 #	9 #	10 #	11 #	##
Informed consent		x											
Demographics		x											
Medical history		x											
Physical examination		x	x						x				x
Vital signs		x	x						x				x
Laboratory tests		x	x		x				x				x
12 lead-ECG		x	x										x
Review of in-/exclusion criteria		x	x										
PK sampling for nintedanib	-00:35								x	x	x		
Dispense nintedanib						x		x		x	x	x	
Continuous intake of nintedanib							x----------						----->
PK Sampling: predose Microgynon®			x						x				
Standardised meal before Microgynon® intake	-00:30		x						x				
Administration Microgynon®			x										
Administration Microgynon® and Nintedanib									x				
PK Sampling after	00:30		x						x				
Microgynon®	01:00		x						x				
intake (in hours)	01:30		x						x				
	2:00*		x						x				
	03:00		x						x				
	4:00*		x						x				
	06:00		x						x				
	08:00		x						x				
	12:00		x						x				
	24:00			x						x			
	48:00				x						x		
	72:00					x						x	
Adverse events		x	x	x	x	x		x	x	x	x	x	x
Compliance check			x	x	x	x		x	x	x	x	x	x
Concomitant therapy		x	x	x	x	x		x	x	x	x	x	x
Completion of patient participation													x

\# day of nintedanib intake;
Microgynon® PK day during Period 1 may take place within day - 27 and day - 7 prior to first intake of nintedanib; results of screening examinations need to be awaited prior to proceeding with period 1;
if PK sampling in period 1 takes place between day -27 and -20, physical examination, vital signs, laboratory tests and 12 lead ECG do no not need to be repeated on day -7 unless AE occurred during that timeframe or it is clinically indicated;
laboratory test results need to be checked prior to dispension of Nintedanib;
administration of Microgynon® during Period 2 may take place within day 8 and 16 of continuous nintedanib intake;
day 1 in Period 2 is an optional visit that might be performed in case nintedanib was not handed out in Period 1

\## at the earliest on day 3 after last intake of Microgynon®

* administration of 240 mL of water

** It is assumed that Period 2 will happen during the first treatment course of docetaxel/nintedanib. However, if the patient would not be able to continuously take nintedanib for at least seven days before intake of Microgynon® during the first treatment course, then the second administration of Microgynon® might also be administered during one of the next treatment courses

Detailed Overview for PK days

Period	Day	Planned Time	Approximate clock time of actual day [h:min]	Event and comment	PKblood for EE and LE	PKblood for nintedanib
		[h:min]				
1	-7	pre-dose		Physical examination		
		pre-dose		Review inclusion/exclusion criteria		
		pre-dose		Vital signs		
		pre-dose		Laboratory tests		
		pre-dose		12 lead-ECG		
		pre-dose		Adverse events		
		pre-dose		Concomitant therapy		
		pre-dose		Compliance check		
		-00:35			X	
		-00:30		Breakfast		
		00:00		Drug administration Microgynon®		
		00:30			X	
		01:00			X	
		01:30			X	
		02:00		240 mL tap water	X	
		03:00		Adverse events	X	
		04:00		240 mL tap water, lunch	X	
		06:00			X	
		08:00			X	
		10:00		Snack		
		12:00		Adverse events	X	
	-6	24:00		Adverse events, Concomitant therapy, Compliance Check	X	
	-5	48:00		Adverse events, Concomitant therapy, Compliance Check	X	
	-4	72:00		Adverse events, Concomitant therapy, Compliance Check	X	
2	8	pre-dose		Physical examination		
		pre-dose		Vital signs		
		pre-dose		Laboratory tests		
		pre-dose		Adverse events		
		pre-dose		Concomitant therapy		
		pre-dose		Compliance check		
		-00:35			X	X
		-00:30		Breakfast		
		00:00		Drug administration Microgynon® and Nintedanib intake		
		00:30			X	
		01:00			X	
		01:30			X	
		02:00		240 mL tap water	X	
		03:00		Adverse events	X	
		04:00		240 mL tap water, lunch	X	
		06:00			X	
		08:00			X	
		10:00		Snack		
		11:55			X	
		12:00		Adverse events, Nintedanib intake		
	9	23:55		Adverse events, Concomitant therapy, Compliance Check	X	X
		24:00		Nintedanib intake		
	10	47:55		Adverse events, Concomitant therapy, Compliance Check, Laboratory tests	X	X
		48:00		Nintedanib intake		
	11	71:55		Adverse events, Concomitant therapy, Compliance Check	X	
		72:00		Nintedanib intake		

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AMP	Auxiliary Medicinal Product
ANOVA	Analysis Of Variance
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
BLQ	Below the Limit of Quantification
CA	Competent Authority
CI	Confidence Interval
gCV	Coefficient of variation
C_{max}	Maximum blood concentration
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP3A4	Cytochrome P450 3A4
DEDP	Drug Exposure during Pregnancy
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
EE	EthinylEstradiol
EMA	European Medicines Agency
ES	Entered Set
EDTA	Ethylene Diamine-Tetraacetic Acid
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
γ-GT	Gamma Glutamyl Transferase
GMP	Good Manufacturing Practice
gMean	geometric Mean
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalised Ratio

IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
ISF	Investigator Site File
HPLC-MS/MS	High-Performance Liquid Chromatography tandem Mass Spectrometry
LE	Levonorgestrel
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRHD	Maximum Recommended Human Dose
MTD	Maximum Tolerated Dose
NC	Not Calculated
NIMP	Non Investigational Medicinal Product
NOA	Not Analysed
NOS	No Sample
NOR	No valid result
NSCLC	Non-Small Cell Lung Cancer
OPU	Operating Unit
PK	Pharmacokinetic(s)
PKS	PK analysis Set
PMDA	Pharmaceuticals and Medical Devices Agency
PXR	Pregnane X Receptor
RDC	Remote Data Capture
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
SAE	Serious Adverse Event
SOP	Standard Operation Procedures
S(m)PC	Summary of Product Characteristics
TCM	Trial Clinical Monitor
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UGT1A1	UDP-Glucuronyltransferase 1A1
US	United States of America
WBC	White Blood Cell Count
WHO	World Health Organisation

1. INTRODUCTION

Nintedanib was approved on 12 November 2014 by the European Medicines Agency (EMA) as follows: Nintedanib 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 nintedanib is 200 mg twice daily, administered approximately 12 hours apart, on days 2 to 21 of a standard 21 day docetaxel treatment cycle.

In addition to the indication NSCLC, nintedanib is also registered for the treatment of Idiopathic Pulmonary Fibrosis (IPF) in adult patients. The recommended dose is 150 mg nintedanib twice daily administered approximately 12 hours apart.

In the current Summary of Product Characteristics (SmPC), women of childbearing potential and eligible to treatment with nintedanib must use an effective contraceptive method as nintedanib may cause foetal harm in humans due to its mechanism of action. In addition, it is stated that the effect of nintedanib on the metabolism and efficacy of contraceptives has not been investigated. Thus, barrier methods should be applied as a second contraception method, to avoid pregnancy.

Considering the teratogenic potential of nintedanib, the combination of nintedanib and oral contraceptives containing ethinylestradiol (EE) and levonorgestrel (LE) may be widely used in a real world setting as part of the routine clinical practice. The concomitant administration of both nintedanib and an oral contraceptive must be safe and effective. This study will investigate the potential drug-drug interaction of both drugs as requested by the EMA.

1.2 DRUG PROFILE

1.2.1 Nintedanib

Mechanism of action

Nintedanib is a small molecule kinase inhibitor blocking vascular endothelial growth factor receptors 1-3, platelet-derived growth factor receptors α and ß and fibroblast growth factor1

receptors 1-3 kinase activity. Nintedanib binds competitively to the adenosine triphosphate 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 Fms-like tyrosine-protein kinase -3, lymphocyte-specific tyrosine-protein kinase and proto-oncogene tyrosine-protein kinase Src are inhibited.

The clinical development programme for nintedanib includes several cancer indications: NSCLC, ovarian cancer, colorectal cancer, renal cell carcinoma, and hepatocellular carcinoma. Nintedanib has also been studied in the non-cancer indication IPF and has been approved for this indication by United States of America Food and Drug Administration (US-FDA), EMA, Japanese PMDA and in several other countries.

A wide range of nintedanib monotherapy doses was investigated in Phase I and II trials, by using doses from 50 to 450 mg once daily and from 150 to 300 mg twice daily. In Phase I dose escalation trials, the predominant dose limiting toxicities were gastrointestinal adverse events and fully reversible increases of liver enzymes (Alanine Aminotransferase [ALT], Aspartate Aminotransferase [AST], gamma glutamyl transferase [γ-GT]) not accompanied by relevant bilirubin increases, and the maximum tolerated dose (MTD) was determined as 2 x 250 mg in Caucasian patients (U10-1846).

In Phase I trials combining nintedanib with docetaxel, pemetrexed, paclitaxel/carboplatin or mFOLFOX6, the recommended dose of nintedanib was established to be 2 x 200 mg in Caucasians (c01632700). The pattern of adverse events (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 trials, a nintedanib dose of 2 x 200 mg was selected for further Phase III trials.

Of over 3300 cancer patients included in 3 Phase III trials in NSCLC or ovarian cancer, approximately 1900 patients have received nintedanib in combination with the cytotoxic chemotherapy that is standard for the respective indication, namely, docetaxel, pemetrexed or paclitaxel/carboplatin.

After administration as a soft gelatine capsule, nintedanib is absorbed quickly; maximum plasma concentrations are reached within 2 to 4 h. Nintedanib follows at least bi-phasic disposition kinetics. After intravenous administration, it showed a volume of distribution of 1050 L. Non-clinical data suggest a homogenous distribution of the drug, with the exception of the central nervous system, and no marked affinity or retention in any tissue. Nintedanib undergoes a high first-pass metabolism and is primarily metabolised by hydrolytic cleavage by esterases, resulting in the free acid moiety BIBF 1202. Subsequently, BIBF 1202 is glucuronidated by various UGT enzymes, forming BIBF 1202 glucuronide. Metabolism via CYP enzymes plays a minor role. After intravenous administration, nintedanib showed a high total plasma clearance (gMean: 1390 mL/min). Nintedanib is predominantly eliminated via metabolism and biliary/faecal excretion (about 94%). Renal excretion is a minor elimination pathway, both after intravenous and oral administration. The gMean terminal half-life of nintedanib in patients was 10 to 15 h. Dose-proportional behaviour of C_{max} and AUC was concluded based on several studies in cancer patients investigating doses from 50 to 450 mg once daily and from 150 to 300 mg twice daily.

Based on *in vitro* investigations, relevant interactions of nintedanib with other drugs via the CYP enzyme system or via glucuronidation reactions are not expected. Transporter profiling was performed for nintedanib and its 2 main metabolites. In general, any interactions with

transporter substrates were considered unlikely. Nintedanib is a P-gp substrate. In the drug-drug interaction trial 1199.161 (c01762736), exposure to nintedanib in healthy volunteers increased by about 1.6- to 1.7-fold for AUC and by about 1.8-fold for C_{max} following concomitant administration with the potent P-gp inhibitor ketoconazole. Thus, if administered concomitantly with nintedanib, potent P-gp inhibitors (e.g. ketoconazole, erythromycin) may increase nintedanib exposure. After concomitant administration with the potent P-gp inducer rifampicin, exposure to nintedanib decreased to approximately 50% based on AUC and to approximately 60% based on C_{max}. Thus, potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, St. John's Wort) may decrease the exposure to nintedanib.

Additional data on the pharmacokinetics (PK) of nintedanib in patients with hepatic impairment are available from a dedicated single dose trial in otherwise healthy patient volunteers with hepatic impairment (Child Pugh categories A and B) plus matched healthy controls. Exposure in study 1199.200 increased by approximately 2-fold in patients with mild liver impairment defined as Child Pugh category A, and by approximately 8-fold in patients with moderate liver impairment defined as Child Pugh category B (c03149997).

Pharmacodynamic effects

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. vascular endothelial growth factor receptors and fibroblast growth factor) 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 a 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.

Reproduction toxicity

In rats, embryo-foetal lethality and teratogenic effects were observed at exposure levels below human exposure at the Maximum Recommended Human Dose (MRHD) of 150 mg twice daily. Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels.

In rabbits, embryo-foetal lethality and teratogenic effects were observed at an exposure approximately 3 times higher than at the MRHD but equivocal effects on the embryo-foetal development of the axial skeleton and the heart were noted already at an exposure below that at the MRHD of 150 mg twice daily.

In a pre- and postnatal development study in rats, effects on pre- and post-natal development were seen at an exposure below the MRHD.

A study of male fertility and early embryonic development up to implantation in rats did not reveal effects on the male reproductive tract and male fertility.

In rats, small amounts of radiolabelled nintedanib and/or its metabolites were excreted into the milk (≤ 0.5% of the administered dose).

Drug-drug interaction

Nintedanib does not induce CYP enzymes *in vitro* nor in rats *in vivo* (U09-1731, U04-2195). Therefore, the likelihood of nintedanib causing a relevant pharmacokinetic drug-drug interaction on oral contraceptives by induction of their metabolism that would lead to a loss of the pharmacodynamic action of these drugs is considered to be very low. Due to nintedanib´s teratogenic potential it is nevertheless required to perform a clinical study to investigate the potential effect of nintedanib on the pharmacokinetics of oral contraceptives.

For a more detailed description of the nintedanib profile please refer to the investigator drug brochure (c01632700) and to the product information for nintedanib (see Investigator Site File [ISF]).

1.2.2 Ethinylestradiol

Ethinylestradiol is a synthetic estrogen with actions similar to those of estradiol. It is frequently used as the estrogenic component of combined oral contraceptives; a typical daily dose is 20 to 40 µg. Ethinylestradiol is also used as an emergency contraceptive drug combined with levonorgestrel or norgestrel. A combined preparation of ethinylestradiol with the anti-androgen cyproterone is used for the hormonal treatment of acne and hirsutism, particularly when contraception is also required. Ethinylestradiol has also been used for hormone replacement therapy; doses of 10 to 20 µg daily are given (with a progestogen in women with a uterus), but natural estrogens are usually preferred. Ethinylestradiol is also used for the treatment of female hypogonadism and the palliative treatment of prostate cancer and malignant breast cancer.

The adverse effects of estradiol and other estrogens are related, in part, to dose and duration of therapy, and to the sex and age of the recipient. In addition, adverse effects may be modified by administration of progestogen in combined oral contraceptives or hormone replacement therapy. Whether adverse effects of natural and synthetic estrogens differ, and whether the route of administration has an effect, is less clear. The use of estrogens in girls may cause premature closure of the epiphyses resulting in decreased final adult height. Large doses of estrogens used in palliative care have also been associated with nausea, fluid retention, venous and arterial thrombosis, and cholestatic jaundice. In men, large doses of estrogen cause impotence and feminising effects, such as gynaecomastia. In women, uterine bleeding may occur after the cessation of estrogen therapy.

Ethinylestradiol is rapidly and well absorbed from the gastrointestinal tract with maximum plasma concentrations occurring after 1 h. The presence of an ethinyl group at the 17-position greatly reduces hepatic first-pass metabolism compared with estradiol, enabling the compound to be much more active after oral dosing, but there is some initial conjugation by the gut wall and systemic bioavailability is only about 45% (20-65%). Ethinylestradiol is highly protein bound (98%), but unlike naturally occurring estrogens, which are mainly bound to sex-hormone binding globulin, it is principally bound to albumin. The apparent volume of distribution is 2.8 to 8.6 L/kg. It is metabolised in the liver by hydroxylation (mediated by CYP3A4) followed by glucuronidation (UDP-Glucuronyltransferase 1A1 [UGT1A1]) and sulfation of metabolites that undergo enterohepatic recycling. Metabolites are excreted via urine (40%) and bile (60%). The terminal half-life of ethinylestradiol is 10 to 20 h (R12- 0034).

For a more detailed description of ethinylestradiol, please refer to the SmPC of Microgynon® (R12- 0034).

1.2.3 Levonorgestrel

Norgestrel and its active (-)-isomer, levonorgestrel, are progestogens derived from nortestosterone. They are more potent inhibitors of ovulation than norethisterone and have androgenic activity. Levonorgestrel is more commonly used than norgestrel and is twice as potent. Both are used as hormonal contraceptives. The typical daily levonorgestrel dose is 30 or 37.5 µg when used as an oral progestogen-only contraceptive, 100 to 250 µg when used for the monophasic portion of combined oral contraceptives, and 50 to 125 µg when used in triphasic preparations. Levonorgestrel is also used as a long-acting progestogen-only contraceptive by subcutaneous implantation. An intrauterine device containing levonorgestrel is available for contraception or menorrhagia. For emergency contraception, levonorgestrel may be given alone or in combination with ethinylestradiol.

Progesterone and the progestogens may cause gastrointestinal disturbances, changes in appetite or weight, fluid retention, oedema, acne, chloasma (melasma), allergic skin rashes, urticaria, mental depression, breast changes including discomfort or occasionally gynaecomastia, changes in libido, hair loss, hirsutism, fatigue, drowsiness or insomnia, fever, headache, premenstrual syndrome-like symptoms, and altered menstrual cycles or irregular menstrual bleeding. Anaphylaxis or anaphylactoid reactions may occur rarely (<0.01%).

Levonorgestrel is rapidly and almost completely absorbed after an oral dose and undergoes little first-pass hepatic metabolism. Maximum plasma concentrations occur 1 to 2 h after oral administration. Levonorgestrel is highly bound to plasma proteins, with 42 to 68% bound to sex hormone binding globulin and 30 to 56% bound to albumin. The proportion bound to sex hormone binding globulin is higher when levonorgestrel is given with an oestrogen.

Levonorgestrel is metabolised in the liver to sulfate and glucuronide conjugates, which are excreted in the urine (40 to 68% of dose) and to a lesser extent in the faeces (16 to 48% of dose). Levonorgestrel distributes into breast milk. The terminal half-life of levonorgestrel is approximately 25 h (R12-0034).

For a more detailed description of levonorgestrel, please refer to the SmPC of Microgynon® (R12- 0034 and R16-0717).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

According to the EMA guideline on the investigation of drug interactions (P15-06991) "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". This trial will be performed to fulfil requirements of the EMA guideline.

2.2 TRIAL OBJECTIVES

The aim of the trial is to evaluate the effect of chronic nintedanib intake on the pharmacokinetics of a contraceptive drug containing ethinylestradiol and levonorgestrel.

2.3 BENEFIT - RISK ASSESSMENT

2.3.1 Nintedanib

The patients will receive nintedanib according to the label in the most current SmPC (included in the ISF) to treat their underlying NSCLC. The potential side effects of nintedanib are as follows (as per SmPC): diarrhoea which may lead to loss of fluid and salts. To avoid loss of fluid, patients have to be reminded to drink enough fluid and antidiarrheal treatment shall be started. Further side effects are: painful, numb and/or tingling feeling in fingers and toes (peripheral neuropathy), feeling sick (nausea), throwing up (vomiting), pain in the stomach (abdomen), bleeding, rash, mucositis (including stomatitis), decreased appetite, electrolyte imbalance, increased liver enzyme values (alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase) in the blood as seen from blood tests and neutropenia (including febrile neutropenia and sepsis). Please refer to the SmPC for further potential side effects of Nintedanib.

The patients will not receive any additional benefit from participation in this trial, but are exposed to the risks of the trial procedures and the known risks of the trial medication. However, their participation in this trial may help guide the safe use of nintedanib together with ethinylestradiol / levonorgestrel in patients requiring this treatment.

2.3.2 Microgynon®

Microgynon® has been used for over 10 years and is generally well tolerated (R11-0382, R11-0385). The intake of combined oral contraceptives is associated with an increased risk of serious side effects such as cardiovascular diseases (myocardial infarction, cerebrovascular insult, venous thromboembolism) and breast and liver tumours. The incidence of venous thromboembolic events is 5-10 per 100,000 women in 1 year, if no hormonal contraceptives

are used. The incidence is increased to about 20/100,000 after intake of 2nd generation combined oral contraceptives (containing levonorgestrel, e.g. Microgynon®). In contrast, the intake of 3rd generation combined oral contraceptives (containing gestoden or desogestrel) is associated with a higher risk (up to 40/100,000) of thromboembolic events (R12-0033).

The most frequent side effects (>10%) of Microgynon® are headache, spotting and intermenstrual bleeding. Furthermore, the following undesirable effects have been observed: gastric upset, nausea, vomiting, breast tenderness, changes in body weight, changes in libido, and depression. In predisposed women, use of Microgynon® can sometimes cause chloasma which is exacerbated by exposure to sunlight. Women with a predisposition to pigment changes should avoid prolonged exposure to sunlight. Individual cases of poor tolerance of contact lenses have been reported with use of oral contraceptives; therefore, contact lens wearers who develop changes in lens tolerance should be assessed by an ophthalmologist. Menstrual changes associated with the use of oral contraceptives include reduction of menstrual flow and missed menstruation. Intermenstrual bleeding may occur, but normally ceases spontaneously.

Two doses of Microgynon® will be administered during this trial. Therefore, no undue risk is expected to trial participants.

2.3.3 Potential interaction between nintedanib and Microgynon®

The major enzyme involved in biotransformation of ethinylestradiol is CYP3A4. Based on *in vitro* data, nintedanib is neither an inducer nor an inhibitor of CYP enzymes. Therefore, the co-administration of nintedanib is not expected to cause an interaction with Microgynon®.

2.3.4 Drug induced liver injury

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.3.6.1.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The trial will be performed according to an open-label, two-period, fixed sequence design. Patients who are considered eligible for therapy with nintedanib to treat their non-small cell lung cancer, have given their informed consent, and meet all inclusion criteria and none of the exclusion criteria, will receive the first dose of Microgynon® at the latest 7 days before the first administration of nintedanib. A second dose of Microgynon® will be administered after continuous nintedanib intake for at least 7 consecutive days. Depending on the patient condition, this time point may vary between Day 8 and Day 16 of nintedanib administration. Blood for pharmacokinetic evaluation will be collected on the days of Microgynon® administration, and on the following 3 days. Adverse events and concomitant therapies will be recorded throughout the trial period, which ends once the patient has performed the end of trial visit. An overview of all relevant trial activities is provided in the Flow Chart. For visit schedule and details of trial procedures at selected visits, refer to Section 6.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate Investigators at different centres participating in this multicentre trial. Tasks and responsibilities are defined in a contract.

The trial will be performed by investigational sites who are experienced in performing clinical trials. The trial sites will be oncological sites, sites experienced in treating cancer patients or sites specialised in performance of clinical trials, and/or using a referral network of oncologists / physicians.

Boehringer Ingelheim has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOPs),
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CMLs), Clinical Research Associates (CRAs), and Investigators of participating country(ies).

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit [OPU]) in accordance with applicable regulations and internal SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management, Pharmacokinetics and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the investigator site file (ISF).

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

Patients, who are selected by their physician for therapy with nintedanib to treat their non-small cell lung cancer according to the market authorisation of nintedanib, may be eligible for this trial if they meet the inclusion and none of the exclusion criteria. Patients will be asked before starting the nintedanib therapy whether they would agree to participate in this Phase I trial. The patients will not have any benefit from intake of Microgynon® on two days during the trial period. The patients will be supervised by their treating physicians and adverse events occurring during the trial phase will be reported.

A non-randomised design was selected because the interaction with Microgynon® will be investigated in patients with a clearly defined treatment schedule of nintedanib. Therefore, kinetics of Microgynon® alone can only be determined before the start of nintedanib treatment. Systematic errors resulting from the fixed sequence are expected to be low because the trial duration is short enough so that nonspecific time-effects will be less important.

In the fixed sequence design, each patient serves as her own control. The comparison between treatments is based on a comparison within patients rather than between patients. This trial design, therefore, removes inter-patient variability from the comparison between treatments (R94-1529).

As requested per EMA Guideline (P15-06991), this trial will be performed to exclude potential inductive effects of nintedanib on the kinetics of Microgynon®. Induction of CYP3A4, the major enzyme involved in biotransformation of ethinylestradiol and levonorgestrel, is mediated by the nuclear receptor Pregnane X Receptor (PXR). Referring to the well characterized PXR inducer rifampicin, a full induction of drug metabolizing enzymes is reached in about one week after start of rifampicin treatment (P03-08008). Potential inductive effects of nintedanib will be investigated after 7 consecutive dosing days with nintedanib.

The open-label treatment is not expected to bias the results, since the study endpoints are derived from measurement of plasma concentrations of the analytes.

3.3 SELECTION OF TRIAL POPULATION

A total of 14 patients, who completed the trial and can be analysed for both treatment periods, are needed for the purpose of the trial. It is assumed that up to approximately 24 patients may have to be enrolled in several centres to achieve the goal that 14 patients completed the trial and are evaluable for the pharmacokinetic analysis..

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF at the investigational site, irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

Patients, who are selected by their physician for therapy with nintedanib to treat their non-small cell lung cancer according to the market authorisation of nintedanib, may be eligible for this trial if they meet the inclusion and none of the exclusion criteria. Please refer to Section

8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Female patients ≥ 18 years at screening
2. Female patient is postmenopausal or surgically sterilised (a postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy; in questionable cases a blood sample with simultaneous levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory [R16-0373])
3. Patient with locally advanced, metastatic or locally recurrent NSCLC with histology of adenocarcinoma
4. Nintedanib (Vargatef®) is planned to be prescribed in accordance with the marketing authorisation (SmPC)
5. Signed and dated written informed consent in accordance with Good Clinical Practice (GCP) and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

1. Any contraindication to nintedanib (Vargatef®), ethinylestradiol or levonorgestrel (Microgynon®), as specified in the respective labels
2. Use of hormone containing contraceptives (including vaginal and intrauterine devices and including hormone replacement therapy) within 30 days prior to first administration of Microgynon®
3. Systemic use of drugs known to induce (e.g. rifampicin, St. John's Wort, carbamazepine) or to inhibit (e.g. azole antimycotics, macrolides) CYP3A4 within 7 days prior to first trial drug administration until last PK-sampling in the trial. Exception: allowed is the intake of corticosteroids as docetaxel (pre)medication
4. History of major thrombotic or clinically relevant major bleeding event in the past 6 months
5. Persistence of clinically relevant therapy related toxicities (i.e. > Common Terminology Criteria for Adverse Events [CTCAE] grade 2) from previous chemotherapy and/or radiotherapy
6. Treatment with other investigational drugs or treatment in another clinical trial within the past four weeks before start of therapy or concomitantly with this trial
7. Gastrointestinal disorders or abnormalities that would interfere with absorption of the trial drugs
8. Major surgery (major according to the investigator's assessment) performed within 4 weeks prior to first treatment within the trial and without complete wound healing

9. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1 and Section 10) or any drug considered likely to interfere with the safe conduct of the trial
10. Patients unable to comply with the protocol
11. Previous enrolment in this trial

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep patients in the trial as scheduled. This includes careful patient selection and appropriate explanation of the trial requirements and procedures prior to enrolment, as well as an explanation of the consequences of premature withdrawal.

An individual patient is to be withdrawn from trial treatment if:

- The patient withdraws consent for trial treatment or trial participation, without the need to justify the decision
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases)
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and Section 6.2.3.

For all patients, the reason for withdrawal (e.g. adverse events) must be recorded in the Case Report Form (CRF). These data will be included in the trial database and reported.

If one of the following situations occurs, the patient may be replaced after discussion between investigator and the TCM.

- Microgynon® cannot be administered in Period 1 and Period 2
- Interruption of nintedanib therapy for a longer period of time so that no continuous intake of 7 consecutive days is given within this trial
- Dose reduction of nintedanib to less than 2 x 150 mg per day before end of PK sampling
- Administration of forbidden drugs (refer to Section 10)
- Noncompliance with dietary restrictions
- Inability of the patient to comply with the food intake on the days of Microgynon® administration

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the Clinical Trial Protocol (CTP), or the contract disturbing the appropriate conduct of the trial

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

All patients will be treated with Microgynon® and nintedanib. Nintedanib will be considered as Investigational Medicinal Product (IMP) in this trial.

4.1.1 Identity of the Investigational Medicinal Product (IMP)

Table 4.1.1: 1 Microgynon®

Substance:	combination of ethinylestradiol and levonorgestrel
Pharmaceutical formulation:	tablet
Source:	local manufacturer
Unit strength:	30 microgram ethinylestradiol (EE) / 150 microgram levonorgestrel (LE) per tablet
Posology:	1 tablet (in each trial period)
Route of administration:	oral

Table 4.1.1: 2 Nintedanib soft gelatine capsule

Substance:	nintedanib
Pharmaceutical formulation:	capsule
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	100 mg per capsule, 150 mg per capsule
Posology:	2 x 2 capsules containing 100 mg (2 x 1 capsule containing 150 mg in case of dose reduction)*
Route of administration:	oral

*nintedanib shall be taken continuously throughout Period 2. In case of a temporary interruption of nintedanib intake, patients can receive Microgynon® in Period 2 only if they have taken nintedanib for 7 consecutive days before intake of Microgynon®

4.1.2 Selection of doses in the trial

The recommended dose of nintedanib for treatment of NSCLC is 200 mg twice daily administered approximately 12 hours apart.

Dose adjustments of nintedanib shall follow the recommendation in the SmPC (included in the ISF). As initial measure for the management of adverse reactions (see SmPC) 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 as described in the SmPC.

Microgynon® will be administered only as single administration on the PK profiling days. One tablet of Microgynon® will be administered.

4.1.3 Method of assigning patients to treatment groups

This is a fixed sequence trial. All patients will undergo the respective treatment periods in an identical order.

4.1.4 Drug assignment and administration of doses for each patient

Patients will take one tablet of Microgynon® before the first intake of nintedanib (Period 1) and after continuous nintedanib administration for at least 7 consecutive days (Period 2).

On both pharmacokinetic profile days, a standardised meal (breakfast) has to be consumed within 30 minutes prior to Microgynon® intake. The meal should preferably be identical in both treatment periods. 30 Minutes after start of the standardised meal, Microgynon® will be administered. On the day of Microgynon® administration in Period 2, the morning dose of nintedanib will be taken together with Microgynon®.

The trial drugs will be administered in the standing position under supervision of the investigating physician or an authorized designee.

During the first 4 h after Microgynon® administration on the pharmacokinetic profile days, patients are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) unless supine positioning is required for trial related measurements.

Nintedanib will be taken by the patients at home except for the PK profiling days. The patients will be handed out the nintedanib medication (one bottle containing the medication for the respective time period) at the time points indicated in the Flow Chart. Nintedanib capsules shall be taken orally, preferably with food, swallowed whole with water, and must not be chewed or crushed. The patient shall be instructed to not skip any doses. If a dose is missed the next dose should be taken as scheduled. Under no circumstances should two doses be taken at the same time. In case of vomiting, the patient should not take a replacement dose.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This open-label trial will be handled as an unblinded trial by the sponsor.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The Investigator and/or Pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the Investigator / Pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

All patients are expected to be treated with nintedanib according to the labelling instructions i.e. in combination with docetaxel on days 2 to 21 of a standard 21 day docetaxel treatment cycle. Docetaxel therapy as well as pre-medication therapy for docetaxel shall be documented in the CRF.

There are no specific rescue drugs foreseen for the treatment of AEs. For treatment of adverse events such as diarrhoea, please refer to the SmPC of nintedanib. No special emergency procedures are to be followed. Treatment of the underlying cancer disease, concomitant diseases and/or adverse events and/or prophylactic antimicrobial therapy is allowed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy shall be administered except for therapy needed to treat the underlying cancer disease, baseline conditions, adverse events occurring during the trial, and/or as prophylaxis if considered necessary by the treating physician.

Concomitant therapy which may influence the motility or absorption of drug substance in the gastrointestinal tract (e.g. metoclopramide, erythromycin, loperamide, opioid analgesics) should be avoided 72 h prior to PK sampling. If such concomitant therapy is needed less than 72 h prior to the planned PK day, the PK day should preferably be moved such that 72 h without the respective concomitant therapy occurs.

All concomitant or rescue therapies will be recorded (including time of intake on the days of PK sampling) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site the patients are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart. No food is allowed for 4 h after Microgynon® intake.

Green tea, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 7 days before the first intake of Microgynon® in Period 1 and until the last PK sample has been collected in the trial in Period 2.

Alcoholic beverages are not allowed on the days when PK sampling takes place.

Smoking is not allowed during in-house confinement at the trial site.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed during in-house confinement at the trial site.

On the pharmacokinetic profile days, between breakfast and lunch, fluid intake is restricted to the water administered with the study drugs, and an additional 240 mL of water at 2 h and 4 h after intake of trial medication (mandatory for all patients).

A standardised meal will be served 30 min prior to Microgynon® administration.

4.2.2.3 Restrictions regarding women of childbearing potential

Not applicable.

4.3 TREATMENT COMPLIANCE

Patients will be asked to take their nintedanib medication as instructed by their treating physician. They shall be asked to report any instances when they could not take nintedanib as prescribed. The trial site will document the intake of nintedanib medication and provide an explanation in case the number of capsules expected to be taken differs from the actual number.

Microgynon® will be administered under the supervision of the treating physician or trial staff to whom this task was delegated. The intake will be documented in the CRF.

Patients will also be asked to adhere to the dietary restrictions.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

The primary objective is to assess the potential influence of continuous intake of nintedanib on the systemic exposure of ethinylestradiol and levonorgestrel when administered in combination, as assessed by the endpoints described in the following sections.

5.1.1 Primary Endpoints

C_{max} and AUC_{0-tz} for ethinylestradiol and levonorgestrel will be analysed after a single dose of the combination of ethinylestradiol and levonorgestrel before intake of nintedanib and after continuous intake of nintedanib for at least 7 consecutive days.

5.1.2 Secondary Endpoints

$AUC_{0-\infty}$ for ethinylestradiol and for levonorgestrel will be assessed after intake of a single dose of the combination of ethinylestradiol and levonorgestrel before intake of nintedanib and after continuous intake of nintedanib for at least 7 consecutive days.

5.2 ASSESSMENT OF EFFICACY

Not applicable.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A physical examination will be performed at the time point as indicated in the Flow Chart. Weight and height will be recorded at screening only.

5.3.2 Vital Signs

Vital signs, including blood pressure, temperature and heart rate, will be measured as indicated in the Flow Chart. Any new findings observed after the baseline assessment have to be reported as adverse events.

5.3.3 Safety laboratory parameters

Blood samples have to be collected at the time points specified in the Flow Chart. More frequent blood sampling may be done whenever the investigator deems necessary. Unscheduled safety laboratory examinations will be reported in the CRF along with the results. Blood sampling should not be done immediately before ECG recording.

Safety laboratory examinations will include haematology, biochemistry and coagulation parameters.

Haematology: haemoglobin, white blood cell count (WBC) with differential (manual differential count and absolute values if possible), platelets.

Biochemistry: glucose, sodium, potassium, calcium, creatinine, AST, ALT, alkaline phosphatase, lactate dehydrogenase, bilirubin (direct and indirect in case values are above upper limit of normal), uric acid, total protein, albumin.

Coagulation: activated partial thromboplastin time (aPTT) and international normalised ratio (INR).

5.3.4 Electrocardiogram

A 12-lead Electrocardiogram (ECG) has to be recorded at the time points specified in the Flow Chart. Any new findings observed after the baseline assessment have to be reported as adverse events.

5.3.5 Other safety parameters

Not applicable.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- results in death
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- requires inpatient hospitalisation or
- prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Planned hospitalisations due to periodic administration of chemotherapy for treatment of the underlying cancer disease will not be reported as serious adverse events.

AEs considered "Always Serious"

Every new occurrence of cancer of new histology must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.

The latest list of "Always Serious AEs" can be found in the RDC system. A copy of the latest list of "Always Serious AEs" will be provided to the Investigator upon request. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI

need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.

The following are considered as AESIs:

Hepatic injury

In this trial protocol, signs of hepatic injury are defined as:

- ALT and/or AST ≥8 fold ULN
- ALT and/or AST ≥3 fold ULN and total bilirubin ≥ 2 fold ULN*
- ALT and/or AST ≥3 fold ULN and unexplained INR > 1,5*
- ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%)*
- ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

* in the same blood draw sample.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to immediately stop the trial medication or are not allowed to start treatment and need to be followed up according to the "drug-induced liver injury (DILI) checklist" provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST and total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Gastro-intestinal perforation

Gastro-intestinal perforation shall be reported as AESI.

Intensity of AEs

The intensity of adverse events should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE Version 4.03).

Causal relationship of AEs

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.

- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

5.3.6.2 Adverse event collection and reporting

AE <u>Collection</u>

The Investigator shall maintain and keep detailed records of all AEs in their patient files.

The following must be collected and documented on the appropriate CRF(s) by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP), until individual patient's end of trial:
  -all AEs (serious and non-serious) and all AESIs.
- However, if an individual patient discontinues trial medication prematurely but stays in the trial (i.e. if further visits incl. telephone visits, or vital status assessments are planned) from then on and until the individual patient's end of the trial the Investigator must report related SAEs and related AESIs. Note: This is not applicable for the present trial.

- After the individual patient's end of trial:
  the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.

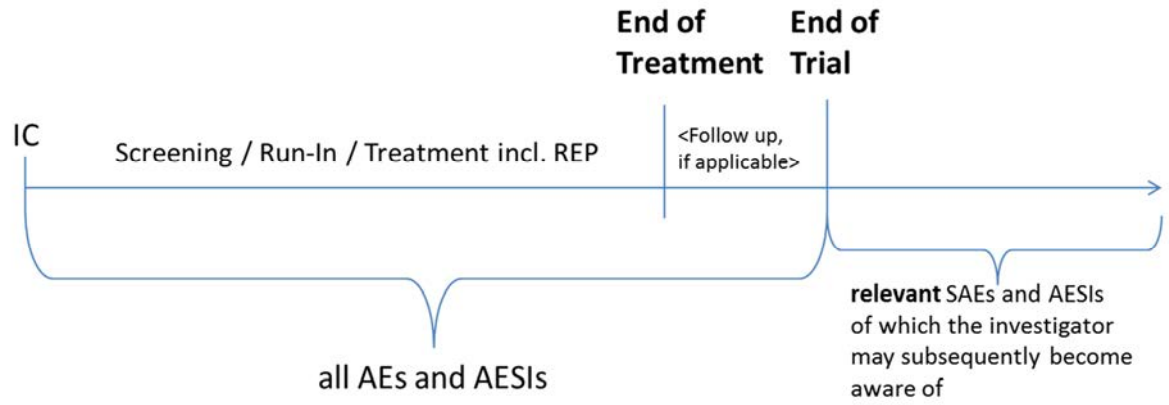

Figure 5.3.6.2: 1 Adverse Event Collection

The REP for Microgynon® is defined as 3 days after the intake of Microgynon®. The REP for nintedanib is 30 days. However, collection of adverse events will stop for an individual patient once the trial was completed for this respective patient, because nintedanib is expected to continue at the end of trial as standard of care. If a relevant SAE or AESI would be reported after the end of the trial for an individual patient, then this SAE / AESI would be considered as on-treatment for nintedanib if it occurred within 30 days after end of intake of nintedanib. All AEs which occurred through the treatment phase and throughout the REP will be considered as on-treatment, please see Section 7.3.4.

AE reporting to sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 h) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required

For each AE, the Investigator should provide the information requested on the appropriate CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drug(s) and a Non-Investigational Medicinal Product (NIMP) / Auxiliary Medicinal Product (AMP).

The following should also be recorded as an (S)AE in the CRF and SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions

- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

  If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

C_{max}, AUC_{0-tz}, and $AUC_{0-\infty}$ for ethinylestradiol and levonorgestrel will be evaluated to assess whether or not nintedanib has an influence on ethinylestradiol and/or levonorgestrel exposure. Pharmacokinetic plasma sampling will occur according to the Flow Chart.

After completion of the trial the plasma samples may be used for further methodological investigations, e.g. for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.4.2 Methods of sample collection

A detailed description of sample collection and handling is provided in the ISF. For plasma sampling time points, please refer to the Flow Chart. For quantification of drug plasma concentrations of ethinylestradiol, levonorgestrel, nintedanib and its metabolites BIBF 1202 and BIBF 1202 glucuronide, venous blood will be collected using a pre-labelled potassium ethylene-diamine-tetraacetic acid (EDTA) containing blood drawing tube. For quantification of ethinylestradiol, levonorgestrel and nintedanib and its metabolites plasma concentrations, approximately 8 mL of blood will be collected per time point. The obtained plasma will be transferred into 2-3 aliquots (nintedanib [when applicable], ethinylestradiol, levonorgestrel, and one back-up sample).

5.4.3 Analytical determinations

Nintedanib (in form of its free base BIBF 1120 BS), its metabolites BIBF 1202 (in form of the free zwitterion BIBF 1202 ZW) and the acylglucuronid thereof (BIBF 1202 glucuronide) plasma concentrations will be determined by a validated assay based on liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Plasma concentrations of ethinylestradiol and levonorgestrel will be determined by a validated HPLC-MS/MS assay (high performance LC-MS/MS).

The procedures and specifications of the analytical method are available at the bioanalytical site ([redacted]).

5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

Not applicable.

5.5 ASSESSMENT OF BIOMARKER

Not applicable.

5.5.1 Biobanking

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements conducted in the trial are using standard methods.

The pharmacokinetic parameters and measurements outlined in Section 5.4 are generally used as measurements to assess drug exposure.

6. INVESTIGATIONAL PLAN

For details see Flow Chart.

6.1 VISIT SCHEDULE

The patients will come to the hospital or Phase I unit at the time points specified. If a patient misses an appointment, it will be rescheduled if possible.

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and end of trial examination are given in the Flow Chart.

For planned individual plasma concentration sampling times, refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameters

The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

Days spent (including overnight stays) in hospital or Phase I unit for the purpose of the trial (e.g. collection of blood for PK analysis) will not be reported as serious adverse events.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Screening Period

The screening period starts with signature of the informed consent by the patient and ends before the administration of Microgynon® in period 1. The screening period may have a duration of up to 28 days (4 weeks), but may also be shorter.

Baseline Conditions

Any concomitant disease that requires therapy shall be recorded.

Medical History:

The medical history with regard to non-small cell lung cancer shall be documented (i.e. date of first diagnosis, as well as details concerning first-line therapy with start and end dates and the reason why second-line therapy is indicated i.e. date of most recent progression) and a statement is to be provided that the patient is a candidate for therapy with nintedanib according to the marketing authorisation.

6.2.2 Treatment period

Period 1: Microgynon®

Administration of Microgynon® alone will be performed in the time interval given in the Flow Chart. In the morning of the respective PK day (or the evening before depending on the patient situation and the agreement between investigator and patient) the patients will be admitted to the hospital or phase I unit and kept under medical surveillance for at least 12 h

following drug administration. The patients will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. In case the patient and the investigator would decide that the patient will stay overnight for administrative reasons, this planned overnight stay will not be reported as SAE. All other blood samplings of this trial period will be performed in an ambulatory fashion.

Period 2: Microgynon® during continuous intake of nintedanib

The patients will be instructed to take nintedanib every morning and every evening with food during Period 2. The intake of nintedanib on the non-PK days may be performed in an ambulatory fashion.

It is assumed that Period 2 will happen during the first treatment course of nintedanib. However, if the patient would not be able to continuously take nintedanib for at least 7 consecutive days during the first treatment course, then the second administration of Microgynon® might also be administered during one of the next treatment courses.

The administration of Microgynon® may vary between Day 8 and Day 16 of nintedanib intake. The second PK-profile day may take place only if a continuous intake of nintedanib for at least 7 consecutive days was confirmed.

In the morning of the respective PK day (or the evening before depending on the patient situation and the agreement between investigator and patient) the patients will be admitted to the hospital or Phase I unit and kept under medical surveillance for at least 12 hours following drug administration. Microgynon® and Nintedanib will be given concomitantly 30 minutes after the breakfast started. After the 12 h blood sample has been obtained, the evening dose of nintedanib will be administered. Thereafter the patients will be allowed to leave the trial site after formal assessment and confirmation of their fitness. In case the patient and the investigator would decide that the patient will stay overnight for administrative reasons, this planned overnight stay will not be reported as SAE.

All other blood samplings of this trial period may be performed in an ambulatory fashion. Nintedanib should be administered at least for the following 2 days (i.e. the morning administration is to be done after blood sampling at the trial site, while the evening intake is ambulatory).

6.2.3 Trial Completion

At the end of trial examination, the investigations, as documented in the Flow Chart, will be performed. The end of trial examination may take place at the earliest 3 days after last intake of Microgynon®.

The patient and investigator will assess whether the patient will continue nintedanib therapy according to the marketing authorization.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

The primary objective of the current study is to investigate the relative systemic exposure of EE and LE when given alone compared to administration in combination with steady-state nintedanib.

This open-label study consists of two periods. There will be a fixed sequence design: a single oral dose of Microgynon® will be administered alone (reference treatment, R), and in combination with 2 x 200 mg nintedanib at steady-state (test treatment, T).

For each comparison between test and reference treatment, the statistical model used will be an ANOVA (analysis of variance) model on the logarithmic scale (see Section 7.3.1).

7.2 NULL AND ALTERNATIVE HYPOTHESES

There is no hypothesis to be tested in a confirmatory sense. Instead, all parameters will be described in their entirety and evaluated by descriptive methods.

7.3 PLANNED ANALYSES

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol violations will be identified no later than in the Report Planning Meeting and provided in the Trial Statistical Analysis Plan (TSAP).

The following analysis sets will be defined for this trial:

- Entered set (ES):
  This patient set includes all patients who entered the trial, i.e., who have been assigned a patient number, whether treated or not.
- Treated set (TS):
  This patient set includes all patients in the ES who were documented to have received one dose of study drug. This is the full analysis set population in the sense of ICH-E9.
- PK parameter analysis set (PKS):
  - Plasma concentration data and parameters of a patient will be included in the statistical PK analyses if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a patient's data will be documented in the CTR.

- Relevant protocol violations may be
  - incorrect trial medication taken, i.e. the patient received at least one dose of trial medication the patient was not assigned to
  - incorrect dose of trial medication taken
  - use of restricted medications.
- Plasma concentrations and/or parameters will be considered as non-evaluable if, for example
  - the patient experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the patients experiencing emesis),
  - a pre-dose concentration is >5% of the C_{max} value of that patient,
  - missing samples/concentration data at important phases of PK disposition curve.
- The PK parameter analysis set includes all patients in the TS who provide at least one primary or secondary PK parameter that was not excluded according to the description above. Thus, a patient will be included in the PKS, even if she contributes only one PK parameter value for one period to the statistical assessment.

7.3.1 Primary endpoint analyses

The primary analyses will be based on the PKS (Section 7.3).

For each comparison between test and reference treatment, the statistical model used will be an ANOVA (analysis of variance) model on the logarithmic scale. Thus, prior to fitting the ANOVA model, the PK parameters described in 5.1.1 will be log-transformed (natural logarithm). The difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding Least Squares Means (point estimate).

Furthermore, the two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the ratio between response under test treatment and response under reference treatment.

The above mentioned ANOVA model will include effects accounting for the following sources of variation: ‘subjects’ and ‘treatment’. The effect ‘subjects’ will be considered as random, whereas the ‘treatment’ effect will be considered as fixed. The model is described by the following equation:

- $y_{km} = \mu + s_m + \tau_k + e_{km}$, where
- y_{km} = logarithm of response ($AUC_{0\text{-}tz}$ / C_{max}) measured on subject m receiving treatment k
- μ = the overall mean,
- s_m = the effect associated with the m^{th} subject
- τ_k = the k^{th} treatment effect, k = 1, 2,

- e_{mk} = the random error associated with the m^{th} subject who received treatment k.

7.3.2 Secondary endpoint analyses

The secondary PK parameters described in Section 5.1.2 will be analysed as described for the primary PK endpoints.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced.

The safety analysis will be based on the TS. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

The analyses will be done by 'treatment at onset'.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the REP (see Section 5.3.6.2) will be considered 'treatment-emergent'. Therefore, AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first Microgynon® intake until end of the REP of Microgynon® in Period 1 will be assigned to the Microgynon® treatment period. AEs from intake of Microgynon® until the REP of Microgynon® during Period 2 will be considered as on-treatment for Microgynon® plus nintedanib. All other AEs during nintedanib treatment up to the end of the trial will be assigned to on-treatment on nintedanib. Events after the REP of Microgynon® during Period 1 but prior to the start of nintedanib treatment in Period 2 will be considered as 'post-treatment' for Microgynon®. AEs after the end of trial examination will be assigned to 'post-study' unless they are within 30 days after last nintedanib intake. In this event they would be counted as on-treatment for nintedanib. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

Frequency, severity, and causal relationship of adverse events will be tabulated by treatment, system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Laboratory data and vital signs data will only be listed. Laboratory data will be compared to their reference ranges. Values outside the reference range will be flagged.

Relevant ECG findings will be reported as AEs.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Sections 5.1.1, 5.1.2 and 5.1.3 will be calculated according to the relevant BI internal procedures.

Descriptive evaluations of PK parameters will be based on the PKS (refer to Section 7.3).

Patients who are not included in the PKS will be reported with their individual plasma concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessments.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

The following descriptive statistics will be calculated for plasma concentrations and PK parameters: number (N), arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The exception to this is t_{max}, where only median, minimum and maximum will be calculated. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. Thereafter, the individual values, as well as the descriptive statistics, will be reported with three significant digits in the clinical trial report.

For handling of missing data, please refer to Section 7.5.3.

Analyses will be carried out using Phoenix® WinNonlin® 6.3 (or later) and/or SAS® software, version 9.4 (or later).

7.4 INTERIM ANALYSES

An interim analysis may be performed in case recruitment of patients is very slow and intermediate data would be needed for submission to regulatory authorities. Due to the exploratory nature of the trial, no adjustment of the analyses is necessary.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.5.2 Plasma concentration - time profiles

Handling of missing PK data will be performed according to the relevant Corporate Procedure of the Sponsor (001-MCS-36-472).

Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analysed), or BLQ (below the limit of quantification) will be ignored and not replaced by zero at any time point (applies also to the lag phase). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, NOA are included)

7.5.3 Pharmacokinetic parameters

In the non-compartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ values of the profile will be ignored.

Every effort will be made to include all concentration data in an analysis. If not possible, a case-by-case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.
- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However, the excluded concentration itself will be listed in the tables in section 15 of the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time is not recorded or is missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.6 RANDOMISATION

As this is a single fixed sequence trial, no randomisation is necessary.

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to obtain 14 patients who can be analysed with regard to the pharmacokinetic parameters in both periods. This sample size is considered sufficient to achieve the aims of this exploratory trial. Considering possible drop outs due to safety or administrative reasons and the potential intake of co-medication that might interfere with pharmacokinetics of Microgynon® (see Section 4.2.2.1) a total of approximately 24 patients may be enrolled (see Section 3.3.4.1). If there are less than 14 patients evaluable in both periods, the Trial Clinical Monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many patients will have to be enrolled in addition.

The observed intra-individual coefficient of variation (gCV) for EE and LE in previous trials in healthy volunteers (U12-1031; U09-1393; U07-1867; U03-3408; U09-1853) was roughly up to 20% for C_{max} and 15% for $AUC_{0\text{-}tz}$ or $AUC_{\tau,ss}$, respectively. Assuming a gCV of 20% and given the chosen sample size of 14 patients, the precision of the two-sided 90% confidence interval of the ratio test/reference (AUC and C_{max}) will be approximately 1.19 (upper confidence limit / point estimate); if only 12 patients will be evaluable in both periods, the precision would still be approximately 1.21. Table 7.7: 1 provides an overview of the 90% confidence intervals that are expected with 95% probability, for possible scenarios of the gCV and intra-patient ratios (test/reference) (T/R), and assuming available data for both periods.

Table 7.7: 1 Expected two-sided 90% confidence intervals for gCV=20% and different ratios T/R (N=8, 10, 12, 14 and 16)

gCV	N	Precision upper CL/ lower CL	Precision upper CL/ point estimate	T/R [%][1]	90% CI [%]
20%	8	1.702	1.305	70%	(53.65, 91.33)
				80%	(61.32, 104.38)
				90%	(68.98, 117.43)
				100%	(76.64, 130.47)
	10	1.562	1.250	70%	(56.01, 87.49)
				80%	(64.01, 99.99)
				90%	(72.01, 112.48)
				100%	(80.01, 124.98)
	12	1.474	1.214	70%	(57.66, 84.99)
				80%	(65.89, 97.13)
				90%	(74.13, 109.27)
				100%	(82.37, 121.41)
	14	1.416	1.190	70%	(58.82, 83.30)
				80%	(67.22, 95.20)
				90%	(75.63, 107.11)
				100%	(84.03, 119.01)

Table 7.7: 1 (con't) Expected two-sided 90% confidence intervals for gCV=20% and different ratios T/R (N=8, 10, 12, 14 and 16)

gCV	N	Precision upper CL/ lower CL	Precision upper CL/ point estimate	T/R [%]1	90% CI [%]
	16	1.372	1.171	70%	(59.77, 81.98)
				80%	(68.31, 93.69)
				90%	(76.85, 105.40)
				100%	(85.38, 117.12)

[1] Ratio of the geometric means (test/reference) for a PK endpoint defined by $\exp(\mu_T)/\exp(\mu_R)$

The expected 90% confidence limits in the table were derived by

$$\text{CI limit}_{\text{upper,lower}} = \exp(\ln(\theta) \pm \omega)$$

with θ being the ratio T/R on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

For these calculations the MOC3 routine from commercial software nQuery Advisor® 7.0 (Statistical Solutions, Ltd., Cork, Ireland; [R15-1331]) was used.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for GCP, relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the Investigator and of the sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report unless otherwise specified in the publication plan.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The Investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

The patients will receive reimbursement for participation in the trial which will cover the time they spent in the trial unit on the days of PK sampling, and the adherence to the dietary and other restrictions.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

Case Report Forms (CRF) for individual patients will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements the Investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

Before providing any copy of patients' source documents to the sponsor the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, date or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))

- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of Patient's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The Investigator / institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents / data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.

8.3.3 Storage period of records

Trial sites:

The trial sites must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.

Sponsor:

The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.
Data protection and data security measures are implemented for the collection, storage and

processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first patient in the whole trial.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out").

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

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10. APPENDICES

10.1 DRUGS THAT ARE NOT ALLOWED DURING THE TRIAL

CYP3A strong inhibitors:

- boceprevir,
- clarithromycin,
- conivaptan,
- indinavir,
- itraconazole,
- ketoconazole,
- lopinavir,
- mibefradil,
- nefazodone,
- nelfinavir,
- posaconazole,
- ritonavir,
- saquinavir,
- telaprevir,
- telithromycin,
- voriconazole.

CYP3A - strong inducers

- avasimibe
- carbamazepine,
- phenytoin,
- rifampin.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		28 April 2016
EudraCT number		2015-005664-41
BI Trial number		1199.238
BI Investigational Product(s)		Nintedanib, Vargatef®
Title of protocol		A Phase I trial to investigate the effect of nintedanib on the pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in patients with non-small cell lung cancer
To be implemented only after approval of the IRB / IEC / Competent Authorities		x
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		3.3
Description of change		male patients will not be included in the trial
Rationale for change		request by German Health Authority
Section to be changed		Synopsis, section 4.1.1, 4.1.2, 4.1.4
Description of change		one tablet of Microgynon® will be administered
Rationale for change		originally two tablets were planned to be administered to achieve a higher exposure that would be more close to the clinical use. Since female patients have a sufficiently high exposure after one tablet, it appears justified to administer one table as described in the SmPC of Micrgynon®
Section to be changed		5.3.6.2
Description of change		the paragraph describing pregnancy will be removed

Rationale for change		no female partner of male patients could become pregnant as males will not be included in the trial and the female patients included are surgically sterilised or postmenopausal

Number of global amendment		2
Date of CTP revision		09 Mar 2017
EudraCT number		2015-005664-41
BI Trial number		1199.238
BI Investigational Product(s)		Nintedanib, Vargatef®
Title of protocol		A Phase I trial to investigate the effect of nintedanib on the pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in patients with non-small cell lung cancer
To be implemented only after approval of the IRB / IEC / Competent Authorities		x
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Synopsis
Description of change		Change in responsibility: took over TCM ship
Rationale for change		Organisational change
Section to be changed		Flow chart
Description of change		Microgynon® PK day during Period 1 may take place within day - 27 and day - 7 prior to first intake of nintedanib; results of screening examinations need to be awaited prior to proceeding with period 1; if PK sampling in period 1 takes place between day

		-27 and -20, physical examination, vital signs, laboratory tests and 12 lead ECG do no not need to be repeated on day -7 unless AE occurred during that timeframe or it is clinically indicated; laboratory test results need to be checked prior to dispension of Nintedanib;
Rationale for change		One of the reasons for low recruitment is the fact that patients would like to receive their anti-cancer therapy as rapidly as possible after the diagnosis of relapse. In order to meet the patients' needs, enrolment of patients which have fulfilled dietary restrictions with regard to intake of green tea, grapefruits, Seville oranges (sour or bitter oranges) and their juices, dietary supplements and products including St. John's wort (Hypericum perforatum) and restricted concomitant therapies prior to enrolment and 7 days before the first intake of Microgynon® in Period 1 will be allowed. Confirmation and appropriate documentation of meeting the dietary restrictions and the restrictions regarding concomitant therapies in the time period prior to informed consent is regarded acceptable.
Section to be changed		Flow chart
Description of change		Laboratory tests on day -5
Rationale for change		Baseline laboratory tests upfront start of Nintedanib therapy are required in order to have the possibility to distinguish between Microgynon® and Nintedanib related effects.
Section to be changed		5.3.6.1
Description of change		These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to immediately stop the trial medication or are not allowed to start treatment and need to be followed up according to the "drug-induced liver injury (DILI) checklist" provided in the ISF.
Rationale for change		Laboratory test results on day -5 need to be checked prior to starting Nintedanib therapy.
Section to be changed		2.3.1
Description of change		Update of potential side effects of Nintedanib
Rationale for change		Update of Nintedanib SmPC

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Pharmacokinetics		09 Mar 2017 15:37 CET
Author-Trial Statistician		09 Mar 2017 15:42 CET
Approval-Therapeutic Area		09 Mar 2017 15:43 CET
Approval-Clinical Pharmacokinetics		09 Mar 2017 16:11 CET
Approval-Team Member Medicine		09 Mar 2017 23:22 CET
Approval-Trial Clinical Monitor		10 Mar 2017 08:05 CET
Verification-Paper Signature Completion		28 Mar 2017 10:11 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed