Clinical Trial Protocol

Doc. No.: c02035745-05

EudraCT No.:	2012-005201-48
BI Trial No.:	1199.93
BI Investigational Product:	Nintedanib, BIBF 1120
Title:	LUME-Meso: Double blind, randomised, multicentre, phase II/III study of nintedanib in combination with pemetrexed / cisplatin followed by continuing nintedanib monotherapy *versus* placebo in combination with pemetrexed / cisplatin followed by continuing placebo monotherapy for the treatment of patients with unresectable malignant pleural mesothelioma
Clinical Phase:	II/III
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax [redacted]
Co-ordinating Investigator:	[redacted] Telephone: [redacted] Fax [redacted]
Status:	Final Protocol (Revised Protocol (based on global amendment(s))
Version and Date:	**Version:** 3.0 **Date:** 22 Jun 2016

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Nintedanib			
Name of active ingredient: BIBF 1120			
Protocol date: 22 Mar 2013	**Trial number:** 1199.93		**Revision date:** 22 Jun 2016

Title of trial:	LUME-Meso: Double blind, randomised, multicentre, phase II/III study of nintedanib in combination with pemetrexed / cisplatin followed by continuing nintedanib monotherapy *versus* placebo in combination with pemetrexed / cisplatin followed by continuing placebo monotherapy for the treatment of patients with unresectable malignant pleural mesothelioma
Co-ordinating Investigator:	[redacted]
Trial sites:	Multicentre trial
Clinical phase:	II/III
Objective:	To evaluate the safety and efficacy in terms of progression-free survival (PFS) and overall survival (OS) of nintedanib + pemetrexed / cisplatin followed by nintedanib *versus* placebo + pemetrexed / cisplatin followed by placebo as first line treatment for patients with unresectable malignant pleural mesothelioma (MPM). The primary objective of this study is to evaluate whether treatment with nintedanib + pemetrexed / cisplatin followed by nintedanib monotherapy is more effective than treatment with placebo + pemetrexed / cisplatin followed by placebo monotherapy, as assessed by PFS. The key secondary objective is to evaluate whether treatment with nintedanib + pemetrexed / cisplatin followed by nintedanib monotherapy is more effective than treatment with placebo + pemetrexed / cisplatin followed by placebo monotherapy, as assessed by OS. The secondary objectives are to assess the objective tumour response rate and the disease control rate.
Methodology:	Two-arm, randomised, double-blind, placebo-controlled, parallel-group comparison of nintedanib plus chemotherapy versus placebo plus chemotherapy
No. of patients: **total entered:**	537 (87 Phase II and 450 Phase III patients)

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each treatment:	50% of the patients will be randomised and treated with nintedanib and 50% of the patients will be randomised and treated with nintedanib matching placebo (1:1 randomisation) Patients in both arms will receive standard treatment with pemetrexed/cisplatin for up to 6 cycles
Diagnosis :	Histologically confirmed, unresectable MPM
Main criteria for inclusion:	• Histologically confirmed MPM (subtype: epithelioid or biphasic for Phase II or subtype epithelioid only for Phase III) • Not eligible to undergo surgical resection • Measurable disease according to modified Response Evaluation Criteria In Solid Tumours (RECIST) criteria (R12-1990) • No prior first line therapies for MPM • Eastern Cooperative Oncology Group (ECOG) Performance Status 0 -1
Test product: **dose:** **mode of admin.:**	Nintedanib 200 mg twice daily Oral
Comparator product: **dose:** **mode of admin.:**	Nintedanib matching placebo Not applicable Oral
Duration of treatment:	Nintedanib or matching placebo will be administered in combination with standard pemetrexed and cisplatin for a maximum of 6 cycles of a 21-day cycle. For patients who have not progressed, nintedanib or matching placebo will continue to be administered orally on a daily basis until disease progression, unmanageable toxicity, withdrawal of consent or death.
Criteria for efficacy:	Primary Endpoint: Progression free survival (PFS) Secondary Endpoints: • Overall survival (OS) (key secondary endpoint) • Objective tumour response according to modified RECIST criteria • Disease control according to modified RECIST criteria

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Criteria for safety:	• Frequency and severity of adverse events (AEs) graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (R06-1666) for Phase II and Version 4.03 (R15-5988) for Phase III patients. • Changes in safety laboratory parameters		
Statistical methods:	Phase II The analyses will be exploratory using Kaplan-Meier methods and a stratified Cox proportional hazards model. Phase III The analysis of the primary endpoint PFS and the key secondary endpoint OS will be performed according to a hierarchical testing procedure. The log-rank test will be used for PFS to test for the effect of nintedanib at the one-sided alpha level of 0.025. For OS, an adaptive design with event number reassessment will be used. The analysis of OS will be performed using the weighted inverse normal method with one sided p-values from the log-rank test. The alpha-level for OS will follow an O`Brien and Fleming spending function to preserve the overall alpha of 0.025 (one-sided) for the final OS analysis.		

PHASE II FLOW CHARTS

Phase II Combination: Nintedanib (BIBF 1120) or Placebo + Pemetrexed / Cisplatin Treatment Cycles 1 – 6[1]

Study Activity	Screening	Cycle 1[1]				Cycles 2-6[1]				EoT[2]	FU[3]
Visit		V1		V2	V3	V1		V2	V3		
Days	- 14 to -1	1	2	8 ±2	15 ±2	1 ±2	2	8 ±2	15 ±2		FU1 ≥28 days after last study medication intake FU2 - FUn every 6-12 weeks
Informed consent	X[4]										
[redacted]		[redacted]									
[redacted]		[redacted]								[redacted]	
[redacted]	[redacted]										
Demographics	X										
Medical history	X										
Inclusion/exclusion criteria	X	X									
Randomisation		X									
Eligibility for next cycle[8]						X					
Physical examination	X	X				X				X	X
Vital signs	X	X		X	X	X		X	X	X	
Body weight and height[9]	X	X				X				X	
ECOG score	X	X				X				X	X
ECG[10]	X	X				X				X	
[redacted]		X				X				X	
Safety lab parameters[12]	X	X		X	X	X		X	X	X	
Urinalysis[12]	X	X				X				X	
Pregnancy test[13]	X	X								X	
Tumour assessment	X[14]	X[15]									
Pre-medication for chemotherapy[16]	X	X	X	X	X	X	X	X	X	X	
Pemetrexed and cisplatin administrations[17]		X				X					
Dispense nintedanib / placebo[18]		X				X					
Nintedanib / Placebo treatment[18]			X	X	X		X	X	X		
Compliance check[19]		X		X	X	X		X	X	X	
Adverse events	X	X		X	X	X		X	X	X	X[20]
Concomitant therapy	X	X		X	X	X		X	X	X	X
Patient vital status and other anti-cancer therapy											X
Conclusion of active treatment										X	

1 Duration of each treatment cycle is 21 days.
2 End of Treatment (EoT) to be performed at the time of the last visit when patient discontinues study treatment (pemetrexed/cisplatin and nintedanib/placebo); to be documented only once in the EoT visit electronic case report form (eCRF) page. If a patient discontinues treatment without progression, additional imaging does not need to be performed at EoT if performed within the past three weeks. If progression is suspected at EoT, imaging must be done irrespective of last imaging timepoint. If patient continues treatment with nintedanib / placebo, see monotherapy flow chart.
3 See Section 6.2.3.2. The first follow up visit (FU1) will be performed ≥28 days after discontinuing study medication. Further follow up visits will be performed every 6 weeks for progressive disease (PD) and every 12 weeks for OS:
Follow-up for PD: Patients who did not progress on treatment will continue to perform imaging every 6 weeks until PD, start of new subsequent anti-cancer therapy, death, lost-to follow up, withdrawal of consent, or when the required OS events for the primary analyses of the key secondary endpoint OS for Phase II have been reached.
Follow-up for OS: Patients remaining on study as of the primary analysis for the key secondary endpoint OS for Phase II, regardless of whether they progressed on treatment, will be followed every 12 weeks until death, lost to follow-up, withdrawal of consent, or until the time of the primary PFS analysis for Phase III (follow-up for OS can be conducted by phone interview).
[redacted]
8 Evaluation of eligibility for next cycle will be performed prior to administration of chemotherapy. See Sections 4.1.4.4, 4.1.4.5 and 6.2.2.
9 Height at screening visit only.
10 12-lead resting Electrocardiogram (ECG) to be performed at every cycle up to 3 days before administration of chemotherapy.
[redacted]
12 For safety lab parameters and urinalysis, see Section 5.2.3. Laboratory parameters must be obtained prior to re-treatment, see Sections 4.1.4.4 and 4.1.4.5.
13 Serum or urine pregnancy test will be performed in women of childbearing potential at screening and on Day 1 of cycle 1. The results have to be checked prior to the first chemotherapy administration. Pregnancy test will be repeated at EoT visit, see Section 5.2.2.4. Additional pregnancy test can be performed during treatment period if required according to local regulations.
14 Tumour assessment (imaging) at screening must be performed within 4 weeks prior to first treatment
15 Tumour assessments according to modified RECIST criteria (R12-1990) to be performed every 6 weeks starting from the time of the first pemetrexed/cisplatin administration irrespective of any delay in treatment courses, until progression of the tumour or initiation of any other anti-cancer therapy outside of current study. Imaging is acceptable +/- 1 week around the scheduled date. If patients continue on study treatment beyond progression, imaging should continue to be performed every 6 weeks. Imaging can be performed outside of scheduled visits if progression is suspected. See Section 5.1.2.1 for further details.
16 All patients should be pre-medicated during the study starting at least 7 days before the first dose of pemetrexed, and continue daily during pemetrexed therapy courses and for 21 days after the last dose of pemetrexed, see Section 4.1.4.3.
17 Chemotherapy (pemetrexed/cisplatin) will be administered during the combination chemotherapy period for a maximum of 6 cycles. If one of the combination partners has to be stopped, the other chemotherapy can continue for up to 6 cycles. In case nintedanib/placebo will be discontinued before combination cycle 6, administration of the chemotherapy should be continued until combination cycle 6. See Section 3.3.4.1 and Section 4.1.4.
18 Nintedanib / placebo will be dispensed on Day 1 of each treatment cycle. Patient should start nintedanib / placebo in the morning of Day 2 of each treatment cycle (i.e. the day after each chemotherapy administration), and continue daily until Day 21 of the cycle. In case the next visit is delayed, patient should continue taking daily treatment as instructed.
19 Check patient's compliance with administration schedule for nintedanib / placebo and chemotherapy pre-medication, see Section 4.3.
20 See Section 6.2.3.2 for management of AEs ongoing at EoT.

Phase II Monotherapy: Nintedanib or Placebo From End of Combination Therapy (Treatment Cycle ≤ 6) to EoT

Study Activity	Repeated Cycles[1]	EoT[2]	FU[3]
Visit	V1		FU1 ≥28 days after last study medication intake FU2 - FUn every 6-12 weeks
Day	1		
Variance allowed (± days)	±2		
Physical examination	X	X	X
Eligibility for monotherapy with nintedanib / placebo[4]	X		
Vital signs	X	X	
Body weight	X	X	
ECOG score	X	X	X
ECG	X	X	
[redacted]	[redacted]	[redacted]	
Safety lab parameters[6]	X	X	
Urinalysis[6]	X	X	
Pregnancy test[7]		X	
[redacted]	[redacted]		
Tumour assessment[9]	X		
Dispense nintedanib / placebo medication[10]	X		
Nintedanib / placebo treatment[11]	X		
Nintedanib / placebo compliance check[12]	X	X	
Adverse events	X	X	X[13]
Concomitant therapy	X	X	X
Patient status and other anti-cancer therapy			X
Conclusion of nintedanib / placebo treatment		X	

1 Duration of treatment cycle is 21 days.

2 EoT to be performed at the time of the last visit when patient discontinues treatment with nintedanib / placebo; to be documented only once in the EoT visit eCRF page. If a patient discontinues treatment without progression, additional imaging does not need to be performed at EoT if performed within the past three weeks. If progression is suspected at EoT, imaging must be done irrespective of last imaging time point.

3 See Section 6.2.3.2. The first follow up visit (FU1) will be performed ≥28 days after discontinuing study medication. Further follow up visits will be performed every 6 weeks for PD and every 12 weeks for OS:
Follow-up for PD: Patients who did not progress on treatment will continue to perform imaging every 6 weeks until PD, start of new subsequent anti-cancer therapy, death, lost-to follow up, withdrawal of consent, or when the required OS events for the primary analyses of the key secondary endpoint OS for Phase II have been reached.
Follow-up for OS: Patients remaining on study as of the primary analysis for the key secondary endpoint OS for Phase II, regardless of whether they progressed on treatment, will be followed every 12 weeks until death, lost to follow-up, withdrawal of consent, or until the time of the primary PFS analysis for Phase III (follow-up for OS can be conducted by phone interview).

4 Evaluation of eligibility for next cycle will be performed prior to administration of nintedanib/placebo. See Sections 4.1.4.5 and 6.2.2.

[redacted]

6 For safety lab parameters and urinalysis, see Section 5.2.3. Laboratory parameters must be obtained prior to re-treatment, see Section 4.1.4.5.

7 Serum or urine pregnancy test to be performed in women of childbearing potential at EoT, see Section 5.2.2.4. Additional pregnancy test can be performed during treatment period if required according to local regulations.

[redacted]

9 Tumour assessments according to modified RECIST criteria (R12-1990) to be performed every 6 weeks starting from the time of the first pemetrexed/cisplatin administration irrespective of any delay in treatment courses, until progression of the tumour or initiation of any other anti-cancer therapy outside of current study. Imaging is acceptable +/- 1 week around the scheduled date. If patients continue on study treatment beyond progression, imaging should continue to be performed every 6 weeks. Imaging can be performed outside of scheduled timepoints if progression is suspected. See Section 5.1.2.1 for further details.

10 Nintedanib / placebo will be dispensed on Day 1 of each treatment cycle.

11 Patient should start nintedanib / placebo in the morning of Day 1 of each treatment cycle and continue daily until Day 21 of the cycle. In case next visit is delayed, patient should continue taking daily treatment as instructed.

12 Check patient's compliance with administration schedule for nintedanib / placebo, see Section 4.3.

13 See Section 6.2.3.2 for management of AEs ongoing at EoT.

PHASE III FLOW CHARTS

Phase III Combination: Nintedanib (BIBF 1120) or Placebo + Pemetrexed / Cisplatin Treatment Cycles 1 – 6[1]

Study Activity	Screen	Cycle 1[1]		Cycle 2[1]		Cycles 3-6[1]		EoT[2]	FU1[3]	FUP PD[3]	FUP OS[3]
Visit		V1	V2	V1	V2	V1	V2				
Days	- 14 to -1	1	8 ±2	1 ±2	8 ±2	1 ±2	8 ±2				
Informed consent	X[4]										
[redacted]		[redacted]									
[redacted]		[redacted]									
[redacted]	[redacted]										
[redacted]					[redacted]						
Demographics	X										
Medical history	X										
Inclusion/exclusion criteria	X	X									
Randomisation		X									
Eligibility for next cycle[9]				X		X					
Physical examination	X	X		X		X		X	X	X	
Vital signs	X	X		X		X		X			
Body weight and height[10]	X	X		X		X		X			
ECOG score	X	X		X		X		X	X	X	
ECG[11]	X	X				X		X			
Safety lab parameters[12]	X	X	X	X	X	X	X	X			
Urinalysis[12]	X	X		X		X		X			
Pregnancy test[13]	X	X						X			
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]		
Tumour assessment	X[15]	X[16]									
[redacted]		[redacted]									
Pre-medication for chemotherapy[18]	X	X		X		X					
Pemetrexed and cisplatin administration[19]		X		X		X					
Dispense nintedanib / placebo[20]		X		X		X					
Nintedanib / placebo treatment[21]		X		X		X					
Compliance check[22]		X		X		X		X			
Adverse events	X	X		X		X		X	X[23]		
Concomitant therapy	X	X		X		X		X	X		
Patient vital status and other anti-cancer therapy									X	X	X
Conclusion of active treatment								X			

1 Duration of each treatment cycle is 21 days.

2 End of Treatment (EoT) to be performed at the time of the last visit when patient discontinues study treatment (pemetrexed / cisplatin and nintedanib / placebo); to be documented only once in the EoT visit electronic case report form (eCRF) page. If a patient discontinues treatment without progression, additional imaging does not need to be performed at EoT if performed within the past three weeks. If progression is suspected at EoT, imaging must be done irrespective of last imaging timepoint. If patient continues treatment with nintedanib / placebo, see monotherapy flow charts.

3 See Section 6.2.3.2. The first follow up visit (FU1) will be performed ≥30 days after discontinuing study medication. Further follow up visits will be performed every 6 weeks for progressive disease (PD) and every 12 weeks for OS:
Follow-up for PD: Patients who did not progress on treatment will continue to perform imaging every 6 weeks until PD, start of new subsequent anti-cancer therapy, death, lost-to follow up, withdrawal of consent, or when the required OS events for the primary analyses of the key secondary endpoint OS have been reached.
Follow-up for OS: Patients who progressed on treatment will be followed every 12 weeks until death, lost to follow-up, withdrawal of consent, or when the required OS events for the primary analyses of the key secondary endpoint OS have been reached (follow-up for OS can be conducted by phone interview if patients cannot visit the site in person).

[redacted]

9 Evaluation of eligibility for next cycle will be performed prior to administration of chemotherapy. See Sections 4.1.4.4, 4.1.4.5 and 6.2.2.

10 Height at screening visit only.

11 12-lead resting Electrocardiogram (ECG) to be performed up to 3 days before administration of chemotherapy at every other cycle.

12 For safety lab parameters and urinalysis, see Section 5.2.3. Laboratory parameters must be obtained prior to re-treatment, see Sections 4.1.4.4 and 4.1.4.5.

13 Serum or urine pregnancy test will be performed in women of childbearing potential at screening and on Day 1 of Cycle 1 Visit 1. The results have to be checked prior to the first chemotherapy administration. Pregnancy test will be repeated at EoT visit, see Section 5.2.2.4. Additional pregnancy test can be performed during treatment period if required according to local regulations.

[redacted]

15 Tumour assessment (imaging) at screening must be performed within 4 weeks prior to first treatment (including brain scan).

16 Tumour assessments according to modified RECIST criteria (R12-1990) to be performed every 6 weeks starting from the time of the first pemetrexed/cisplatin administration irrespective of any delay in treatment courses, until progression of the tumour or initiation of any other anti-cancer therapy outside of current study. Imaging is acceptable +/- 1 week around the scheduled date. If patients continue on study treatment beyond progression, imaging should continue to be performed every 6 weeks. Imaging can be performed outside of scheduled visits if progression is suspected. Patients with stable brain metastases at trial entry must be evaluated at each imaging time point for assessment for brain metastases. See Section 5.1.2.1 for further details.

[redacted]

18 All patients should be pre-medicated during the study starting at least 7 days before the first dose of pemetrexed, and continue daily during pemetrexed therapy courses and for 21 days after the last dose of pemetrexed. See Section 4.1.4.3.

19 Chemotherapy (pemetrexed / cisplatin) will be administered during the combination chemotherapy period for a maximum of 6 cycles. If one of the combination partners has to be stopped, the other chemotherapy can continue for up to 6 cycles. In case nintedanib / placebo will be discontinued before combination Cycle 6, administration of the chemotherapy should be continued until combination Cycle 6. See Section 3.3.4.1 and Section 4.1.4.

20 Nintedanib / placebo will be dispensed on Day 1 of each treatment cycle

21 Patient should start nintedanib / placebo in the morning of Day 2 of each treatment cycle (i.e. the day after each chemotherapy administration), and continue daily until Day 21 of the cycle. In case the next visit is delayed, patient should continue taking daily treatment as instructed.

22 Check patient's compliance with administration schedule for nintedanib / placebo and chemotherapy pre-medication. See Section 4.3.

23 See Section 6.2.3.2 for management of AEs ongoing at EoT.

Phase III Monotherapy: Nintedanib or Placebo From End of Combination Therapy (Treatment Cycle ≤ 6) to EoT

Study Activity	Repeated Cycles[1]	EoT[2]	FU1[3]	FUP PD[3]	FUP OS[3]
Visit	V1				
Day	1				
Variance allowed (± days)	±2				
Physical examination	X	X	X	X	
Eligibility for monotherapy with nintedanib / placebo[4]	X				
Vital signs	X	X			
Body weight	X	X			
ECOG score	X	X	X	X	
ECG	X	X			
Safety lab parameters[5]	X	X			
Urinalysis[5]	X	X			
Pregnancy test[6]		X			
[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]		
Tumour assessment[9]	X				
[redacted]	[redacted]				
Dispense nintedanib / placebo medication[11]	X				
Nintedanib / placebo treatment[12]	X				
Nintedanib / placebo compliance check[13]	X	X			
Adverse events	X	X	X[14]		
Concomitant therapy	X	X	X		
Patient status and other anti-cancer therapy			X	X	X
Conclusion of nintedanib / placebo treatment		X			

1 Duration of treatment cycle is 21 days.

2 EoT to be performed at the time of the last visit when patient discontinues treatment with nintedanib / placebo; to be documented only once in the EoT visit eCRF page. If a patient discontinues treatment without progression, additional imaging does not need to be performed at EoT if performed within the past three weeks. If progression is suspected at EoT, imaging must be done irrespective of last imaging time point.

3 See Section 6.2.3.2. The first follow up visit (FU1) will be performed ≥30 days after discontinuing study medication. Further follow up visits will be performed every 6 weeks for PD and every 12 weeks for OS:
Follow-up for PD: Patients who did not progress on treatment will continue to perform imaging every 6 weeks until PD, start of new subsequent anti-cancer therapy, death, lost-to follow up, withdrawal of consent, or when the required OS events for the primary analyses of the key secondary endpoint OS have been reached.
Follow-up for OS: Patients who progressed on treatment will be followed every 12 weeks until death, lost to follow-up, withdrawal of consent, or when the required OS events for the primary analyses of the key secondary endpoint OS have been reached (follow-up for OS can be conducted by phone interview if patients cannot visit the site in person).

4 Evaluation of eligibility for next cycle will be performed prior to administration of nintedanib / placebo. See Sections 4.1.4.5 and 6.2.2.

5 For safety lab parameters and urinalysis, see Section 5.2.3. Laboratory parameters must be obtained prior to re-treatment, see Section 4.1.4.5.

6 Serum or urine pregnancy test to be performed in women of childbearing potential at EoT, see Section 5.2.2.4. Additional pregnancy test can be performed during treatment period if required according to local regulations.

[redacted]

[redacted]

9 Tumour assessments according to modified RECIST criteria (R12-1990) to be performed every 6 weeks starting from the time of the first pemetrexed / cisplatin administration irrespective of any delay in treatment courses, until progression of the tumour or initiation of any other anti-cancer therapy outside of current study. Imaging is acceptable +/- 1 week around the scheduled date. If patients continue on study treatment beyond progression, imaging should continue to be performed every 6 weeks. Imaging can be performed outside of scheduled timepoints if progression is suspected. Patients with stable brain metastases at trial entry must be evaluated at each imaging time point for assessment for brain metastases. See Section 5.1.2.1 for further details.

[redacted]

11 Nintedanib / placebo will be dispensed on Day 1 of each treatment cycle.

12 Patient should start nintedanib / placebo in the morning of Day 1 of each treatment cycle and continue daily until Day 21 of the cycle. In case next visit is delayed, patient should continue taking daily treatment as instructed.

13 Check patient's compliance with administration schedule for nintedanib / placebo, see Section 4.3.

14 See Section 6.2.3.2 for management of AEs ongoing at EoT.

TABLE OF CONTENTS

ABBREVIATIONS

5-HT_3	5-Hydroxy-Tryptamin Receptor 3
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine AminoTransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
bFGF	Basic Fibroblast Growth Factor
BI	Boehringer Ingelheim
b.i.d.	Twice a Day
BUN	Blood Urea Nitrogen
CA	Competent Authority
CI	Confidence Interval
CML	Clinical Monitor Local
CR	Complete Response
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CRT	Clinical Trial Report
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
EDTA	Ethylene-Diamine-Tetra-Acetic Acid
EMA	European Medicines Agency
EoT	End of Treatment
EudraCT	European Clinical Trials Database
[redacted]	[redacted]
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
FOLFOX	FOLinic acid, Fluorouracil and OXaliplatin
FU	Follow Up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
γ-GT	Gamma-Glutamyl Transferase
GI	Gastrointestinal

HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL-6	Interleukin-6
INN	International Nonproprietary Name
INR	International Normalised Ratio
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
ISF	Investigator Site File
i.v.	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LCSS	Lung Cancer Symptom Scale
LCSS-Meso	Lung Cancer Symptom Scale Mesothelioma
LDH	Lactate Dehydrogenase
mFOLFOX6	Modified FOLFOX6
MMRM	Mixed-effect Model with Repeated Measures
MPM	Malignant Pleural Mesothelioma
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NE	Not Evaluable
NSAID	Non-Steroidal Anti Inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
OPU	Operative Unit
OS	Overall Survival
PD	Progressive Disease
PDGF	Platelet-Derived Growth Factor
PDGFR	Platelet-Derived Growth Factor Receptor
PFS	Progression Free Survival
PFT	Pulmonary Function Test
PGx	Pharmacogenomics
PlGF	Placenta Growth Factor
PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
SD	Stable Disease
SOP	Standard Operating Procedures
SMRP	Soluble Mesothelin-Related Peptide
SPC	Summary of Product Characteristics
Src	Sarcoma Tyrosine Kinase
SUSAR	Suspected Unexpected Serious Adverse Reaction

TCM	Trial Clinical Monitor
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
UV	Ultraviolet
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
VEGF(-C)	Vascular Endothelial Growth Factor (-C)
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White Blood Cell

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Mesothelioma is a rare malignant tumour originating from the cells lining the mesothelial surface of the coelomic cavities of the body. It is estimated to occur in about 2,500 people in the United States every year but its incidence continues to rise worldwide. MPM is the most common type of mesothelioma and typically originates from the lower parietal pleura and the costodiaphragmatic sinus. The disease is deadly and difficult to treat. Median OS is about 1 year. MPM occurs primarily in older men (median age, 72 years).

Chemotherapy is recommended either alone for medically inoperable patients with MPM or as part of a regimen for patients with medically operable MPM. A combined first-line regimen using cisplatin and pemetrexed is considered the gold standard for MPM and is currently the only regimen approved for mesothelioma. The results of the pivotal trial demonstrating the safety and efficacy of the pemetrexed / cisplatin showed significantly longer median OS (12.1 *vs.* 9.3 months, p = 0.02) and time to progression (6.1 vs. 3.9 months, p = 0.008) for the pemetrexed / cisplatin arm compared with the cisplatin arm (R12-2677).

Angiogenesis is involved in tumour growth and development of metastases. Proteins involved in regulating the angiogenic process such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) and their receptors have been implicated in the prognosis of MPM (R12-2651). The vascular endothelial growth factor receptor (VEGFR) is a receptor tyrosine kinase that is over-expressed in a variety of malignancies. The VEGF ligand and VEGF receptors have been shown to be co-expressed in MPM (R12-1928, R02-0591). An inverse relationship has been found between VEGF expression and OS of MPM patients (R02-0591). Both VEGF and VEGF(-C) function as autocrine growth factors for the development of MPM and have been reported to be overexpressed in tissue samples from MPM patients and primary cultures derived from patient samples (R12-2676). VEGF-C is known to stimulate lymphatic vascular growth. A strong correlation has been reported between the expression of VEGF(-C), its receptor, VEGFR-3 (Flt-4), and microlymphatic vessel density in tissue samples from MPM patients (R12-1922).

In addition to the antiangiogenic pathways, there are preclinical data suggesting a potential role of sarcoma tyrosine kinase (Src) as a potential target for the treatment of mesothelioma (R12-2652). Use of the Src-inhibitor dasatinib is being evaluated clinically (R12-2653).

The present trial is designed to evaluate the safety and efficacy of nintedanib in combination with standard pemetrexed / cisplatin followed by nintedanib *versus* placebo in combination with standard pemetrexed / cisplatin followed by placebo for the treatment of patients with unresectable MPM.

1.2 DRUG PROFILE

1.2.1 Nintedanib (BIBF 1120)

Nintedanib is a potent, orally available triple kinase inhibitor specifically targeting VEGFR 1-3, platelet-derived growth factor receptor (PDGFR) α and β, and fibroblast growth factor receptor (FGFR) 1-3 (c01632700).

VEGFR-2 is considered the crucial receptor involved in initiation of the formation as well as the maintenance of tumour vasculature. The specific and simultaneous abrogation of these pathways results in effective growth inhibition of both endothelial and perivascular cells, which may be more effective than inhibition of endothelial cell growth alone, as achieved solely via disruption of the VEGF pathway. Furthermore, signalling by FGF-receptors has been identified as a possible escape mechanism for tumour angiogenesis when the VEGF pathway is disrupted (R08-4315, R08-5173).

In vivo experiments demonstrated anti-tumour efficacy of nintedanib, leading to a substantial delay of tumour growth or even complete tumour stasis in xenografts of a broad range of differing human tumour types, including non-small-cell lung cancer, ovarian cancer, renal cell carcinoma, colorectal cancer, and head and neck squamous cell carcinoma

Histological examination of treated tumours showed a marked reduction of tumour vessel density by approximately 80%. *In vivo*, the combination of nintedanib with docetaxel, pemetrexed or vinorelbine in xenografts showed clear anti-tumour efficacy with a tumour/control ratio of 30%, 23% and 124% at suboptimal dose levels with the single agents. In a xenograft model of human ovarian cancer using the SKOV-3 tumour line, nintedanib was active (tumour control ratio of 25% at 50 mg/kg daily) and the combination of low doses of nintedanib and cisplatin showed more than additive efficacy.

In addition preclinical models show that nintedanib may have a direct anti-tumour effect on those malignant cells which overexpress PDGFR and/or FGFR (e.g. H1703 Non-small cell lung cancer [NSCLC] cells).

Considering its anti-angiogenic mechanism of action, it is anticipated that treatment with nintedanib will slow tumour growth in human cancers. Moreover, tumour regression may also be achieved by induction of apoptosis of immature tumour vessels. In addition, a therapeutic effect may also result from inhibition of tumour autocrine and paracrine growth factor loops involving VEGF, PDGF and basic fibroblast growth factor (bFGF). It is likely that long-term treatment may be needed to ensure maximal clinical benefit.

Data from 4-week, 13-week, and 26-week toxicity studies in rats as well as 4-week, 13-week and 52-week toxicity studies in monkeys are available. Relevant histopathological findings in these studies were observed in the gastrointestinal (GI) tract, lymphatic tissues, kidneys, bone marrow, liver, extrahepatic bile duct, exocrine glands and the skin. Bone changes in growing animals (thickening of epiphyseal growth plate) were interpreted as a typical mechanism-related toxicity associated with a VEGFR-2 inhibitor. Mild changes in haematological and clinical chemistry parameters (increases in gamma-glutamyl transferase [γ-GT], aldolase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], leucine aminopeptidase

[LAP], glutamate dehydrogenase [GLDH]) were seen in rats. Minimal to slight changes in immunotoxicological parameters (T-cell antigen [CD4] count) and lymphoid tissues may correlate to the additional inhibition of Src family non-receptor tyrosine kinases such as lymphocyte specific protein kinase (lck) and lyn. Overall, the histopathological findings and changes of laboratory parameters were mild to moderate and generally confined to the high dose groups.

Nintedanib is non-mutagenic, even at high doses. One compound in a batch of potential degradation products that may be formed under systemic and/or acidic conditions was found to be weakly Ames positive at high concentration after metabolic activation, while a second batch of the same products was Ames negative. The compound was not found in any of the drug substance batches of nintedanib used and thus did not occur within the limits of detection. Further experiments (mouse lymphoma assay, micronucleus assay) indicated that the compound does not raise a safety concern for cancer patients.

Two exploratory studies in rats revealed a teratogenic effect of nintedanib with a steep dose/effect relationship and an early onset of embryofoetal deaths at low dosages. This effect was observed at dose levels resulting in plasma drug concentrations comparable to or below those in humans. Because the concentration of nintedanib in semen is unknown, males receiving nintedanib and having sexual intercourse with females of childbearing potential should use latex condoms.

The main metabolite of nintedanib was BIBF 1202 (25% in liver microsome preparations). Both nintedanib and BIBF 1202 were further glucuronidated to the corresponding glucuronide via the uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzyme. In humans, 93.4% of total [^{14}C] radioactivity was excreted in the faeces within 120 hours after oral administration of nintedanib. Only 0.7 % of total [^{14}C] radioactivity was eliminated via the urine.

In experiments with human liver microsomes (U03-1386, U08-1256-01), no relevant inhibition of CYP450 isoenzymes was observed for nintedanib or its main metabolite BIBF 1202. In animal experiments, no relevant changes of CYP450 enzymes were found to occur during treatment with nintedanib (U04-2195).

Phase I dose selection studies revealed that nintedanib is generally well tolerated with mild to moderate adverse effects (U05-2191-01 and U06-1697).

The predominant AEs were nausea, diarrhoea, vomiting, abdominal pain and fatigue of mostly low to moderate intensity after monotherapy with nintedanib. Dose limiting toxicities were dose dependent hepatic enzyme elevations that were reversible after discontinuation of nintedanib treatment.

These liver enzyme elevations were only in few cases accompanied by a simultaneous increase of bilirubin. In general, common terminology criteria for AEs (CTCAE) version 3.0, (R04-0474) grade three liver enzyme increases were reported in the dose groups of 250 mg twice daily or higher. They also were reversible and usually occurred within the first two months of treatment.

Combination of nintedanib with other anti-cancer drugs revealed a similar AE profile as compared to nintedanib monotherapy except for the chemotherapy related toxicities. There was no change of the pharmacokinetic parameters of nintedanib or of the cytotoxic compounds due to the combined treatment. Dose limiting toxicity (DLT) consisted mostly of liver transaminase elevations as in the monotherapy Phase I trials with the exception of the combination of nintedanib with pemetrexed, where fatigue was the most relevant DLT.

Hypertension or thromboembolic events were rare and did not suggest an increased frequency as a consequence of therapy with nintedanib.

All AEs observed in healthy volunteers after single administration of nintedanib were of CTCAE Grade 1 intensity and fully reversible.

Available pharmacokinetic data indicate that the systemic exposure required for biological activity can be achieved in cancer patients. Maximum plasma concentrations occurred mainly 1 to 4 hours after administration. There was no deviation detected in dose proportionality in the pharmacokinetic state of nintedanib. The latest steady state was reached within 9 days of treatment. The geometric mean value (gMean) terminal half-life was between 7 to 19 hours.

In the Phase I trials where nintedanib was combined with chemotherapeutic regimens, there was no change of the PK parameters of nintedanib or of the cytotoxic compounds due to the combined treatment.

Data from patients with advanced solid tumours demonstrate a pharmacodynamic effect of nintedanib treatment on selected tumour lesions as shown by dynamic contrast-enhanced magnetic resonance imaging (MRI). Based on pharmacokinetic analysis, a sufficient systemic exposure for biologic activity was observed in these advanced cancer patients.

A randomised Phase II maintenance trial in ovarian cancer in which the efficacy and safety of nine months of continuous twice daily doses of nintedanib following chemotherapy was investigated, has identified the potential activity of nintedanib with a 36-week PFS of 14.3 % compared to 5.0 % in the control group. The safety profile was consistent with findings previously reported for nintedanib administered as monotherapy as mentioned above (P09-08422). Nintedanib (Vargatef®), in combination with docetaxel, was granted marketing authorization by the European Medicines Agency (EMA) for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first‑line chemotherapy. In addition, the Food and Drug Administration (FDA) granted a marketing authorization for nintedanib in patients with idiopathic pulmonary fibrosis (IPF).

The European marketing authorization was based on the data from the LUME LUNG 1 trial. LUME-Lung 1 was an international, randomised, double-blind, phase III trial assessing the efficacy and safety of docetaxel plus nintedanib as second line therapy for NSCLC. In total, 1314 patients with Stage IIIB/IV or recurrent NSCLC (all histologies) who had progressed after 1st line chemotherapy were randomised in 1:1 fashion to either receive nintedanib 200mg twice a day (b.i.d.) + docetaxel (n=655) or Placebo b.i.d. + docetaxel (n=659). LUME-Lung 1 showed a significant and clinically meaningful improvement in OS in patients with adenocarcinoma (HR 0.83, p=0.0359, median 10.3 to 12.6 months) (P14-00479).

Grade 3 or worse AEs that were more common in the docetaxel plus nintedanib group than in the docetaxel plus placebo group were diarrhoea (43 [6·6%] of 652 *vs* 17 [2·6%] of 655), reversible increases in ALT (51 [7·8%] *vs* six [0·9%]), and reversible increases in AST (22 [3·4%] *vs* three [0·5%]).

In the studies investigating the monotherapy with nintedanib, the predominant AEs were nausea, diarrhoea, vomiting, abdominal pain, fatigue and reversible liver enzyme elevation of mostly low to moderate intensity.

Overall in Phase I and II monotherapy studies, the pattern of AEs was similar with gastrointestinal AEs as the most frequent events. The majority of CTCAE Grade 3 liver enzymes increases were reported in the higher dose group of 250 mg b.i.d. in Phase II trials. Overall in the Phase I and II studies, ALT increases were generally more frequent than AST increases. In patients with advanced NSCLC, nintedanib showed comparable signs of efficacy in ECOG 0-1 patients compared to historical data of other VEGFR inhibitors in a similar patient population.

In summary, based on the available preclinical and clinical data, nintedanib displays a manageable safety profile and signal of efficacy in various tumour types. The observed AEs are considered manageable in the context of the therapeutic area. Efficacy data of Phase I to III trials indicate that patients with advanced solid tumours may benefit from therapy with nintedanib either as component in a combination treatment with standard chemotherapy or as monotherapy.

For more details please refer to the Investigator's Brochures (IB) (c01632700).

1.2.2 Pemetrexed

Pemetrexed is an antifolate agent which inhibits folate-dependent enzymes in both the thymidylate and purine synthetic pathways essential for DNA nucleotide synthesis required for cell division. Pemetrexed gains entry into the cell through the reduced folate carrier, where it is polyglutamated, thereby enhancing its intracellular retention. Three folate dependent enzymatic pathways, thymidylate synthetase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, necessary for purine and pyrimidine synthesis are inhibited, resulting in cytotoxicity and cell death (R05-1060).

The toxicity profile of pemetrexed when used as a single agent includes neutropenia, thrombocytopenia, mucositis, fatigue, diarrhoea, rash and/or anorexia. Additional side effects include asthenia, pedal oedema and decreased creatinine clearance (R05-1061). Drug related bone marrow suppression and mucositis associated with decreased folate levels can be prevented by supplementation of patients with folic acid prior to the first pemetrexed dose

and continued daily through the 21-day treatment cycle and by administration of vitamin B12 one week prior to therapy, repeated every 3 cycles while on therapy.

Pemetrexed in combination with cisplatin is the approved standard of care chemotherapy treatment for patients with unresectable MPM.

1.2.3 Cisplatin

Cisplatin was first synthesised in the nineteenth century and was approved by US FDA for the clinical use of ovarian and testicular cancer treatment in 1978. Cisplatin is a platinum-based chemotherapy agent used either as a single agent or in combination with other chemotherapies to treat various types of cancers, including sarcomas, some carcinomas (e.g. small cell lung cancer, and ovarian cancer), lymphomas and germ cell tumours. Cisplatin is also used for treatment of mesothelioma. It was the first member of a class of platinum-based anti-cancer drugs which now also includes carboplatin and oxaliplatin. These platinum complexes act during all parts of the cell cycle and impair DNA synthesis which ultimately triggers apoptosis (programmed cell death).

Side effects of cisplatin include nausea, vomiting, nephrotoxicity, neurotoxicity, ototoxicity, alopecia, electrolyte imbalance, decrease of blood cells in bone marrow, thrombocytopenia, leucopenia, myelosuppression, dysgeusia, diarrhoea and fatigue. The toxicity of cisplatin probably results from the formation of lesions that block polymerases or disrupt the integrity of the genome. The side effects are generally reversible and subside when treatment ends. However, renal toxicity is cumulative and can result in complications months after treatment ends. Myelosuppression also accumulates over the course of the treatment but it subsides with the end of treatment.

Cisplatin in combination with pemetrexed is the approved standard of care chemotherapy treatment for first-line treatment of unresectable MPM.

1.2.4 Combination of nintedanib with pemetrexed

Pemetrexed

An open label Phase I study (U08-3886-01) was conducted to determine the maximum-tolerated dose (MTD) using a standard 3+3 dose escalation design in patients with recurrent NSCLC, who had been treated with one prior platinum based chemotherapy regimen. Patients received standard dose pemetrexed (500 mg/m^2) on day 1 of a 21-day cycle and nintedanib twice a day (b.i.d.) on Days 2 to 21. A total of 26 patients (13 male, 13 female, median age 61.5 years, range 36-81, ECOG performance status of 0-1) entered the trial, 24 patients concluded at least the first treatment course. In this trial nintedanib was escalated from 100 to 250 mg administered twice daily. The MTD was determined to be 200 mg orally b.i.d.

Fatigue Grade 3 represented the most common DLT in the first treatment course and all courses overall. Almost all AEs were fully reversible and mostly of low to moderate intensity (CTCAE Grade 1 and 2) irrespective of the dose. There were no CTCAE grade 4 toxicities observed. At the DLT determining dose of nintedanib given as 250 mg b.i.d. among 2 patients, one episode each of Grade 3 fatigue, Grade 3 ALT elevation and Grade 3 oesophageal pain occurred. Looking at all courses of therapy at the MTD dose of 200 mg

b.i.d. nintedanib a total of 5 of 12 patients had drug related CTCAE Grade 3 toxicity: fatigue: (25%), anorexia (16.7%), diarrhoea (8.3%), ALT elevation (8.3%), insomnia (8.3%). Below the MTD at the 150 mg bid dose a total of 6 patients were treated. One patient had Grade 3 fatigue and one patient had Grade 3 fatigue and Grade 3 nausea and vomiting. The relationship of fatigue to therapy with nintedanib is uncertain in the former patient as there was no recovery from fatigue more than 1 year after therapy discontinuation. In the nintedanib cohort of 100 mg b.i.d. one of six patients showed ALT and AST increases of CTCAE Grade 3 during the first treatment course. This patient was known to be infected with hepatitis C. The frequency of Grade 3 liver enzyme elevation for the combination of nintedanib and pemetrexed was low and did not suggest an increased incidence compared to historical pemetrexed data. For further listing of all AEs please see the IB (c01632700).

1.2.5 Combination of nintedanib with cisplatin (+ gemcitabine)

Cisplatin (+ gemcitabine)

A Phase I/II study evaluated the combination of nintedanib with cisplatin and gemcitabine for the treatment of squamous-cell NSCLC patients. During the initial phase of the study patients were enrolled in a 3+3 design. The dose of nintedanib was administered on days 2 – 21 of each cycle starting at 150 mg b.i.d. in the first cohort of patients and, if no DLTs were observed, was escalated to a maximum dose of 200 mg b.i.d. for the second cohort. The MTD for nintedanib was 200 mg bid when used in combination with cisplatin (75 mg/m^2) + gemcitabine (1250 mg/m^2). The continuous bid dosing of 200 mg nintedanib with cisplatin/gemcitabine combination was found to be tolerable, and PK data demonstrated no interaction. The triplet showed promising antitumour activity for 1st-line treatment of patients with advanced sqNSCLC (M15-0007).

1.2.6 Combination of nintedanib with other compounds

Carboplatin (+ paclitaxel)

The combination of nintedanib with carboplatin / paclitaxel was evaluated in two Phase I studies. The first study was conducted with paclitaxel (200 mg/m^2), carboplatin (AUC 6) and nintedanib (doses 50 – 250 mg b.i.d continuous except on the day of chemotherapy administration) in 26 previously untreated patients with advanced stage NSCLC. The MTD of nintedanib in combination with carboplatin AUC 6 and paclitaxel 200 mg/m2 was determined to be 200 mg b.i.d. (U08-3890-01).

The second study was conducted with paclitaxel (175 mg/m^2), carboplatin (AUC 5) and nintedanib (doses 100 – 250 mg b.i.d. continuous except on the day of chemotherapy administration), in 22 patients with advanced gynaecological malignancies. The MTD of nintedanib in combination with carboplatin AUC 5 and paclitaxel 175 mg/m^2 was determined to be 200 mg b.i.d. (U08-1000-02).

Oxaliplatin (mFOLFOX6)

A Phase I/II study evaluated the combination of nintedanib with modified FOLFOX6 (mFOLFOX6) compared to bevacizumab in combination with mFOLFOX6 in first line metastatic colorectal cancer patients. The nintedanib recommended phase II dose was 200 mg

b.i.d. plus mFOLFOX6 based on safety data from phase I (n = 12). Of 128 patients randomised in the phase II part of the study, 126 received treatment (nintedanib plus mFOLFOX6, n = 85; bevacizumab plus mFOLFOX6, n = 41). PFS at 9 months was 62.1% with nintedanib and 70.2% with bevacizumab [difference: −8.1% (95% confidence interval (CI) −27.8 to 11.5)]. Confirmed objective responses were recorded in 63.5% and 56.1% of patients in the nintedanib and bevacizumab groups, respectively. The incidence of AEs considered related to treatment was 98.8% with nintedanib and 97.6% with bevacizumab; the incidence of serious AEs was 37.6% with nintedanib and 53.7% with bevacizumab. The PK of nintedanib and the components of mFOLFOX6 were unaffected by their combination. Nintedanib in combination with mFOLFOX6 showed efficacy as first-line therapy in patients with metastatic colorectal cancer with a manageable safety profile and further studies in this population are warranted (U12-2578-03).

Docetaxel (+ prednisone)

Twenty-one patients with hormone-refractory prostate cancer were included in this dose escalation trial assessing the combination of continuous oral nintedanib (dose escalation from 100 mg b.i.d. to 250 mg b.i.d. administration daily except on the days of chemotherapy infusion) with docetaxel (75 mg/m^2) and prednisone (5 mg b.i.d.) (U08-1273-02).

No DLTs were observed ≤ 200 mg b.i.d. of nintedanib. Only one patient was considered to have developed a DLT at the highest dose level of 250 mg b.i.d. (reversible ALT and γ-GT increase of CTCAE grade 3) during the first course. Therefore, the formal MTD as per protocol was 250 mg b.i.d. of nintedanib in combination with docetaxel (75 mg/m^2). However, based on the frequency of clinically significant increases of liver laboratory values of 6/12 patients (50%) at the MTD versus 0/9 patients at the doses below the MTD, 200 mg b.i.d. nintedanib should be the recommended dose for further trials investigating the combination of nintedanib with docetaxel.

1.2.7 Combination of nintedanib with pemetrexed and cisplatin

[redacted]

The most commonly reported drug-related AEs in the placebo arm were nausea (75.6%), vomiting (39.0%), and fatigue (34.1%); in the nintedanib arm, the most frequently reported drug-related AEs were nausea (70.5%), diarrhoea (54.5%), and vomiting (43.2%). AEs requiring dose reduction were reported for 14.6% of patients in the placebo arm and 31.8% of patients in the nintedanib arm. AEs leading to permanent discontinuation of last study medication were reported for 14.6% (placebo) and 6.8% (nintedanib) of patients.

[redacted]

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The treatment of MPM remains a major challenge. A combined first-line regimen using pemetrexed /cisplatin is considered the gold standard with a median OS of approximately one year. Therefore, there is still an urgent need to find innovative treatments for this rare disease.

Proteins involved in regulating the angiogenic process such as VEGF and PDGF and their receptors have been implicated in the prognosis of MPM (R12-2651). The vascular endothelial growth factor receptor (VEGFR) is a receptor tyrosine kinase that is over-expressed in a variety of malignancies. The VEGF ligand and VEGF receptors have been shown to be co-expressed in MPM (R12-1928, R02-0591). An inverse relationship has been found between VEGF expression and OS of MPM patients (R02-0591). Both VEGF and VEGFC function as autocrine growth factors for the development of MPM and have been reported to be overexpressed in tissue samples from MPM patients and primary cultures derived from patient samples (R12-2676). VEGF-C is known to stimulate lymphatic vascular growth. A strong correlation has been reported between the expression of VEGF-C, its receptor, VEGFR-3 (Flt-4) and microlymphatic vessel density in tissue samples from MPM patients (R12-1922).

Nintedanib exerts migration and proliferation inhibition in MPM cells *in vitro* and prolongs survival in an orthotopic xenograft model (M15-0005)

Bevacizumab, a monoclonal antibody against VEGF (R12-1922) and several small molecule inhibitors of the VEGF receptor tyrosine kinase (sorafenib [R12-1923], vatalanib [R12-1933), sunitinib [R12-1926], cediranib and pazopanib) have been tested in Phase II studies in first-line and second-line settings primarily as monotherapy, except for bevacizumab which is being evaluated in combination with chemotherapy. Bevacizumab is specific for VEGF but it does not neutralize other members of the VEGF family including VEGF-C (R10-4862). The other agents are multikinase inhibitors but have not been evaluated in combination with standard chemotherapy in MPM.

Proof of efficacy of the inhibition of VEGF pathway was demonstrated in the MAPS trial investigating the combination of bevacizumab, pemetrexed and cisplatin versus pemetrexed and cisplatin. OS was significantly longer in the bevacizumab arm (median: 18.8 months, 95%CI[15.9-22.6] *vs*. 16.1 months, 95%CI[14.0-17.9] for the reference arm, (adj.HR = 0.76, 95%CI[0.61; 0.94], p = 0.012). Median PFS was 9.6 months, 95%CI[8.5-10.6] in bevacizumab arm *vs*. 7.5 months, 95%CI[6.8-8.1] (adj.HR = 0.62, 95%CI[0.50-0.75], p < 0.0001). Though grade 3/4 hematological toxicities did not significantly differ in the two arms (49.5% *vs*. 47.3%) , there were significantly more grade 3 proteinuria (0.0 *vs*. 3.1%), grade 3 hypertension (0.0 *vs*. 23%), grade 3/4 arterial thrombotic events (0.0 *vs*. 2.7%) observed in bevacizumab arm (R15-4440).

Nintedanib is a tyrosine kinase inhibitor that can be combined with chemotherapy (see Section 1.2.4). It has been proposed that coadministration of angiogenesis inhibitors and chemotherapy acts to improve delivery of small molecules, such as chemotherapy, to the

tumour (R12-2690). In as much as all three major components of pro-angiogenic signalling are inhibited (VEGFR 1-3, PDGFR α and β and FGFR 1-3 (c01632700), nintedanib offers a particularly wide spectrum of activity. Its potent activity against VEGFR-3, the receptor for VEGF-C, makes it a strong candidate for evaluation in MPM. In addition, nintedanib shows *in vitro* inhibitory activity against Src and Abl signalling proteins. In light of exploratory studies with other molecules that inhibit Src, it would be of interest to see if this pathway contributes to the effect of nintedanib in MPM.

The present study was initiated as an exploratory Phase II study and has been amended as a confirmatory study (based on data monitoring committee [DMC] recommendation) by adding a confirmatory Phase III part. In addition, as noted above in Section 1.2.7, the data from the 87 Phase II patients were unblinded and analyzed (data on file). Based on these results, the population to be studied in the Phase III part of the study will be limited to patients with unresectable MPM of epithelioid histology to evaluate the efficacy and safety of nintedanib versus placebo when added to pemetrexed/cisplatin.

2.2 TRIAL OBJECTIVES

The primary objective of the randomised, parallel-controlled Phase II/III study is to evaluate the safety and efficacy in terms of progression-free survival of nintedanib + pemetrexed / cisplatin followed by nintedanib (arm A) *versus* placebo + pemetrexed / cisplatin followed by placebo (arm B), as first line treatment for patients with unresectable MPM.

The key secondary objective is to evaluate OS in patients treated with the nintedanib regimen (arm A) *versus* the placebo regimen (arm B). Further secondary objectives are to evaluate the objective tumour response rate and to evaluate the disease control rate. [redacted]

2.3 BENEFIT - RISK ASSESSMENT

In this randomised Phase II/III study, all patients will receive the standard of care therapy regimen (pemetrexed+cisplatin) approved for the treatment of patients with unresectable MPM – the target patient population. The addition of the orally bioavailable agent nintedanib to this regimen, offers the opportunity to evaluate the potential benefit of antiangiogenic treatment in combination with standard chemotherapy. Furthermore, the study will evaluate whether there may be potential additive benefit to continuing treatment with nintedanib after completion of the chemotherapy treatment.

Antiangiogenic treatment with the orally available triple angiokinase inhibitor nintedanib offers the chance to control both locally recurrent and distant metastatic disease on an outpatient basis. Treatment with nintedanib may have the potential to provide significant benefit to patients with unresectable MPM by slowing tumour progression and metastasis, since its cellular target is expressed on the tumour vasculature in most malignancies.

Induction of endothelial cell apoptosis may result in subsequent degradation of tumour vessels and subsequent tumour necrosis.

In addition to these known targets, nintedanib has demonstrated preclinical activity against Src and Abl tyrosine kinases. These intracellular, non-receptor kinases have been implicated in the pathogenesis of MPM and therefore are potential additional targets for the activity of nintedanib in this disease.

The risks of antiangiogenic therapy with nintedanib in adult patients are primarily related to:

- the gastro-intestinal tract (nausea, vomiting, diarrhoea, abdominal pain)
- increases in liver enzymes (AST, ALT, γ-GT)
- fatigue, asthenia and anorexia

Liver enzymes must be followed closely during treatment with nintedanib. Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety.

Therapy with the trial drugs must be interrupted in the event of relevant hepatic toxicity and further treatment is to be withheld until recovery of the abnormal laboratory parameters. The respective dose reduction schemes should be followed (see Section 4.2.1.2.2).

Impairment of immune and of kidney function, thromboembolic events and GI perforations and increases in blood pressure are considered potential class-side effects of angiogenesis inhibitors as they have been reported for some other drugs in the class of angiogenesis inhibitors. Thus far these side effects have not been observed to a relevant degree in the trials conducted with nintedanib.

The major clinical side effects observed after therapy with pemetrexed and cisplatin are distinct from nintedanib induced AEs, yet some overlap may occur e.g. regarding mild GI toxicity or hepatotoxicity (please refer to the current local Summary of Product Characteristics (SPC) included in the investigator site file (ISF) for listed AEs). In view of the low potential for drug-drug interactions of nintedanib, it is not likely that enhanced toxicity due to pharmacokinetic interaction between the drug and the cytotoxic chemotherapy will occur. Due to the partially overlapping GI side effect profile, the occurrence of nausea, vomiting, diarrhoea and fatigue may be increased.

The DMC has raised no safety concerns and have recommended expanding from a Phase II exploratory trial to a Phase III confirmatory trial. Based on the results of the Phase II analysis, as described in Sections 1.2.7, 2.1 and 3.1, the benefit-risk assessment for this trial is considered positive.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The trial is designed as an international, multicentre, randomised, double-blind, placebo-controlled, two-arm study to evaluate the efficacy and safety profile of nintedanib + pemetrexed / cisplatin followed by nintedanib monotherapy (Arm A), in comparison with a matching placebo + pemetrexed / cisplatin followed by placebo monotherapy (Arm B) until disease progression, in patients with histologically confirmed, unresectable MPM. A graphic illustration of the study designs for Phase II and Phase III are shown below.

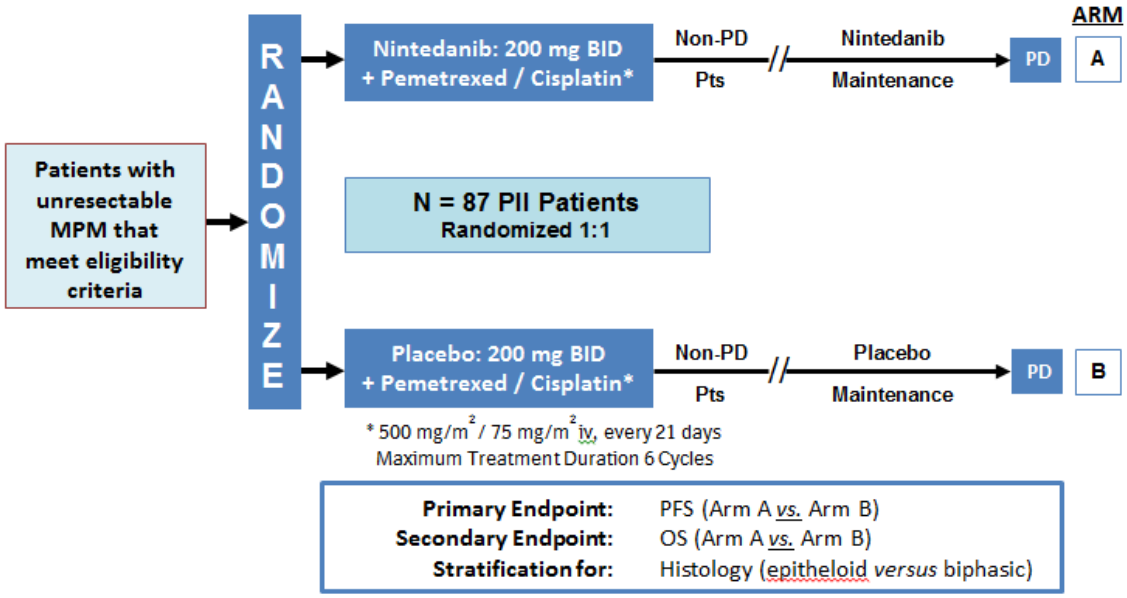

Figure 3.1: 1 Illustration of study design for Phase II part

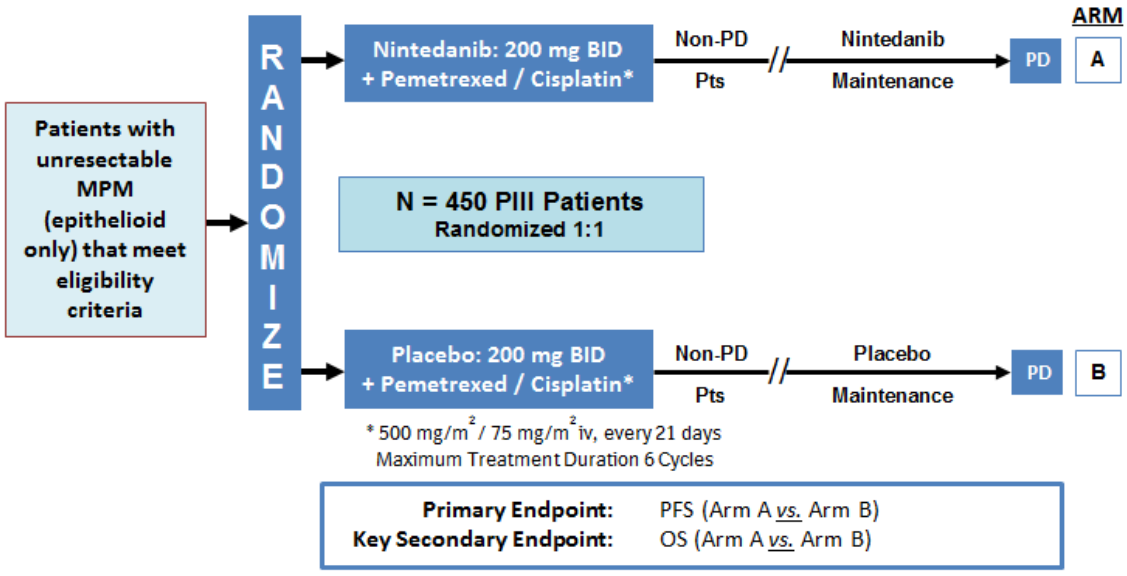

Figure 3.1: 2 Illustration of study design for Phase III part

All patients randomised as of 08-Dec-2014 will be considered Phase II patients and all patients randomised after 08-Dec-2014 will be considered Phase III patients. A total of 87 Phase II patients were randomised in this trial in a 1:1 ratio to receive either Arm A or Arm B treatment in a parallel group study design. Randomisation was stratified for epithelioid *versus* biphasic histology for the Phase II part. No stratification will be used for the Phase III part of this trial.

The trial will continue with randomising 450 additional patients (otherwise referred to as Phase III patients) of epithelioid tumour histology. All Phase III patients will be randomised in a 1:1 ratio to receive either Arm A or Arm B treatment in a parallel group study design.

The primary PFS analysis will be conducted after approximately 199 PFS events of the Phase III patients have occurred.

1. If PFS is positive and significant, an interim OS analysis will be conducted.

    - If OS is positive and statistically significant (based on a hierarchical testing procedure), the trial will be declared positive for the primary and key secondary endpoint, and enrolment into the trial will be stopped.
    - If OS is not yet statistically significant, the DMC will adjust the number of OS events needed for the primary OS analysis of Phase III.

2. If PFS is not statistically significant, the trial will be declared negative, and enrolment into this trial will be stopped.

The primary PFS analysis and interim OS analysis for the Phase III part is expected to occur approximately 23 months after the start of enrolment into the Phase III part of the study. At the time of these analyses, it is expected that recruitment into the Phase III part will still be ongoing.

A graphical illustration of the trial design as well as of the enrolment and follow-up periods and of the calendar time points can be found in Figure 3.1: 3.

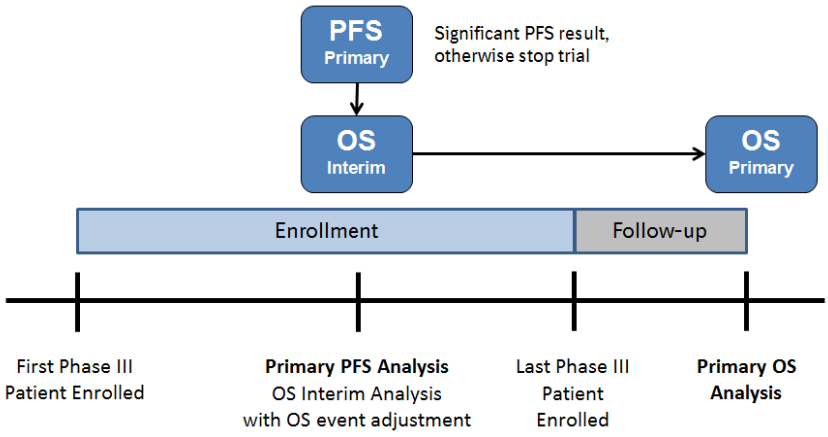

Figure 3.1: 3 Illustration of study analyses of the Phase III part

Pemetrexed / cisplatin will be administered at standard doses of 500 mg/m^2 and 75 mg/ m^2 respectively. Nintedanib / placebo will be administered at a starting dose of 200 mg twice daily. Safety will be monitored on a continuous basis throughout the study. In the event of treatment-limiting AEs, dose delay and dose reduction criteria are provided in Section 4.2.1. Patients will be evaluated for eligibility to receive study drug prior to initiation of each treatment cycle (see Sections 4.1.4.4; 4.1.4.5 and 6.2.2).

The trial will comprise four periods:

- **Screening period (up to 2 weeks):** During this period the investigators will screen the patient's eligibility.
- **Combination chemotherapy period (maximum of 6 cycles):** A total of 537 patients (all Phase II and Phase III patients) will be randomised to receive treatment with either nintedanib + pemetrexed / cisplatin (Arm A) or placebo + pemetrexed / cisplatin (Arm B).
- **Monotherapy period:** Once the treatment of pemetrexed / cisplatin is discontinued at the end of cycle 6 or earlier if necessary, patients who have not experienced disease progression will continue to receive nintedanib monotherapy (Arm A) or placebo monotherapy (Arm B) until disease progression.
- **End of Treatment and Follow-up period:** All patients will attend an EoT visit when they discontinue study treatment permanently. All patients will then return for the first follow-up visit ≥28 days after end of study treatment for Phase II patients and ≥30 days for Phase III patients. Patients who do not discontinue due to PD will be followed for unequivocal progression every 6 weeks (follow-up for PD) and those who discontinue due to unequivocal PD will be followed up for survival every 12 weeks (follow-up for OS). Please find more details in Section 6.2.

3.1.1 Administrative structure of the trial

Boehringer Ingelheim (BI) has appointed a Trial Clinical Monitor (TCM), responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal standard operating procedures (SOPs), directing the clinical trial team in the preparation, conduct, and reporting of the study, and ensuring appropriate training and information for Clinical Monitors Local (CMLs), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the study in the participating countries will be performed by the respective local BI-organisation Operative Unit (OPU) or a by a Contract Research Organisation (CRO) with which the responsibilities and tasks have been agreed and a written contract filed before initiation of the clinical study. In each OPU participating in this study, a CML will be appointed responsible for coordinating the activities required in order to manage the study in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU.

The co-ordinating investigator, who will sign the clinical trial report of this trial, has been appointed by BI. The co-ordinating investigator has experience in this type of trial and investigations.

[redacted]

Further DMC reviews will be performed as required according to the DMC charter (for details, see Section 7.3.4).

Tumour images evaluated according to modified RECIST criteria (R12-1990) for disease progression and response to treatment will be assessed at regular intervals at the investigator sites by the investigators experienced in the evaluation of MPM. The tumour measurements and clinical assessment will be recorded in the eCRF and will be used for clinical decisions on whether or not patient should continue study treatment. [redacted]

The safety laboratory investigations will be performed at local laboratories associated with the sites and no central laboratory will be used for this purpose. The certification for each laboratory or evidence that it participates in an established quality program must be provided by the investigator and filed at the Sponsor and the local ISF of the site.

[redacted]

An Interactive Voice Response System (IVRS) or Interactive Web-based Response System (IWRS) will be provided by a CRO/vendor. Details will be provided in the IVRS/IWRS manual available in the ISF.

An ISF containing all relevant study related documentation will be maintained according to local regulations and BI-SOPs at each study site. A copy of the ISF documents will also be kept as an electronic trial master file (TMF) at BI according to BI SOPs. Documents related to participating investigators and other important participants, especially their curricula vitae, will be filed in the TMF.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

Nintedanib has been successfully co-administered with various classes of chemotherapeutic drugs. These studies revealed that continuous treatment with 200 mg b.i.d. of nintedanib is the recommended dose for the combination of nintedanib with docetaxel, pemetrexed, paclitaxel/carboplatin or folinic acid, fluorouracil and oxaliplatin (FOLFOX) (see Section 1.2.6). The combination regimen of pemetrexed / cisplatin has been selected as the background therapy because it is established as the approved standard of care for the treatment of patients with unresectable MPM. The safety and efficacy of nintedanib in combination with pemetrexed / cisplatin will be evaluated in comparison to the standard of care chemotherapy regimen pemetrexed / cisplatin combined with matching placebo. Furthermore, patients who do not exhibit evidence of progressive disease after completion of the combination regimen will continue treatment with the investigational agent (nintedanib/placebo) to evaluate whether they may derive additional benefit. Patients will be stratified by histology (epithelioid vs. biphasic) to balance any potential effect of this baseline variable on efficacy.

Patients will continue trial treatment until disease progression as confirmed by imaging. However, in case of clinical benefit as judged by the investigator after careful clinical assessment, patients may be allowed to continue study treatment beyond radiological progression as defined by modified RECIST criteria (R12-1990). Patients who continue beyond radiological progression will follow the trial schedule (see the flow charts), including the imaging and clinical tumour evaluations. Trial treatment may be continued as long as judged beneficial by the investigator; however, the time of progression will not change if it was decided to continue the treatment. The decision to continue study treatment should be discussed with the sponsor and documented in the study records.

3.3 SELECTION OF TRIAL POPULATION

A total of 537 patients will be entered into the trial (87 Phase II and 450 Phase III patients) from approximately 27 countries and 140 sites. A log of all patients included into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they commenced trial drug.

3.3.1 Main diagnosis for study entry

Adult patients with unresectable MPM can be entered into this trial. The ECOG performance score must be 0 or 1.

3.3.2 Inclusion criteria

1. Male or female patients age 18 years or older
2. Histologically confirmed MPM:
    a) Epithelioid or biphasic subtype (Phase II patients)
    b) Epithelioid subtype only (Phase III patients)
3. Life expectancy of at least 3 months in the opinion of the investigator
4. ECOG score of 0 or 1
5. Measurable disease according to modified RECIST criteria (R12-1990)
6. Signed and dated written informed consent prior to admission to the study in accordance with ICH-GCP guidelines and the local legislation

3.3.3 Exclusion criteria

1. Previous systemic chemotherapy for MPM
2. Prior treatment with nintedanib or any other prior line of therapy
3. Patients with:
    a) Sarcomatoid subtype MPM (Phase II patients)
    b) Sarcomatoid and biphasic subtype MPM (Phase III patients)
4. Patients with symptomatic neuropathy
5. Patients with mild to moderate renal insufficiency (creatinine clearance of 60-79 mL/minute) taking Non-steroidal Anti Inflammatory Drugs (NSAIDs) with short half lives unable or unwilling to interrupt NSAIDs for 5 days (2 days before, day of and 2 days after treatment with pemetrexed)
6. Patients with mild to moderate renal insufficiency (creatinine clearance of 60-79 mL/minute) taking NSAIDs with long half lives unable or unwilling to interrupt NSAIDs for 8 days (5 days before, day of and 2 days after treatment with pemetrexed)
7. Known hypersensitivity or any contraindications to the trial drugs, including pemetrexed/cisplatin, to their excipients or to contrast media

8. Radiotherapy (except extremities) within 3 months prior to baseline imaging (localised radiotherapy treatment for symptomatic relief is allowed if occurred at least 2 weeks before randomisation and the measurable disease is outside of the field of radiotherapy; radiotherapy of the scars post thoracoscopy is allowed)

9. In opinion of the investigator, persistence of clinically relevant therapy related toxicity from previous radiotherapy

10. Patients that may be eligible for or being considered for radical resection or elective surgery during the course of the study. *Note: prior surgery is allowed if occurred at least 4 weeks prior to randomisation, there is complete healing and there is residual measurable disease*

11. Radical surgery within 4 weeks prior to randomisation

12. Active brain metastases (e.g. stable for < 4 weeks, no adequate previous treatment with radiotherapy, symptomatic, requiring treatment with anti-convulsants; dexamethasone therapy will be allowed if administered as stable dose for at least one month before randomisation)

13. Leptomeningeal disease

14. Radiographic evidence (CT or MRI) of cavitary or necrotic tumours or local invasion of major blood vessels by MPM

15. Treatment with other investigational drugs or treatment in another clinical trial within the past 4 weeks before randomisation or concomitantly with the trial

16. Therapeutic anticoagulation (except low-dose heparin and/or heparin flush as needed for maintenance of an in-dwelling intravenous devise) or anti-platelet therapy (except for low-dose therapy with acetylsalicylic acid < 325 mg per day

17. Major injuries within the past 4 weeks prior to randomisation with incomplete wound healing

18. History of clinically significant haemorrhagic or thromboembolic event within 6 months of screening

19. Known inherited predisposition to bleeding or thrombosis

20. Significant cardiovascular diseases (i.e. hypertension not controlled by medication, unstable angina, history of myocardial infarction within the past 12 months prior to randomisation, congestive heart failure > NYHA II, serious cardiac arrhythmia, pericardial effusion)

21. Proteinuria ≥ CTCAE Grade 2 (if 24 hour urine is collected > 1.0 g/24 hrs)

22. Total bilirubin above the upper limit of normal

23. ALT and/or AST > 1.5 x ULN in patients without liver metastasis

    ALT and/or AST > 2.5 x ULN in patients with liver metastasis

24. International normalised ratio (INR) > 2

25. Prothrombin time (PT) and/or partial thromboplastin time (PTT) > 50% deviation from institutional ULN

26. Absolute neutrophil count (ANC) < 1,500/µl ($1.5x10^9$/L)

27. Platelets < 100,000/µl ($100x10^9$/L)

28. Haemoglobin < 9.0 g/dl or requiring transfusions

29. Creatinine clearance <60 mL/min (using the standard Cockcroft and Gault formula (below) or Glomerular Filtration Rate (GFR) measured by Tc99m-DPTA serum clearance method:

    Males: $$\frac{[140 - \text{Age in years}] \times \text{Actual Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}} - \text{mL/min}$$

    Females: Estimated creatinine clearance for males × 0.85

30. Other malignancies within 3 years prior to screening other than basal cell skin cancer or carcinoma in situ of the cervix

31. Active serious infections in particular if requiring systemic antibiotic or antimicrobial therapy

32. Known active or chronic hepatitis C and/or B infection

33. Gastrointestinal disorders or abnormalities that would interfere with absorption of the study drug

34. Serious illness or concomitant non-oncological disease such as neurologic, psychiatric, infectious disease or active ulcers (gastro-intestinal tract, skin) or laboratory abnormality that may increase the risk associated with study participation or study drug administration and in the judgment of the investigator would make the patient inappropriate for entry into the study

35. Patients who are sexually active and unwilling to use a medically acceptable method of contraception (e.g. such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomised partner) during the trial and for at least three month after ceasing nintedanib / placebo and for at least twelve months after ceasing chemotherapy (see Section 5.2.2.4)

36. Pregnancy or breast feeding

37. Psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule

38. Active alcohol or drug abuse

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

A patient has to be withdrawn from active treatment in case any of the following applies:

- Documented unequivocal progressive disease according to modified RECIST (R12-1990). Study treatment can only be continued beyond radiological progression if it is deemed in the patients' interest following a careful risk benefit assessment by the investigator (refer to Section 5.1.2.1.5). For equivocal findings of progression (e.g. very small and uncertain new lesions, cystic changes or necrosis in existing lesions, etc.), treatment should continue until next scheduled assessment.
- The patient requests discontinuation of active treatment
- The patient is no longer able to participate in the study (e.g. AE, surgery, pregnancy, concomitant diagnoses, concomitant therapies, or administrative reasons). The investigator may also stop a patient's treatment, if the patient is no longer able to attend study visits
- Significant deviation from the protocol or eligibility criteria. The decision to continue or withdraw treatment will be made after discussion between the sponsor and the investigator
- The patient cannot tolerate nintedanib / placebo treatment either as monotherapy or in combination with pemetrexed /cisplatin despite dose reductions. Patients who interrupt or discontinue nintedanib/placebo during the combination therapy period can continue pemetrexed and/or cisplatin for up to 6 cycles, without being removed from the trial. Likewise, patients who discontinued chemotherapy (pemetrexed and/or cisplatin) during the combination therapy period can continue with one remaining compound combined with nintedanib/placebo or nintedanib/placebo monotherapy.
- The patient receives prohibited concomitant medication (refer to Section 4.2.2)

The EoT information has to be obtained. All patients who end active treatment (but not the trial) will be followed up as described in Section 6.2.3.2.

All withdrawals will be documented and the reason for withdrawal recorded in the eCRF and discussed, as necessary, in the clinical trial report.

Patients who fail screening will not be included in the analysis but will be entered into the trial database. The reason for failure will be documented and reported descriptively and by patient listing in the report of this trial.

Patients who fail screening will be replaced (Phase III patients only). Patients who initially may not meet eligibility criteria (e.g. for administrative reasons or assessments are out of time window) may be re-screened at investigator's discretion after consulting with the Sponsor.

Regardless, all screening assessment requirements as detailed in the flow charts must be followed.

Patients who withdraw from the study after randomisation will not be replaced.

3.3.4.2 Discontinuation of the trial by the sponsor

BI 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 that could significantly affect continuation of the trial,
3. Violation of good clinical practice (GCP), the clinical trial protocol (CTP), or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Patients will initially be treated with nintedanib / placebo in combination with standard chemotherapy (pemetrexed / cisplatin) for a maximum of 6 cycles of 21 days duration.

After completion of combination therapy, patients who have not progressed will continue to be treated with nintedanib / placebo monotherapy.

4.1.1 Identity of investigational and comparator products

4.1.1.1 Nintedanib (investigational product)

Substance (International Nonproprietary Name [INN]):	Nintedanib
Pharmaceutical form:	Soft gelatine capsule
Pharmaceutical code	BIBF 1120
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	100 mg and 150 mg capsules
Daily dose:	400 mg (200 mg twice daily)
Route of administration:	Oral
Duration of use:	Continuous daily dosing until disease progression or until criteria for treatment interruption are met.

4.1.1.2 Placebo (comparator)

Substance (INN):	Not applicable
Pharmaceutical form:	Soft gelatine capsule
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Placebo contains 0 mg of nintedanib in capsules matching 100 mg and 150 mg of Nintedanib
Daily Dose	Capsules matching 400 mg of nintedanib (200 mg twice daily)
Route of administration:	Oral
Duration of use:	Continuous daily dosing until disease progression or until criteria for treatment interruption are met

Substance (INN):	Pemetrexed / Cisplatin
Pharmaceutical form:	Injectable
Source:	Manufacturer for (local) market
Unit strength:	Pemetrexed: 100 mg or 500 mg single-use vials Cisplatin: 50 mL of 1 mg/ml solution
Daily dose:	500 mg/m^2 Pemetrexed followed by 75 mg/m^2 Cisplatin on day 1 of each cycle
Route of administration:	Intravenous infusion
Duration of use:	Each cycle is 21 days in duration. Patient may receive a maximum of 6 cycles
Additional information:	Drugs should be administered according to the SPC. The recommendations for supportive care should be followed (see SPC)

4.1.1.3 Non-investigational product

4.1.2 Method of assigning patients to treatment groups

When a patient qualifies for entry into the study, treatment randomisation to nintedanib or placebo will be implemented by either IVRS and/or IWRS. Instructions for using IVRS/IWRS will be provided to the investigator.

An internal Clinical Trial Support Group will provide the randomisation scheme and the stratification factors. The randomisation code will be kept blinded by Clinical Trial Support Group until database lock. For all details of the randomisation please refer to Section 7.5.

4.1.3 Selection of doses in the trial

Nintedanib in combination with standard treatment of pemetrexed / cisplatin is being investigated in this study.

Nintedanib 200 mg b.i.d. has been studied in combination with pemetrexed (U08-3886-01) and is the recommended dose for this and other combinations (see Section 1.2.4 to 1.2.6).

The starting dose of nintedanib will be 200 mg b.i.d. The dose of pemetrexed will be 500 mg/m^2 and cisplatin will be 75 mg/m^2. In the event of treatment-limiting AEs, dose delay and dose reduction criteria are provided in Section 4.2.1.

During the combination treatment phase, both pemetrexed and cisplatin will be administered intravenously on Day 1 of a 21-day cycle for a maximum of 6 cycles. Nintedanib / placebo will be administered orally twice daily starting on Day 2 and continue daily for 20 days in a

21-day cycle. Study medications should not be administered before PK sampling is performed on Day 8 of Cycle 2.

If pemetrexed/cisplatin administration needs to be interrupted and patient tolerates therapy with nintedanib/placebo, daily treatment with nintedanib/placebo should continue until the next pemetrexed /cisplatin administration.

After completion of combination therapy and if patients have not progressed, nintedanib/placebo will be administered orally twice daily starting on Day 1 to Day 21 of each treatment cycle.

4.1.4 Drug assignment and administration of doses for each patient

During the combination phase, stopping rules and retreatment criteria for each compound should be considered separately, e.g. if pemetrexed has to be interrupted or permanently discontinued, cisplatin and nintedanib/placebo should continue for the remainder of the combination therapy period provided stopping criteria are not met for either compound.

4.1.4.1 Nintedanib (BIBF 1120) and placebo

Nintedanib (200 mg) and placebo (matching capsule) will be swallowed twice daily un-chewed with a glass of water of about 250 mL every 12 hours (± 1 hour) after food intake, at about the same time in the morning and in the evening.

No nintedanib/placebo will be taken on the days of pemetrexed and cisplatin administration.

If a patient misses one or more doses of nintedanib/placebo, the patient should continue to take the next treatment as per schedule and notify the study team looking after them that they have missed doses.

4.1.4.2 Pemetrexed and cisplatin

The pemetrexed and cisplatin infusion should be administered under the supervision of the investigator or designated personnel at the trial site.

For treatment of MPM, the starting dose of pemetrexed is 500 mg/m^2 administered as an intravenous (i.v.) infusion over approximately 10 minutes on Day 1 of each 21-day cycle, followed by cisplatin 75 mg/m^2 infused over 2 hours approximately 30 minutes after completion of pemetrexed administration. Patients should receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin in accordance with the local current SPC.

The duration (actual start and end time) of the infusion needs to be documented in the eCRF. Every attempt should be made to adhere to the planned infusion time with a constant infusion rate. The use of an infusion pump is recommended.

The details of the procedure to prepare the infusion solution and the instructions for intravenous (i.v.) administration will be provided in the ISF.

4.1.4.3 Pre-medication Regimen

Corticosteroid - skin rash has been reported more frequently in patients not pretreated with a corticosteroid. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction. All patients should be pre-medicated with dexamethasone 4 mg by mouth twice daily the day before, the day of, and the day after pemetrexed administration.

Vitamin Supplementation - to reduce toxicity, patients treated with pemetrexed must be instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid (350 µg to 1000 µg, most commonly used dose of 400 µg) on a daily basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of pemetrexed; and dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular injection of vitamin B12 (1000 µg) during the week preceding the first dose of pemetrexed and once every 3 cycles (9 weeks) until pemetrexed is discontinued. Subsequent vitamin B12 injections may be given on the same day as pemetrexed.

Hydration - Adequate hydration must be maintained from 2 to 12 hours prior to administration until minimum 6 hours after the administration of cisplatin. Hydration is necessary to cause sufficient diuresis during and after treatment with cisplatin.

It is necessary that the patient drinks large quantities of liquids for 24 hours after the cisplatin infusion to ensure adequate urine secretion.

4.1.4.4 Re-treatment criteria for pemetrexed and cisplatin therapy

Re-treatment criteria for further pemetrexed and cisplatin course are as follows (the laboratory parameters must be obtained prior to re-treatment):

- ANC of at least 1.5 x 10^9/L
- Platelet count of at least 100 x 10^9/L
- Bilirubin values within normal ranges
- ALT and AST ≤ 1.5 x upper limit of normal (ULN) for patients without liver metastasis and ≤ 2.5 x ULN for patients with liver metastasis with concomitant alkaline phosphatase (ALP) ≤ 2.5 x ULN, respectively
- Creatinine clearance >45 mL/min

In addition to the above mentioned criteria, the following values have to be reached for cisplatin re-treatment (the laboratory parameters must be obtained prior to re-treatment):

- Serum creatinine ≤ 130 µmol/l or ≤ 1.5 mg/100 ml
- Blood urea < 25 mg/100 ml or < 8.92 mmol/l

Stopping criteria for pemetrexed / cisplatin therapy:

If any of the following events occur, pemetrexed or cisplatin must be permanently discontinued:

- Peripheral neuropathy of CTCAE grade ≥ 3
- Cisplatin induced hearing loss of CTCAE grade ≥ 3
- Severe hypersensitivity reaction to pemetrexed or cisplatin is noted
- The occurrence of AEs that would require a third dose reduction

If any of the above events occur, patients can continue therapy with nintedanib / placebo if:

- None of the withdrawal criteria have been met
- All drug-related AEs that occurred during the previous treatment courses have recovered to baseline levels, or to CTCAE grade levels that would allow further therapy with nintedanib / placebo

4.1.4.5 Temporary treatment interruption of nintedanib / placebo

Treatment with nintedanib / placebo shall be temporarily interrupted for up to 2 weeks and adequate therapy should be initiated as per outlined in Section 4.2.1 if one of the following AEs occurs:

Diarrhoea:

- CTCAE grade 2 for > 7 consecutive days despite optimal medical management
- CTCAE grade ≥ 3 or diarrhoea event leading to hospitalisation

Nausea / vomiting (if onset >3 days since pemetrexed/cisplatin administration):

- Vomiting of CTCAE grade ≥ 2
- Nausea of CTCAE grade ≥ 3

Liver enzyme elevations:

- ALT and/or AST >2.5 x ULN in conjunction with Bilirubin of ≥ 1.5 x ULN
- ALT and/or AST > 5 x ULN

Haematological Adverse Events:

- Platelet < 50 x 10^9/L associated with bleeding of CTCAE grade ≥ 2 regardless of nadir ANC
- Neutropenia of any grade accompanied by fever >38.5°C
- Neutropenia of CTCAE grade 4 without fever > 7 days

Other non-haematological drug related AEs of CTCAE grade ≥ 3

In case a delay for more than 2 weeks would be required by the investigator or the patient, this needs to be discussed and agreed between the investigator and the sponsor.

4.1.4.6 Re-treatment criteria for nintedanib / placebo

Treatment with nintedanib / placebo may be resumed as long as the events causing temporary treatment interruption had recovered to baseline levels or to a CTCAE grade which would allow further therapy:

- Nausea CTCAE Grade ≤ 1

- Vomiting CTCAE Grade ≤ 1
- Diarrhoea CTCAE Grade ≤ 1
- Other non-hematological or hematological toxicity recovered to baseline levels or to a CTCAE grade 1

Dose modifications of nintedanib / placebo should be followed and the criteria should be met in order to allow the recommencing of nintedanib / placebo treatment at a reduced dose as outlined in Section 4.2.1.

With respect to liver enzyme elevations, the following values have to be reached:

- Bilirubin values within normal ranges
- ALT and AST ≤ 1.5 x ULN for patients without liver metastasis and ≤ 2.5 x ULN for patients with liver metastasis with concomitant alkaline phosphatase (ALP) ≤ 2.5 x ULN, respectively

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This trial will be performed according to a parallel group, double-blind, placebo controlled design. Patients, investigators and the sponsor's trial team involved in the analysis of this double-blind trial will remain blinded with regard to the randomised treatment assignments up to database lock of the respective parts of the trial, with the exception of particular instances which require immediate unblinding according to BI's standard operation procedures (e.g. emergency situations).

An internal Clinical Trial Support Group will arrange for the randomisation. The randomisation code will be kept separate from the trial team by Clinical Trial Support up to database lock. The randomisation code will only be released according to protocol. With regard to the two separate parts of this trial, two separate randomisation lists have been created. The first randomisation list refers only to the Phase II patients in this trial; the second randomisation list refers to the Phase III patients in this trial.

Investigators, patients, and the trial team involved in the continuing trial will not be unblinded until final analysis of the study. The first 87 randomised patients (Phase II) were internally unblinded on 04-Mar-2016 as recommended following consultation with regulatory authorities (EMA and FDA) and prior to any enrolment in the Phase III part. This analysis represents the primary PFS analysis of the Phase II part. The primary OS analysis of the Phase II part will be conducted when approximately 61 OS events of the Phase II patients have occurred.

For the primary PFS analysis and the interim OS analysis of the Phase III part, the trial database will be locked and unblinded by a team independent from the trial team tasked to analyze the data and write the primary PFS analysis report and, subsequently a regulatory submission dossier if requested. Investigators, patients, clinical monitors, trial team and others involved in the continuing trial will remain blinded. Details about the unblinding and firewalls to protect the blinding will be described separately in an interim logistics plan.

For the planned adaptive design at the time of the interim OS analysis as well as for all DMC safety meetings, the external DMC will be unblinded to the data of the patients. The unblinding will be done by a CRO on a secure data platform that can only be accessed by DMC members and the CRO. Further details of the unblinding of these data will be described in the DMC charter. It will be ensured that investigators, patients and the trial team will be kept blinded with regard to all Phase III patients until the final analysis of this trial.

4.1.5.2 Procedures for emergency unblinding

For this blinded trial, emergency unblinding procedures will be available to the investigator / pharmacist / investigational drug storage manager via IVRS/IWRS. This code break may only be opened in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or if required to assure safety of trial participants. If the code break for a patient is opened, the sponsor must be informed immediately. The reason for the unblinding should be documented in the patient's medical record along with the date and the initials of the person who broke the code.

4.1.6 Packaging, labelling, and re-supply

Nintedanib or matching placebo will be packaged in one-week blister cards. Blister cards will be labelled with a unique identifier for drug accountability and will be labelled according to the participating countries' regulatory requirements. Blisters will be packaged in one month boxes (21 days treatment plus 1 week reserve medication).

Packaging and labelling will not be applicable for pemetrexed / cisplatin as these will be sourced locally.

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

4.1.7 Storage conditions

Nintedanib and matching placebo must be stored in the original package, at study site in a temperature-controlled area maintained at room temperature (between 15^{o} C and 30^{o} C) and with restricted access.

Pemetrexed and Cisplatin must be stored in the original package according to the manufacturer's storage instructions.

If the storage temperature deviates from the required range, immediately contact the local clinical monitor (see Contact List filed in the ISF).

4.1.8 Drug accountability

Nintedanib and matching placebo will be provided by the sponsor, and pemetrexed / cisplatin will be procured locally. Drug supplies must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. A temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The investigator and/or pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- approval of the study protocol by the institutional review board (IRB) / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the trial site
- approval/notification of the regulatory authority, e.g. competent authority (CA),
- availability of the curriculum vitae of the principal investigator,
- availability of a signed and dated CTP or immediately imminent signing of the CTP,
- if applicable, availability of the proof of a medical licence for the principal investigator,
- availability of the Form 1572 (for USA only).

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 alternative disposition of unused products.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational products 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 when the trial site is closed out.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

Before infusion of pemetrexed / cisplatin, patients must be pre-medicated as described in Section 4.1.4.3 and according to the local current SPC.

Concomitant medications, or therapy to provide adequate care, may be given as clinically necessary. Restrictions in Section 4.2.2 apply.

All concomitant (non-oncological) medications which are taken between trial informed consent and follow-up visit 1, as well as the required pre-medication and further anti-cancer treatment should be recorded in the eCRF. If patients receive parenteral nutrition during the trial, the components need not be specified in detail, it should just be indicated as "parenteral nutrition". If a patient requires anaesthesia, it will be sufficient to indicate "anaesthesia" without specifying the details.

For screen failures, only concomitant medications given for trial related AEs will be collected.

4.2.1 Rescue medication, emergency procedures, and additional treatments

Rescue medication to reverse the actions of nintedanib is not available. Potential side effects of nintedanib have to be treated symptomatically. Recommended symptomatic treatments of study medication side effects or tumour-associated symptoms that may occur are listed below.

Investigators should use the following guidelines for the management of side effects related to the treatment of nintedanib / placebo in combination with pemetrexed / cisplatin and nintedanib / placebo monotherapy.

Full details can be found in the SPC for pemetrexed and cisplatin filed in the ISF.

4.2.1.1 Dose Reduction Recommendations

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum non-hematologic toxicity experienced by the patient according to CTCAE (version 3.0 for Phase II and version 4.03 for Phase III patients) from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be retreated using the guidelines in Sections 4.2.1.2 and 4.2.1.3 below.

Only two dose reductions will be allowed throughout the study duration. Once a patient has undergone a dose reduction as required per the following recommendations, the dose will not be re-escalated. If a patient receives a reduced dose in error, the dose can be re-escalated to allow adequate treatment.

Dose reductions for cisplatin induced ototoxicity or nephrotoxicity: in case of significant clinical hearing loss or renal dysfunction, cisplatin therapy should be reduced or stopped. The clinician will make the decision regarding cisplatin dosing and also whether to continue pemetrexed alone or to withdraw the patient from the combination treatment.

4.2.1.2 Management of non-haematological toxicity

In general, for grade ≥ 3 non-haematological toxicity, therapy should be withheld or decreased depending on the judgment of the treating physician. Doses should be withheld until toxicity has resolved either to baseline or values which would allow further re-treatment.

4.2.1.2.1 Management of diarrhoea

In the event of diarrhoea considered to be related to nintedanib the following algorithm should be used:

Table 4.2.1.2.1:1 Recommendation for the management of drug-induced diarrhoea

CTCAE Grade	Anti-diarrhoeal treatment	Dose of nintedanib/placebo
Grade 1 or 2	Anti-diarrhoeal treatment e.g. loperamide	Continue treatment, no dose reduction

Table 4.2.1.2.1:1 (cont'd) Recommendation for the management of drug-induced diarrhoea

CTCAE Grade	**Anti-diarrhoeal treatment**	**Dose of nintedanib/placebo**
Grade 2 > 7 consecutive days despite optimal medical management Or Grade ≥3 or any diarrhoea independent of CTCAE grade leading to hospitalisation of the patient		
First episode	Anti-diarrhoeal treatment e.g. loperamide	Treatment pause and resume upon recovery* and reduce dose from 200 mg b.i.d. to 150 mg b.i.d.
Second episode	Treatment as above	Treatment pause and resume upon recovery* and reduce dose from 150 mg b.i.d. to 100 mg b.i.d.
Third episode	Treatment as above	Discontinue treatment

* until resolution to less than, or equal to baseline value or CTCAE ≤ grade 1

4.2.1.2.2 Management of liver enzyme elevations

In the event of liver enzyme elevations, the following algorithm should be followed:

Table 4.2.1.2.2:1 Recommendation for management of liver enzyme elevations

CTCAE Grade	**Combination Therapy (cycle 1 – 6)**	**nintedanib /placebo monotherapy (after cycle 6)**
ALT and/or AST ≤ 5 x ULN with bilirubin < 1.5 x ULN	No dose reduction	No dose reduction
Elevation of AST and/or ALT values to > 2.5 x ULN in conjunction with total bilirubin elevation to ≥ 1.5 x ULN *OR* Elevation of AST and/or ALT values to > 5x ULN		
First Episode	Treatment pause until recovery to less than, or equal to, patient's pre-therapy value at study enrolment.	
	Nintedanib / placebo: reduce dose from 200 mg b.i.d. to 150 mg b.i.d.	
	Pemetrexed: reduce dose to 75% of starting dose	
Second Episode	Treatment pause until recovery to less than, or equal to, patient's pre-therapy value at study enrolment.	
	Nintedanib /placebo: reduce dose from 150 mg b.i.d. to 100 mg b.i.d.	
	Pemetrexed: reduce dose to 50% of starting dose	
Third Episode	Treatment discontinuation	

In case of an elevation of AST/ALT > 3 x ULN in conjunction with bilirubin ≥ 2 x ULN and ALKP < 2 x ULN treatment with nintedanib should be interrupted. Unless there is an alternative cause established, nintedanib should be permanently discontinued.

4.2.1.2.3 Management of nausea and vomiting

Nausea and vomiting may significantly affect patients' adherence to the treatment and quality of life. In order to reduce the occurrence and the intensity of emesis the patients should be treated according to the recommendations / guidelines below.

Table 4.2.1.2.3:1 Management of nausea and vomiting

CTCAE Grade of Emesis	**Antiemetic treatment** Note: Tropisetron or dolasetron should be avoided due to genetically polymorphic metabolism by CYP2D6.	**Emesis occurring ≤ day 3 after combination treatment of cisplatin / pemetrexed**	**Emesis occurring ≥ day 4 after combination treatment of cisplatin / pemetrexed or during nintedanib /placebo monotherapy**
Nausea =1	No antiemetic treatment	No dose reduction	No dose reduction
Nausea = 2 and / or vomiting =1	No Nintedanib treatment pause. Antiemetic treatment e.g. metoclopramide or dimenhydrinate, or prochlorperazine If ineffective, patients should be treated according to treatment of vomiting CTCAE Grade ≥ 2 or nausea CTCAE Grade ≥ 3	No dose reduction	No dose reduction
Vomiting ≥2 and / or Nausea ≥ 3			
First episode	Treatment with nintedanib /placebo discontinued and resumed upon recovery[1] Antiemetic treatment with 5-Hydroxy-Tryptamin Receptor 3 (5-HT3) receptor antagonist and / or corticosteroid **Prophylactic antiemetic treatment with 5-HT_3 receptor antagonist and corticosteroid at all subsequent administrations of chemotherapy from Days 1-3 of chemotherapy. If this is already standard of care, follow second episode**	Cisplatin / pemetrexed: no dose reduction Nintedanib / placebo: no dose reduction	Cisplatin / pemetrexed: no dose reduction Nintedanib / placebo: reduce dose from 200 mg b.i.d. to 150 mg b.i.d.
Second episode	Treatment with nintedanib /placebo discontinued and resumed upon recovery[1]	Cisplatin / pemetrexed: dose reduction Nintedanib / placebo: reduce dose from 200 mg b.i.d. to 150 mg b.i.d.	Cisplatin / pemetrexed: no dose reduction Nintedanib /placebo: reduce dose from 150 mg b.i.d. to 100 mg b.i.d.
Third episode	Treatment as above	Cisplatin / pemetrexed: dose reduction Nintedanib /placebo: reduce dose from 150mg b.i.d. to 100 mg b.i.d.	Cisplatin / pemetrexed: no dose reduction Nintedanib /placebo: discontinuation
Fourth episode	Treatment as above	Cisplatin / pemetrexed: discontinuation Nintedanib / placebo: discontinuation	Not applicable

[1] until resolution to less than, or equal to the patient's pre-therapy value at study enrollment
***** add NK1 receptor antagonist in case that prophylactic antiemetic treatment is foreseen in the protocol

In case vomiting occurs shortly after intake of nintedanib/placebo, patient should not take a replacement dose.

4.2.1.2.4 Management of mucositis and rash

Table 4.2.1.2.4:1 Dose reductions for mucositis and rash

CTCAE Grade ≥ 3	**Combination Therapy:**	**Nintedanib / placebo Monotherapy**
First Episode	Treatment pause until recovery*	
	Nintedanib / placebo: dose reduce from 200 mg bid to 150 mg bid	
	Pemetrexed: 50% of previous dose (mucositis) Pemetrexed: 75% of previous dose (rash)	
Second Episode	Treatment pause until recovery*	
	Nintedanib / placebo: dose reduce from 150 mg bid to 100 mg b.i.d.	
	Pemetrexed: 50% of previous dose (mucositis) Pemetrexed: 75% of previous dose (rash)	
Third Episode	Treatment discontinuation	

* until resolution to less than, or equal to baseline value or CTCAE ≤ grade 1

4.2.1.2.5 Management of neurotoxicity

Table 4.2.1.2.5:1 Dose reductions for pemetrexed and cisplatin - neurotoxicity

CTCAE Grade	**Dose of Pemetrexed (mg/m^2)**	**Dose of Cisplatin (mg/m^2)**
0-1	No dose reduction	No dose reduction
2	No dose reduction	50% of previous dose
≥3	Treatment discontinuation	

4.2.1.3 Management of haematological toxicity

Nintedanib/placebo monotherapy: Based on the current data for monotherapy, nintedanib does not induce haematological side effects. However, in the event of occurrence of CTCAE grade >3 haematological side effects under the nintedanib / placebo monotherapy, treatment should be interrupted and re-initiated at a reduced dose upon recovery.

Nintedanib in combination with pemetrexed / cisplatin: Patients should have an ANC of at least 1.5 x 109/L and platelet count of at least 100 x 109/L prior to receiving the next cycle of chemotherapy. Dose modifications should be performed according to the guidelines below:

Table 4.2.1.3:1 Dose reductions for hematologic adverse events during combination treatment

Haematologic adverse event	**Pemetrexed / cisplatin***	**Nintedanib / placebo***
ANC < 0.5 x 10^9/L and Platelets ≥ 50 x 10^9/L		
First episode	75% of previous dose (both drugs)	No dose reduction
Second episode	75% of previous dose (both drugs)	No dose reduction
Third episode	Discontinuation	No dose reduction
Platelets ≤ 50 x 10^9/L without bleeding regardless of nadir ANC		
First episode	75% of previous dose (both drugs)	No dose reduction
Second episode	75% of previous dose (both drugs)	No dose reduction
Third episode	Discontinuation	No dose reduction
Platelets < 50 x 10^9/L with bleeding CTCAE grade ≥ 2 regardless of nadir ANC		
First episode	50% of previous dose (both drugs)	Dose reduce from 200 mg b.i.d. to 150 mg b.i.d.
Second episode	50% of previous dose (both drugs)	Dose reduce from 150 mg b.i.d. to 100 mg b.i.d.
Third episode	Discontinuation	Discontinuation
Neutropenia of any grade accompanied by fever > 38.5 °C or Neutropenia grade 4 without fever > 7 days		
First episode	75% of previous dose (both drugs)	Dose reduce from 200 mg b.i.d. to 150 mg b.i.d.
Second episode	75% of previous dose (both drugs)	Dose reduce from 150 mg b.i.d. to 100 mg b.i.d.
Third episode	Discontinuation	Discontinuation

* pause treatment and resume when ANC ≥ 1.5 x 10^9/L and the platelet count ≥ 100 x 10^9/L

The use of Granulocyte-Colony Stimulating Factor to treat chemotherapy-induced neutropenia is allowed according to local clinical practice.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Additional antineoplastic therapy not specified in this protocol such as chemo-, immuno-, hormone (with the exception of Hormone Replacement Therapy or palliative radiotherapy) are not allowed during the study. For symptom control, palliative radiotherapy may be permitted after discussion with the CML, provided that other target lesions remain, and the reason for the radiotherapy does not reflect progressive disease.

Patients who require full-dose anticoagulation or heparinisation cannot be enrolled into the study. Intervention with low-dose therapeutic anticoagulation (such as low-dose heparin

and/or heparin flush as needed for maintenance of an in-dwelling i.v. device) or anti-platelet therapy (such as acetylsalicylic acid < 325mg per day) may be allowed if clinically required for a patient to treat AEs. These patients will be monitored at close intervals (refer to Section 5.2.3) until they achieve a stable anticoagulation status.

Concomitant therapy with the 5-HT3 receptor antagonists tropisetron and/or dolasetron which are metabolised by cytochrome 2D6 should be avoided since anti-emetic efficacy may be low in patients who are 'fast metabolisers'. If treatment with a 5-HT3 receptor antagonist is required, another one should be selected.

Treatment with other investigational drugs or enrolment in another clinical trial must not be initiated prior to progression of the disease.

4.2.2.2 Drug specific restrictions

Pemetrexed and cisplatin: refer to the local current SPC for specific restrictions for pemetrexed and cisplatin.

4.3 TREATMENT COMPLIANCE

Pemetrexed and cisplatin will be administered as i.v. infusion in accordance with the current SPCs and in the practice or hospital of the investigator under supervision of authorised personnel. Date of administration as well as a statement whether infusion was done according to protocol and/or whether infusion was interrupted will be recorded in the eCRF.

Nintedanib/placebo will be given as an oral administration in accordance with the study protocol and under the instruction of the investigator. The patients will be asked to return all unused nintedanib and/or matching placebo capsules at the next scheduled visit. The investigator or his/her deputy will check whether the patient has taken the medication according to the protocol. Any discrepancies will be explained in the eCRF by the investigator or his/her deputy.

It is recommended that patients take all doses of nintedanib / placebo according to the trial protocol unless dosing is limited by AEs. However, patients with prolonged treatment interruptions not necessitated by AEs will not automatically be taken off study.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY

5.1.1 Endpoints of efficacy

Primary endpoint:

- Progression free survival measured from the time of randomisation to the time of disease progression according to modified RECIST criteria (R12-1990) or death of any cause, whichever occurs earlier.
- For Phase II, the observation period for PFS is defined from randomisation until the earliest of disease progression, death or the cut-off of 04-Mar-2016 for the primary PFS analysis.
- For Phase III, the observation period for PFS will continue until the earliest of disease progression, death or until approximately 199 PFS events have occurred for Phase III patients or until approximately 23months has elapsed since the first Phase III patient was randomised.

Secondary endpoints:

- OS measured from the time of randomisation to the time of death of any cause (key secondary endpoint).
  For Phase II, the observation period for OS is until the earliest of death or until approximately 61 Phase II patients have died, , whichever occurs first.
  For Phase III, the observation period for OS is from randomisation until the earliest case of death or until approximately 279 to 346 (depending on the event reassessment) OS events have occurred for Phase III patients or until approximately 54 months has elapsed since the first Phase III patient was randomised. If the trial is declared positive also for OS at the time of the interim Phase III OS analysis, the observation period for OS will continue until approximately 199 PFS events have occurred.
- Objective response according to modified RECIST (R12-1990) analysed by objective response rate. Tumour imaging is to be performed every 6 weeks up to approximately 54 months since the first Phase III patient was randomised or until disease progression, death or start of subsequent anti-cancer therapy, whichever occurs earlier
- Disease control according to modified RECIST (R12-1990) analysed by disease control rate. Tumour imaging is to be performed every 6 weeks up to approximately 54 months since the first Phase III patient was randomised or until the disease progression, death or start of subsequent anti-cancer therapy, whichever occurs earlier.

[redacted]

Objective Tumour Response

Objective response is defined as best overall response of CR or PR, where best overall response is determined according to modified RECIST (R12-1990) recorded from randomisation until the earliest of disease progression, death or last evaluable tumour assessment before subsequent non-study anti-cancer therapy, and in case CR and/or PR was confirmed by imaging four weeks or later after the first occurrence of the response. Time to objective response is defined from the time of randomisation until first documented CR or PR among patients with objective response. Duration of objective response is defined as the time from first documented CR or PR until the earliest of disease progression or death among patients with objective response.

Disease Control

Disease control is defined as best overall response of CR or PR or SD where best overall response is defined according to modified RECIST (R12-1990) recorded from randomisation until the earliest of disease progression, death or last evaluable tumour assessment before subsequent non-study anti-cancer therapy.

Duration of disease control is defined as the time from randomisation until the earliest of disease progression or death among patients with disease control.

[redacted]

5.1.2 Assessment of efficacy

5.1.2.1 Tumour assessment by imaging

Tumour assessment by computed tomography (CT) scan or MRI will be performed at the time points specified in the flow charts and will be evaluated according to the modified RECIST criteria (R12-1990) based on RECIST 1.0. The results will be recorded in the eCRF.

All measurable lesions representative of all involved organs should be identified at screening by CT or MRI, as target lesions and will be recorded, measured and numbered at baseline. Target lesions should be selected on the basis of their size and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

All other lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required; these lesions should be assigned the responses for

non-target lesions (CR, Incomplete response/SD, PD or not evaluable) and taken into consideration in tumour response evaluation.

Progression will be assessed by tumour measurements and will be evaluated by the investigator according to modified RECIST (R12-1990) [redacted]

Imaging will be performed at baseline (within four weeks prior to administration of first dose of study medication) and every six weeks (± 1 week) from the time the first dose of study medication (pemetrexed/cisplatin) is taken until unequivocal disease progression or initiation of new non-study anti-cancer treatments. If study treatment continues beyond radiological progression in the case of clinical benefit, as judged by the investigator, imaging should continue until discontinuation of study treatment. At baseline imaging must be performed to fully assess the extent of primary tumour and metastases in an individual patient. This should include CT or MRI of the brain, chest and abdomen (i.e. liver and adrenal glands).

All patients will complete a brain scan (CT or MRI) during screening. Patients with stable brain metastases (for definition please refer to the exclusion criteria in Section 3.3.3) at trial entry must be evaluated at each imaging time point for assessment of their brain metastases. If brain metastasis is not noted on initial screening exam, then brain scanning should only be performed for clinical suspicion.

Bone scans need to be performed at screening in patients with known bone metastases and in case of clinical suspicion of previously unknown bone metastasis (i.e. bone or joint pain associated with relevant increases of calcium and ALP).If the patient has known bone metastases or if bone metastases are detected at screening, correlative conventional imaging should be done of the respective lesion(s) during study treatment. These images should then be performed at every imaging time point. Bone scans need to be repeated only at the time when response confirmation imaging is done or when medically indicated (i.e., in case of suspected new bone metastases). In case treatment has to be rescheduled and/or postponed, imaging should be performed at the pre-specified time points (i.e., every six weeks). Any site radiology findings from imaging that is not forwarded to the central imaging unit need to be described concerning abnormalities and forwarded to the imaging centre.

Post-baseline tumour assessments must utilize the same imaging method and acquisition technique as used for screening assessments to ensure comparability (except for brain metastases where CT and/or MRI can be used).

5.1.2.1.1 Definitions

Details of the guideline for measuring mesothelioma will be provided in the ISF. Responses will be evaluated according to modified RECIST criteria (R12-1990). Confirmation of response will be assessed by the investigator and will require repeat observation at the next scheduled assessment visit. Their assessment will be the basis for continuation or discontinuation of treatment in an individual patient.

Measurable lesions

All imaging in the chest must follow modified RECIST (R12-1990):

- Tumour thickness perpendicular to the chest wall or mediastinum will be measured in two positions of three separate transverse cuts of CT scan.
- The sum of the six measurements will define a pleural unidimensional measure.
- Transverse cuts will be collected at least 1cm apart and related to anatomical landmarks in the thorax.
- If measurable tumour is present, transverse cuts in the upper thorax, above the level of division of the main bronchi are preferred.
- At reassessment, pleural thickness will be measured at the same position.

If any additional nodal, subcutaneous and other bidimensionally measurable lesions are available, they should be measured unidimensionally as per the RECIST 1.0 criteria.

Measurable lesions, according to RECIST 1.0, are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm in a short axis diameter with conventional techniques (CT, MRI). Bone lesions will be considered measurable when lytic with measurable soft tissue component (blastic lesions will be considered non-measurable).

Unidimensional measurements are to be added to obtain the total tumour measurement. All tumour measurements must be recorded in millimeters.

Non-measurable lesions

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable lesions. Bone blastic lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques (not confirmed or followed by CT or MRI), and cystic lesions are all non-measurable.

Lesions in areas irradiated within the past three months are not considered measurable at baseline. However, new lesions occurring in previously irradiated areas have to be considered for assessment of tumour response.

Target lesions

All measurable lesions up to a maximum of five lesions per organ and ten lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size and their suitability for accurate repeated measurements by imaging techniques. Unidimensional measurements are to be added to obtain the total tumour measurement at baseline and will be used as reference by which to characterize the objective tumour response.

Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but should be assessed throughout follow-up.

5.1.2.1.2 Evaluation of target lesions

Complete Response (CR): disappearance of all target lesions

Partial Response (PR): at least a 30 % decrease in the total tumour measurement of target lesions, taking as reference the baseline total tumour measurement.

Progressive Disease (PD): at least a 20 % increase in the total tumour measurement of target lesions, taking as reference the nadir (the smallest total tumour measurement recorded since the treatment started), and/or the unequivocal appearance of new lesions.

Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

To be assigned a status of CR or PR, the respective changes in tumour measurements must be confirmed by repeat assessments that should be performed not earlier than four weeks after the criteria for response are first met. In case of SD, follow-up measurements must have met the criteria for SD at least once after randomisation at a minimum interval of six weeks.

5.1.2.1.3 Evaluation of non-target lesions

Complete Response (CR): disappearance of all non-target lesions

Incomplete response/Non-PD: persistence of one or more non-target lesion(s)

Progressive Disease (PD): appearance of at least one new lesion or unequivocal progression of existing non-target lesions.

5.1.2.1.4 Evaluation of overall response

The best overall response is the best response recorded from the start of study treatment until disease progression or initiation of new non-study anti-cancer treatments, taking into account any requirements for confirmation. Post-treatment assessments will be considered in the determination of best overall response as long as a patient does not initiate new non-study anti-cancer treatments. Overall response at each assessment will be evaluated according to Table 5.1.2.1.4:1.

Table 5.1.2.1.4: 1 Overall response determination*

Target lesions	Non target lesions	New lesions	Overall responses
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

* CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease.

5.1.2.1.5 Progression of disease

Date of disease progression will be recorded based upon modified RECIST (R12-1990). Individual patients should continue treatment with the trial drug(s) until unequivocal progression of the disease is observed.

However, in case of clinical benefit as judged by the investigator after careful clinical assessment, patients may be allowed to continue study treatment beyond radiological progression. Before resuming study treatment, the following criteria should be met:

- Written informed consent should be obtained
- Absence of clinical symptoms or signs of disease progression
- No decline in performance status
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites requiring urgent alternative medical intervention

Trial treatment may be continued as long as judged beneficial by the investigator; however, the time of progression as defined by investigator will not change. The decision to continue study treatment should be discussed with the sponsor and documented in the study records.

Unequivocal progression of the disease will be considered to be present in case of the development of:

- New lesions, including new lesions in a previously irradiated field
- An unequivocal increase in a tumour, including lesions within a previously irradiated field

For equivocal findings of progression (e.g. very small and uncertain new lesions, cystic changes or necrosis in existing lesions, etc.), treatment should continue until next scheduled assessment. If at the next assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected regardless of date when therapy was discontinued. If progression is not confirmed, treatment should be continued until the criteria for unequivocal radiological progression are met. Other anti-cancer therapies should not be started until unequivocal disease progression is documented.

In those cases where patients moved into the follow up (FU) period prior to progression of disease, disease evaluations should be continued every 6 weeks until progression of disease is documented (see Section 6.2.3).

[redacted]

5.2 SAFETY

5.2.1 Endpoints of safety

There will be no formal endpoints based on safety in this trial.

- Frequency and severity of AEs graded according to the common terminology criteria for adverse events (CTCAE version 3.0 for Phase II and CTCAE version 4.03 for Phase III) will be assessed for:
    - Unexpected toxicities
    - Overall incidence and intensity of AE, as well as seriousness and relatedness
    - AE leading to dose reduction or treatment discontinuation
    - AE leading to death
    - AE of special interest

- Changes in safety laboratory parameters (see Section 5.2.3) will be assessed for:
    - Change from baseline
    - Change from worst value

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An AE is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, 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 judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Intensity of adverse event

The intensity of AEs should be classified and recorded according to CTCAE, version 3.0 in Phase II and version 4.03 in Phase III, in the eCRF.

Causal relationship of adverse event

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. Assessment of causal relationship should be recorded in the case report forms.

Yes: There is a reasonable causal relationship between the trial drug(s) administered and the AE.

No: There is no reasonable causal relationship between the trial drug(s) administered and the AE.

If a SAE is reported from a blinded trial, the causal relationship must be provided by the investigator for all potential trial drugs, i.e. the investigational drug (nintedanib/placebo) and for all other non-investigational drugs (pemetrexed/cisplatin).

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the eCRF.

If progressive disease occurs and is associated with symptoms or meets one of the seriousness criteria, the signs and symptoms of progressive disease will be reported as an AE or an SAE (if applicable).

Changes in vital signs, electrocardiogram (ECG), physical examination, and laboratory test results

Changes in vital signs, ECG, physical exam and laboratory test results will be recorded as an (S)AE in the eCRF, if they are judged clinically relevant by the investigator.

Exemption to (S)AE Reporting (Phase III patients only)

Disease Progression (PD) is a trial endpoint for analysis of efficacy and as such is exempted from reporting as an (S)AE. Progression of the patient's underlying malignancy will be recorded on the appropriate pages of the eCRF as part of efficacy data collection only and will not be reported on the SAE Form. Death due to disease progression is also to be recorded on the appropriate eCRF page and not on the SAE Form.

However, when there is evidence suggesting a causal relationship between the study drug(s) and the progression of the underlying malignancy (PD), the event must be reported as an SAE on the SAE Form and on the eCRF.

Examples of exempted events of PD may be:

- Progression of underlying malignancy (if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria).
- Hospitalization/Procedures due solely to the progression of underlying malignancy
- Clinical symptoms and/or signs of PD (without confirmation by objective criteria e.g. imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

Exempted events are monitored at appropriate intervals by the external DMC.

5.2.2.2 Protocol-specified adverse events of special interest (AESI)

The following protocol-specified AESIs are to be reported in an expedited manner similar to SAEs, even if they do not meet any of the seriousness criteria – for details please see Section 5.2.2.3 below.

1. For any GI and non-gastrointestinal perforation, leakage, fistula formation, abscess, the following additional information need to be collected, documented in the respective comment field of the eCRF page and forward the SAE form to BI:
    - location of perforation, leakage, fistula, abscess
    - location/extent of abdominal tumour manifestations,
    - imaging & reports (CT, ultrasound, endoscopy, pathology, etc)
    - prior surgery (location, wound healing complications)
    - concomitant diseases with GI involvement (eg, M Crohn, vasculitis, tuberculosis, diverticulitis)
    - thromboembolic events (or predisposition)

2. Liver enzyme elevations: Drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. ALT, AST and bilirubin will be monitored closely during therapy. The timely detection, evaluation, and follow-up of laboratory

alterations of selected liver laboratory parameters to distinguish an effect of the investigational drug from other causes are important for patient's safety and for the medical and scientific interpretation of the finding.

- An elevation of ALT and / or AST > 5 x ULN without bilirubin elevation measured in the same blood draw sample
- An elevation of AST and/or ALT >2.5 x ULN combined with an elevation of bilirubin to >1.5 x ULN measured in the same blood draw sample

Patients showing above laboratory abnormalities need to be followed up until the protocol specific retreatment criteria have been met and according to Appendix 10.1 of this CTP and the "DILI checklist" provided in the ISF.

5.2.2.3 Adverse event and serious adverse event reporting

All AEs, serious and non-serious, and protocol-specified AESI, occurring between signing of informed consent until the end of the residual effect period (i.e. 28 days after the last administration of the trial drug for Phase II and 30 days for Phase III), see Section 6.2.3.2, will be collected, documented and reported to the sponsor immediately by the investigator on the appropriate eCRFs/SAE reporting forms.

The residual effect period is the time period after the last dose administration of trial medication when measurable drug levels or pharmacodynamics effects are still likely to be present. Only SAEs or AESIs that are related to study medication or study design and that occur after the residual effect period has ended need to be reported. However, if the investigator becomes aware of an (S)AE that occurred after the patient has completed the clinical trial (including protocol required residual effect period) it should be reported by the investigator to the sponsor if considered relevant by the investigator.

For screen failures, only trial related AEs occurring from signing the ICF until the date the patient is considered a screen failure will be collected.

Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the ISF.

For each AE, the investigator will provide the onset date, end date, CTCAE grade, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1.

All AEs, including those persisting at the end of study treatment must be followed up until they have resolved or have been sufficiently characterised or the local clinical monitor and the investigator agree to not further pursue them.

If not stipulated differently in the ISF, the investigator must report the following events via fax using the paper SAE form immediately (within 24 hours or the next business day whichever is shorter) to the sponsor: SAEs, protocol-specified AESIs, and non-serious AEs which are relevant for the reported SAE or AESI.

BI has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these "always serious adverse events", if a non-serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above. The list of these AEs can be found via the Remote Data Capture system.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the ISF). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or protocol-specified AESIs becomes available.

5.2.2.4 Pregnancy

Patients will be considered to be of childbearing potential unless surgically sterilised by hysterectomy or bilateral tubal ligation/salpingectomy, or post-menopausal for at least two years.

Women of childbearing potential should use a highly effective method of birth control during the study and should continue for at least three months after ceasing nintedanib/placebo and for at least 12 months after ceasing chemotherapy. In any case, continuing contraception after ceasing study medication should be done based on the latest information available for nintedanib (see most updated IB (c01632700) and for pemetrexed / cisplatin (see SPC)).

As a precaution, male or female partners of patients should use an acceptable form of contraception while the patient is on study treatment and for three months thereafter.

Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study (including 3 months thereafter), she should inform her treating physician immediately.

In rare cases, pregnancy might occur in clinical trials. Once a female patient has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the ISF). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

5.2.3 Assessment of safety laboratory parameters

Blood samples must be collected at the time points specified in the protocol flow charts. Additional laboratory tests as medically indicated may be performed at the discretion of the

investigator. Safety laboratory examinations include haematology, biochemistry, coagulation, and thyroid parameters.

During the combination treatment period, safety lab parameters must be performed on Day 1 and on Day 8 and assessed by the site. Lab results should be received by the site within 24 hours.

In case a patient has to commence anticoagulation therapy during the study, laboratory examinations concerning the coagulation status of the patient have to be performed at intervals deemed necessary by the investigator until stable anticoagulation is reached. Once a stable therapeutic anticoagulation status has been attained, the therapeutic anticoagulation status should be checked every week for 3 weeks. Thereafter, the anticoagulation status should be monitored at closer intervals if deemed necessary by the investigator.

The following parameters will be determined:

- Haematology: haemoglobin, white blood cell (WBC) count, ANC, and platelets
- Biochemistry: glucose, sodium, potassium, calcium, phosphorus, magnesium, serum creatinine, aspartate transferase (AST), alanine transferase (ALT), ALP, lactate dehydrogenase (LDH), bilirubin (in case of increased bilirubin, direct and indirect bilirubin have to be measured), blood urea or blood urea nitrogen (BUN), total protein, uric acid
- Coagulation parameters: PT and INR and PTT

If laboratory investigations have been performed within 2 weeks prior to screening, the results may be used to assess eligibility at screening. At C1V1, eligibility for inclusion in the study should be based on lab analyses completed within 3 days of randomisation. During the treatment period, if the lab investigations have been performed within 3 days prior to a visit and complete results are available, they do not have to be repeated. However, the reference ranges should be provided to the sponsor in case a different laboratory was used.

Urine (pH, glucose, erythrocytes, leukocytes, protein, nitrite) will be analysed by dipstick (semi quantitative measurements: -, +, ++, +++) at the time points specified in the flow charts. In case of pathological findings, further evaluation should be performed and the findings documented in the eCRF on the AE pages.

If the dipstick result is positive, urinary sediment should be examined (microscopic urinalysis). Clinical relevant abnormal findings in the urinary sediment should be treated or further evaluated according to standard of care. In patients with repeated positive dipstick (++, +++, ++++), creatinine clearance and protein excretion in 24-hour urine or protein/creatinine ratio in a random urine sample should be determined. Proteinuria should be followed up until resolution or until final diagnosis is available.

5.2.4 Electrocardiogram

A 12-lead resting ECG will be performed at every cycle for Phase II and at every other cycle for Phase III according to standard local procedures at the time points specified in the flow charts. If the ECG has been performed within 3 days prior to a visit, it does not need to be

repeated. The investigator should review the ECG during the study and any clinically significant findings will be reported in the eCRF on the AE pages.

5.2.5 Assessment of other safety parameters

5.2.5.1 Physical examination, height, weight, ECOG performance score

A general physical exam will be performed at screening and at the time points specified in the flow charts. Whenever possible, the same investigator should perform this examination.

Measurement of height (in cm), body weight (in kg) and the evaluation of the ECOG performance score will be performed at the time points specified in the flow charts.

5.2.5.2 Vital signs

Vital signs (blood pressure and pulse rate after two minutes supine rest) and temperature (oral and/or tympanic) will be recorded at the time points specified in the flow charts.

5.3 OTHER

5.3.1 Demographics and history

Demographics (sex, birth date, race if allowed by local laws), information on smoking, alcohol history, asbestos exposure and baseline conditions will be collected during the Screening Visit.

The date of first histological diagnosis, the histological subtype (epithelioid or biphasic), the tumour stage (tumour nodes metastases [TNM] and union for international cancer control/American joint committee on cancer [UICC/AJCC]), the number and location of local, lymphogenous or distant metastatic sites, and European organisation for research and treatment of cancer (EORTC) prognosis factor will be documented as obtained at diagnosis and at the time of inclusion into the study. Previous surgeries and radiotherapies must be reported.

[redacted]

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor safety aspects.

The scheduled measurements are appropriate to see drug induced changes in vital signs, standard laboratory values, biomarkers specific to efficacy and ECG. The primary and secondary endpoints are standard and accepted for evaluation of safety and tolerability of an anticancer drug, and they are widely used in this kind of study. AEs are graded according to the CTCAE criteria (version 3.0 for Phase II and version 4.03 for Phase III), which are commonly used in the assessment of AEs in cancer patients.

[redacted]

[redacted]

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the flow charts. In case a patient misses a visit and the patient reports to the investigator between the missed and the next scheduled visit, the delayed visit should be done and the actual date and the reason should be documented for the delayed visit. Subsequent visits should follow the original visit schedule.

Additional unscheduled clinic visits might be arranged at the discretion of the investigator. For unscheduled visit, it is sufficient to record only the clinically relevant labs and safety findings on the AE eCRF.

For a detailed overview of the trial procedures and time windows for visits, please refer to the flow charts.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period

Written informed consent must be obtained before any protocol specific screening assessments are performed. Screening should be completed within the next 14 days, and if the patient qualifies, the first study drug administration should occur within 15 days after informed consent. The screening period may be longer in case of administrative issues and/or if the patient needs to recover from an intercurrent disease.

Patients must satisfy all inclusion and exclusion criteria prior to treatment administration. Details of any patient who is screened for the study but is found ineligible must be entered in an enrolment log (see ISF) and documented in the eCRF.

For a detailed description of the trial procedures at the screening visit, refer to flow chart – Combination Therapy.

6.2.2 Treatment period

A treatment cycle is defined as 21 days. If initiation of a subsequent cycle is delayed due to medical reasons, a visit beyond day 21 may be necessary. Additional unscheduled visits may be performed at investigator's discretion if medically indicated, which should be recorded in the eCRF. For a detailed description of trial procedures during the treatment periods, refer to flow charts.

Patients will be eligible for a new treatment cycle if they:

- Do not present with clinical signs of tumour progression as assessed by the investigator,
- Have not met the criteria for PD assessed with the most recent imaging evaluation,
- Are continuing to benefit from study treatment (in the opinion of the investigator), despite progression,
- Do not present with unacceptable drug related AEs

The investigator will be asked to document in the eCRFs each time they wish to give patient another treatment cycle of study medication.

Once the treatment of pemetrexed / cisplatin has discontinued at the end of cycle 6 (or earlier if necessary), patients who have not experienced disease progression or patients that are benefiting from treatment beyond radiological progression (see Section 5.1.2.1.5) will continue to receive nintedanib monotherapy or placebo monotherapy until the decision to end study treatment. Refer to flow charts – Monotherapy

6.2.3 End of trial and follow-up period

6.2.3.1 End of Treatment (EoT) visit

The EoT visit will be performed in the event of disease progression or decision to end all study medication. The EoT visit should be performed as soon as possible after the permanent discontinuation of study medication. For a detailed description of trial procedures at EoT, please refer to flow charts – only additional critical information is listed below:

- Completion of active treatment including reason for conclusion or if applicable premature discontinuation of study treatment, date of last administration of the trial drug must be recorded.
- If patient has not progressed (unless tumour assessment performed within the past 3 weeks), or if PD is suspected at time of visit, imaging must be performed.

6.2.3.2 Follow-up visit

The whole follow-up period is defined from the end of active treatment with trial medication until death or lost to follow-up, refusal to be followed up, end of the whole trial or until the required OS events have been reached. In case the trial is declared negative at the Phase III interim OS analysis, the follow-up period of Phase III patients will also stop at that time. For Phase II patients, the follow-up period will end after the primary Phase III PFS analysis (see Section 7.3). All patients should return to the investigational site ≥28 days for Phase II and ≥30 days for Phase III after last administration of study treatment for the FU1 visit and preferably before starting a new anti-cancer therapy.

The following will be obtained and/or performed during FU1:

- Date of contact
- Physical exam
- Follow-up of ongoing AEs that were not yet recovered at EoT
- Record performance score (e.g. ECOG)
- [redacted]
- Subsequent anti-cancer treatment (if applicable)
- Outcome (date of and reason for death, in case the patient had PD the actual date of PD shall be recorded)

6.2.3.3 Follow-up for progression

Patients who did not progress before discontinuing study treatment will enter the follow-up for progression period. Follow up for progression visits should be performed at six week intervals or earlier if appropriate (i.e. to meet the six week imaging schedule which starts with the day of first administration of pemetrexed/cisplatin in the first combination cycle). The follow-up for progression period will end when one of the following events is met:

- Lost to follow-up / refusal of follow up
- Disease progression
- Start of subsequent anti–cancer therapy
- Death
- End of the whole trial (see Section 6.2.3.5)
- Phase II patients only: time point of the primary Phase II OS analysis (see Section 7.3)
- Phase III patients only: Required number of OS events have been reached (Section 7.3)

The following will be obtained and/or performed during the follow-up visits for progression.

- Date of contact
- Related SAE/AESI and concomitant medication
- Record performance score (e.g. ECOG)
- Perform tumour assessment and imaging
- Subsequent anti-cancer treatment (if applicable)
- Outcome (date of and reason for death, in case the patient had PD the actual date of PD shall be recorded)

6.2.3.4 Follow-up for OS (Phase II patients)

For Phase II patients, the follow-up for OS period will end after the primary Phase III PFS analysis. Regardless of whether they progressed on treatment, Phase II patients will be followed every 12 weeks until death, lost to follow-up, withdrawal of consent (follow-up for OS can be conducted by phone interview). Aside from survival status, no additional data will need to be collected.

6.2.3.5 Follow-up for OS (Phase III patients)

All Phase III patients will be followed-up for OS every 12 weeks until death, lost to follow-up, end of the whole trial or until the required number of OS events have been reached for the primary analysis, whichever occurs earlier. In case the trial is declared negative at the interim OS analysis of the Phase III part, the follow-up period will also stop at that time.

Patients who progressed before and have discontinued study medication will enter the follow-up for OS period. Patients that progress during the follow-up for progression period will enter the follow up for OS period once they have progressed. These visits may also be performed by telephone interview or via written correspondence in case the patient is unable to visit the investigator.

The following information will be collected during the follow-up for OS period:

- Date of contact
- Subsequent anti-cancer treatment (if applicable)
- Related SAE/AESI and concomitant medication
- Outcome event (e.g. death: Record date of and reason for outcome event / death)

6.2.3.6 End of trial

A patient is considered to have completed the trial in case any of the following applies:

- Completion of planned follow-up period
- Lost to follow-up
- Refusal to be followed-up
- Death

The end of the whole trial will occur when one of the following situations occurs:

- When the required number of OS events has occurred and the last patient has completed the first follow-up visit.
- When the trial is declared positive for PFS and OS at the interim OS analysis of the Phase III part (enrolment into the trial will be stopped) and the last patient has completed the first follow-up visit.
- When the trial is declared negative at the interim OS analysis of the Phase III part (see Section 7.3.1 and Section 7.3.4) (enrolment into the trial will be stopped) and the last patient has completed the first follow-up visit.

If patients are still ongoing or in follow-up at the time of the clinical trial report for the primary OS analysis of the Phase III part, the clinical trial database will be kept open to collect the additional data. After end of trial, the final results will be reported either in a separate clinical trial report or in a revised trial report. The final analysis of the Phase II part of the study will be reported in an analysis report. No unblinding of Phase III data will happen at this time. The Phase III primary PFS analysis and the Phase III primary OS analysis will be reported in a CTR.

If the trial is ended by the sponsor for any reason when patients are still being treated with a clinical benefit, the patients will be offered treatment in a follow-up trial which will allow patients to continue to receive treatment as long as the treating investigator deems it appropriate. If the trial is terminated by the sponsor for safety reasons, patients will not continue treatment with the trial drug.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomised, double-blind, placebo-controlled phase II/III clinical trial in which the efficacy and safety of nintedanib + pemetrexed / cisplatin followed by nintedanib will be evaluated against the matching placebo + pemetrexed / cisplatin followed by placebo, as first-line treatment for unresectable MPM patients. Randomisation is stratified by epithelioid vs. biphasic histology for the Phase II part but is not stratified for the Phase III part.

The Phase III part of this trial will be conducted as a two-stage adaptive design for OS with OS event number reassessment at the interim OS analysis which will take place at the time of the primary Phase III PFS analysis. The Phase II patients will not be included into the confirmatory analyses of this trial (analysed separately).

Progression-free survival, as measured from the time of randomisation to the time of disease progression or death of any cause, is the primary efficacy endpoint. OS, as measured from the time of randomisation to the time of death of any cause, is the key secondary endpoint and objective tumour response and disease control are the secondary efficacy endpoints.

[redacted]

For PFS and OS in the Phase II part as well as PFS in the Phase III part, Kaplan-Meier estimation and log-rank test will be the primary analysis method. For the adaptive design for OS with OS event number reassessment with regard to the Phase III patients, the weighted inverse normal method described by Lehmacher and Wassmer (R14-1197) combining one-sided p-values from a log-rank test will be the primary analysis method for OS. The Lehmacher and Wassmer method is a generalisation of the method described by Cui et al (R08-2069).

7.2 NULL AND ALTERNATIVE HYPOTHESES

Statistical hypotheses will be formally only tested for the Phase III patients. For Phase II patients, all analyses are exploratory, no formal hypotheses will be tested and all p-values are to be understood as exploratory.

For Phase II, two-sided exploratory p-values will be presented throughout. For Phase III, one-sided p-values will be presented throughout since one-sided p-values are required for the weighted inverse normal method. For consistency, they will then be used for all endpoints. If two-sided p-values are to be considered, their derivation will be described in the TSAP.

For Phase III, the alternative hypothesis for the primary analysis of the primary endpoint PFS and the key secondary endpoint OS is that PFS and OS are longer for patients treated with nintedanib plus pemetrexed/cisplatin than for patients treated with placebo plus pemetrexed/cisplatin. According to a hierarchical testing procedure, a benefit of PFS will be

tested first. If this test proves to be significant in favour of nintedanib, a benefit of OS will be tested.

Based on a one-sided test, the null hypothesis for PFS in this trial is

H_{01}: $S_{PFS,\ Nin+Pem/Cis}(t) <= S_{PFS,\ Plac + Pem/Cis}(t)$ for t>0,

where $S_{PFS}(t)$ is the probability that a patient passes time t without dying or experiencing disease progression. The further subscripts represent the two treatment groups. If this null hypothesis can be rejected, the null hypotheses for OS will be tested

H_{02}: $S_{OS,\ Nin+Pem/Cis}(t) <= S_{OS,\ Plac + Pem/Cis}(t)$ for t>0,

where $S_{OS}(t)$ is the probability that a patient passes time t without dying.

The corresponding alternative hypotheses are

H_{A1}: $S_{PFS,\ Nin+Pem/Cis}(t) > S_{PFS,\ Plac + Pem/Cis}(t)$ for some t>0

and

H_{A2}: $S_{OS,\ Nin+Pem/Cis}(t) > S_{OS,\ Plac + Pem/Cis}(t)$ for some t>0.

The effect of nintedanib on PFS and on OS will be based on two one-sided tests, both with a one sided alpha level of 0.025. Due to the hierarchical testing procedure chosen, no alpha adjustment is required to account for multiple testing. However, adjustments accounting for the planned interim Phase III OS analyses are done by using an O'Brien-Fleming like error spending function (see Section 7.3.2.1) and using the weighted inverse normal combination function approach for OS. Thus, control of the global overall significance level of 0.025 (one-sided) for PFS and OS is assured (see Section 7.3.1).

7.3 PLANNED ANALYSES

Efficacy analyses will follow the intention-to-treat principle and will include all randomised patients whether the patient is treated with the study medication or not. For the primary confirmatory analyses of all endpoints in this trial, only the data of the Phase III patients will be included. For the analyses of the Phase II patients the analyses methods for all endpoints are described separately. The time point of primary PFS analysis of the Phase II patients was 04–Mar-2016, the primary OS analysis of the Phase II patients will be done when approximately 61 OS events with regard to the Phase II patients have occurred.

[redacted] Safety analyses will include all treated patients who are documented to have taken any dose of the study medication, and will be reported separately for Phase II and Phase III patients, as well as pooled for all treated Phase II and Phase III patients together. For the pooled safety analyses, a residual effect period of 30 days will be used to determine the on-treatment period.

No per protocol set will be used in the analyses. However potential important protocol violations will be summarised and violations of inclusion and exclusion criteria will be provided in a subject data listing. The Core Trial Statistical Analysis Plan will specify the potential important protocol violations in detail.

Phase II

The analyses for the Phase II primary PFS analysis have been specified in a separate Interim Phase II TSAP. The Phase II primary OS analysis will occur when approximately 61 OS events with regard to the Phase II patients have occurred (see Section 7.6). For the Phase II patients continuing follow for survival after the primary OS analysis, an analysis will be performed approximately one year after the primary OS analysis and in addition at the time of the primary PFS analysis of the Phase III part of this study. The respective analyses will be described in the Phase II TSAP.

Phase III

The primary Phase III PFS analysis will be performed once the required number of approximately 199 PFS events has been reached. At the same time, the interim Phase III OS analysis will be performed. Details about the Phase III analyses will be described in the Phase III TSAP.

In case a statistically significant result for the primary endpoint PFS is observed at the time of the primary PFS analysis, the trial will be declared positive for the primary endpoint. If statistically significant results for the primary endpoint PFS and the key secondary endpoint OS (tested in a hierarchical order) are already observed at the time of the primary PFS analysis, the trial will be declared positive for the primary endpoint PFS and the key secondary endpoint OS, and all secondary and further endpoints will be analysed, and enrolment into the trial will be stopped. If no statistically significant result for PFS is observed at the primary PFS analysis, the trial will be declared negative, and enrolment into the trial will be stopped. Otherwise, the DMC will reassess the needed number of OS events for the primary OS analysis. The number of OS events for the primary OS analysis can then be increased from 279 up to 346 OS events (see Section 7.6). In case a statistically significant result for the key secondary endpoint OS is observed at the time of the primary OS analysis, the trial can be declared also positive for the key secondary endpoint. The testing scheme is further described in Sections 7.3.1 and 7.3.2 below and illustrated in Figure 3.1: 2.

7.3.1 Primary analyses

For Phase II, the primary analysis of PFS has been conducted on 04-Mar-2016 based on 69 PFS events from the 87 Phase II patients.

For Phase III, the primary analysis of the primary endpoint PFS will be conducted when approximately 199 PFS events have occurred for the Phase III patients. This is expected to take approximately 20-27 months after the first Phase III patient has been randomised assuming an accrual rate of 14-22 patients per months. At this point, the database will be locked and un-blinded as described in Section 7.3.4. The investigators, patients, clinical monitors, trial team and others involved in the further conduct of this trial will not be

unblinded. The PFS analysis will be based upon the evaluation of tumour imaging and clinical information as performed by the investigators, who are blinded to treatment assignments. Tumour assessments will be evaluated according to the modified RECIST criteria (R12-1990).

For patients with known date of progression or death:

PFS [days] = earlier date of progression or death – date of randomisation + 1.

For patients who will be censored:

PFS [days] = date of last imaging assessment without disease progression – date of randomisation + 1.

For Phase II, Kaplan-Meier estimates of the survival function of PFS, median PFS and the corresponding 95% CI using Greenwood variance that is incorporated into the Brookmeyer and Crowley method (R09-6372) with a loglog transformation, as well as the p-value of the two-sided stratified (epithelioid vs. biphasic histology) log-rank test on PFS will be provided. For the Phase II analysis, this p-value is only to be understood as exploratory. In addition, stratified Cox proportional hazards model (stratified on epithelioid vs. biphasic histology) will be fitted to estimate the hazard ratio (HR) and the corresponding 95% CI between the two treatment arms. For Phase III, the p-value will be inferred from a one-sided log-rank test without any stratification factor. The HR and the corresponding 95% CI will be estimated by fitting a Cox proportional hazards model.

[redacted]

[redacted]

7.3.2 Secondary analyses

7.3.2.1 Overall Survival (key secondary endpoint)

For patients with known date of death of any cause:

OS [days] = date of death – date of randomisation + 1.

For patients who died but with unknown date of death of any cause:

OS [days] = date of last contact when the patient is known to be alive – date of randomisation + 1 (for patients in the nintedanib arm)

OS [days] = date of data snapshot – date of randomisation + 1 (for patients in the placebo arm)

For patients who will be censored:

OS [days] = date of last contact when the patient is known to be alive – date of randomisation + 1.

For Phase II, the same statistical methods and analyses applied for PFS will also be conducted for OS (primary analysis model, [redacted]

For Phase III, OS will be analysed along with the primary analysis of PFS in a hierarchical order. Thus, no multiplicity adjustment will be made for analysing the two endpoints, PFS (primary endpoint) and OS (key secondary endpoint). The alpha-level for OS will follow an O`Brien and Fleming spending function to preserve the overall alpha of 0.025 (one-sided) for the final OS analysis.

The analysis of the key secondary endpoint OS will be performed using the weighted inverse normal method described by Lehmacher and Wassmer (R14-1197) with right-censoring the patients without event at the interim OS analysis and left-truncation of all patients with regard to the interim analysis time point and right censoring at the time of the primary OS analysis. This is asymptotically equivalent to using the independent, normally distributed increment structure of the respective log-rank statistics (R15-0928). The approach of independent increments is justified since solely OS information will be used for the event number reassessment. The follow-up time will be split into two stages: time for stage 1 (right censoring) and time for stage 2 (left censoring). Two one-sided p-values will be calculated, one for each stage. For the first stage, the p-values is based on the initial log-rank statistics until the interim OS analysis, and for the second stage, the p-value is based on the increment of the log-rank statistics from the time of the primary OS analysis as compared to the interim OS analysis. The final test for statistical significance at the primary OS analysis will be then based on combining these p-values via the weighted inverse combination function.

For the calculation of the final and the interim test statistics, the inverse-normal stagewise p-value based approach will be used according to Lehmacher and Wassmer (R14-1197). This is a generalization of the method described by Cui et al (R08-2069). Here, the p-values of the two different parts will be combined. Based on that principle, the test statistics T_{iOS} (i=1,2), on the p-scale for Stage 1 and Stage 2 are defined as:

Formula 5.1.1:1

$T_{1OS} = 1 - \Phi(z1 - p_{1OS}) T_{1OS} = 1 - \Phi(z_{1-p_{1OS}}$ based on Stage 1

Formula 5.1.1:2

$T_{2OS} = 1 - \Phi(w_1 z_{1-p_{1OS}} + w_2 z_{1-p_{2OS}}) T_{2OS} = 1 - \Phi(w_1 z_{1-p_{1OS}} + w_2 z_{1-p_{2OS}})$ based on Stage 1 and Stage 2

where w_i (i=1,2) are the predefined weights for Stage 1 and 2 with $w_1^2 + w_2^2=1$ $\sum_{i=1}^{2} w_{iX}^2 = 1$. Φ denotes the standard normal distribution function and $z_{1\text{-}piOS}$ (i=1,2) denote the $(1\text{-}p_{iOS})$ -quantiles of the standard normal distribution function. p_{1OS} denotes the stagewise one-sided p-value derived from the log-rank test statistics for OS (for stage 1) and p_{2OS} the one-sided p-value from the increment of the log-rank statistics at the time of the primary OS analysis (for stage 2), respectively.

Here, the weights are chosen to be approximately proportional to the expected stage-wise numbers of OS events.

The expected number of OS events at the time of the interim OS analysis (at the time when approximately 199 PFS events have occurred) is approximately 140 OS events. Depending on the event number reassessment, the total number of OS events can be increased from 279 to 346 OS events. Thus, the fraction of OS events at the interim analyses will be around 0.4 to 0.5. Therefore, the weights are chosen as $w_1 = \sqrt{0.45}$ and $w_2 = \sqrt{0.55}$.

The stopping boundaries in a classical group-sequential design are usually specified by an error spending function. The commonly used O'Brien-Flemming-like error-spending function π^* will be used for OS.

The O'Brien-Fleming-like error-spending function π^* with one-sided α is given by

Formula 5.1.1:3

$$\pi^*(\tau_i) = 2\left(1 - \Phi\left(\frac{z_{1-\alpha}}{\sqrt{\tau_i}}\right)\right),$$

where τ_i is the information fraction at the i-th stage τ_i will be calculated as

Formula 5.1.1:4

$$\tau_i = \frac{d_i}{D},$$

where d_i is the observed number of events for the i-th stage and D is the planned number of OS events at the primary OS analysis. The error-spending function π^* gives the cumulative error spent up to the information fraction τ_i.

The error spending function will ensure an overall alpha level of α (one-sided).

For this trial, the error to spend at stage 1 is $\pi_1 = \pi^*(\tau_1)$, where τ_1 will be calculated as described in Formula 5.1.1:4, d_1 is the observed number of OS events at the interim Phase III OS analysis (events for stage 1) and D = 279 the planned number of OS events at the primary OS analysis.

At the interim OS analysis the log-rank-test will be used to derive the stage-wise one-sided p-value p_{1OS}. p_{1OS} will be derived from the log-rank test based on stage 1(right censoring for all patients without event at the interim OS analysis). The test statistics T_{1OS} on the p-scale for OS will be calculated as described in Formula 5.1.1:1. The stage-wise α_{1OS}-value is $\alpha_{1OS} = \pi_1$.

At the time of the primary Phase III PFS analysis/interim Phase III OS analysis, first PFS will be tested for a statistically significant result as described in Section 7.3.1. If PFS is not significant, OS will not be tested and the trial will be declared negative, and further recruitment into the trial will be stopped. If PFS is significant (i.e. the trial can be declared positive for the primary endpoint), OS will be tested and if $T_{1OS} < \alpha_{1OS}$, a statistically significant result for both endpoints at the primary PFS analysis/interim OS analysis is reached. The trial will then be declared positive for the primary and the key secondary endpoint, and further recruitment into the trial will be stopped.

If the trial is declared positive at the Phase III primary PFS analysis/interim OS analysis for the primary endpoint PFS and the key secondary endpoint OS, all patients will be unblinded. Patients in the nintedanib arm will remain on nintedanib treatment while treatment with placebo will be discontinued and these patients will be offered to switch to nintedanib treatment. All patients will be followed up until they have stopped treatment, and additional safety and efficacy data will be collected. Still, due to the bias introduced by patients switching from the placebo arm to the nintedanib arm, the OS and PFS analyses will not be repeated after all patients have completed treatment. OS and PFS will be only analysed descriptively with regard to all patients (no treatment comparison).

If the study is declared positive for the primary endpoint PFS only at the interim OS analysis, the DMC will reassess the OS event number needed for primary OS analysis based solely on OS data available at the time of the interim OS analysis. In particular, no PFS information will be used to reassess the OS event number. The reassessment rules will be based on a conditional power approach (more details will be described in the DMC Charter). Depending on the event reassessment, the total number of OS events for the primary OS analysis can be increased from approximately 279 to 346 OS events.

For the primary OS analysis, π_2= 0.025 - π_1 The stage-wise p-value p_{2OS} will be derived from the increment of the log-rank test at the time of the primary OS analysis (left truncation of patients at the time of the interim analysis). The test statistics T_{2OS} based on the p-scale will be calculated as described in Formula 5.1.1:2.

The stopping boundary α_{2OS} will be determined such that
$P(T_{1OS} > \alpha_{1OS}, T_{2OS} < \alpha_{2OS} | H_0) = \pi_2$.

If $T_{2OS} < a_{2OS}$, the key secondary endpoint OS will be met, and the trial will be declared positive for the key secondary endpoint as well.

Kaplan-Meier estimates of the survival function of OS, median OS and the corresponding 95% CI using Greenwood variance that is incorporated into the Brookmeyer and Crowley method (R09-6372) with a loglog transformation will be provided.

To estimate the HR for OS, the median unbiased estimator (R14-2334) will be used as primary estimator. In addition, as a secondary estimator, the partial maximum likelihood estimator from the Cox proportional hazards model will be used. The corresponding 95% repeated CIs (R14-2334) and the repeated overall p-value (R99-1290) will be calculated.

Additionally, analyses will be conducted to describe the pattern of time to death, while accounting for the extent and influence of post-progression anti-cancer treatments.

[redacted]

7.3.2.4 Objective Tumour Response (Phase II and Phase III)

Objective tumour response is defined as a best overall response of CR or PR. Objective tumour response rate (ORR) gives the percentage of patients with objective tumour response. Logistic regression will be used to test for a difference between regimens for objective

tumour response rate. For Phase II, the model will be adjusted for the stratification factor tumour histology (epithelioid vs. biphasic). Kaplan-Meier methods will be used for the calculation of duration of objective tumour response.

7.3.2.5 Disease Control (Phase II and Phase III)

Disease control is defined as a best overall response of CR, PR, or SD. Disease control rate gives the percentage of patients with disease control.

Logistic regression will be used to test for a difference between regimens for disease control rate. For Phase II, the model will be adjusted for the stratification factor tumour histology (epithelioid vs. biphasic). Kaplan-Meier methods will be used for the calculation of duration of disease control.

[redacted]

7.3.3 Safety analyses

At the time of the primary OS analysis for Phase II, all treated Phase II patients will be included in the safety analyses. At the time of the primary PFS analysis and the primary OS analysis for Phase III, all treated Phase III patients will be included in the safety analyses.

In case the trial is already declared positive for PFS as well as for OS at the Phase III primary PFS/interim OS analysis, patients on placebo will be offered to switch to nintedanib treatment. For final reporting of all safety data at the end of the whole trial, patients switching from placebo to the nintedanib arm will be analysed separately from all other patients.

In addition, at the time of the primary Phase III PFS analysis and at the time of the primary Phase III OS analysis, safety analysis will be conducted with pooled data of Phase II and Phase III patients together using a REP of 30 days.

For all treated patients the incidence and severity, as graded according to CTCAE (version 3.0 for Phase II and version 4.03 for Phase III) of AEs will be analysed descriptively and the following key safety assessments will be conducted and presented:

- Adverse event overall summary
- Adverse events leading to dose reduction or permanent treatment discontinuation
- Serious adverse events
- Adverse events leading to death
- Related adverse events
- Protocol-specified AESI

Descriptive statistics will also be used to describe changes in laboratory values over time and between the two treatment groups. Furthermore, all abnormal laboratory values of potential clinical significance will be reported.

7.3.4 Interim analyses

Primary PFS analysis of Phase II patients

On 04-Mar-2016, as requested by authorities, data for the 87 Phase II patients in this trial was unblinded to allow for a more precise planning of the Phase III part of this trial. Since the data of these patients will not be included in the confirmatory analyses of this trial, this analysis has been conducted by the trial team. Details about the analyses are described in the interim Phase II TSAP. Once unblinded, access to the summary data was available to BI and externally under confidentiality. Only a limited number of people from the sponsor had access to unblinded patient level data. Details about the restricted access to unblinded information on a patient level are described in the interim Phase II TSAP.

Primary OS analysis of Phase II patients

When approximately 61 OS events from the Phase II patients have occurred, the primary OS analysis of the Phase II part of this trial will be conducted. Only Phase II patients will be unblinded at this time. This analysis will be reported in a clinical trial report.

[redacted]

Formal interim analysis of the key secondary endpoint OS

In line with the Phase III Primary PFS analysis (after approximately 199 PFS events have occurred), the interim Phase III OS analysis will be performed. The trial database will be locked and unblinded by a team independent from the trial team tasked to write a report and,

subsequently, a regulatory dossier if indicated. Thus, investigators, patients, clinical monitors, trial team and others involved in the continuing trial will not be unblinded. An interim logistics plan will be set up to describe the firewalls and how data protection will be ensured.

[redacted]

7.4 HANDLING OF MISSING DATA

In general, missing data will not be imputed. Every effort will be undertaken to obtain the date of progression for patients known to have progressed, obtain the date of death for patients known to have died, and to obtain complete information on all AEs.

For partial or missing AE onset and/or end dates, BI internal rules will be applied for imputation. For the primary PFS analysis of Phase II and Phase III, the censoring rules as outlined in Table 7.4: 1 will be used.

Table 7.4: 1 Description of censoring rules for PFS

Situation**	**Outcome (event or censored)**	**Date of outcome**
No baseline radiological assessment		
Patient with death on or before the second planned radiological assessment	Event	Date of death
Patient without death or patient with death after second performed radiological assessment	Censored	Date of randomisation

Table 7.4: 1 (cont'd) Description of censoring rules for PFS

Situation**	**Outcome (event or censored)**	**Date of outcome**
Without post-baseline radiological assessments		
Vital status is unknown or patient is known to be alive	Censored	Date of randomisation
Death prior or on the second planned radiological assessment	Event	Date of death
Death beyond the second planned radiological assessment	Censored	Date of randomisation
With baseline and post-baseline radiological assessments BUT no subsequent anti-cancer therapy		
Alive and not progressed, no more than one consecutively missed radiological assessments	Censored	Date of last radiological assessment
Alive and not progressed, two or more consecutively missed radiological assessments	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed, zero or one missed radiological assessment prior to progression	Event	Date of radiological assessment of progression
Progressed, but two or more consecutively missed radiological assessments prior to progression	Censored	Date of last radiological assessment prior to missed assessment
Death but no progression, zero or one missed radiological assessment prior to death	Event	Date of death
Death without progression, but two or more consecutively missed radiological assessments prior to death	Censored	Date of last radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death*	Censored	Date of last radiological assessment before subsequent anti-cancer therapy
No baseline and/or post-baseline imaging and subsequent-anti cancer therapy started prior to a death	Censored	Date of randomisation

*Subsequent treatment with pemetrexed/cisplatin/nintedanib will not trigger censoring of PFS
**If appropriate, a sensitivity analysis will be done using interval censoring methods

Table 7.4: 2 Description of the classification of patients for the analysis of OS.

Status at time of analysis	**Outcome (event or censored)**	**Date of outcome**
Patient died and the date of death is known	Event	Date of death
Patient died and date of death is unknown	Event	Nintedanib arm: Date patient last known to be alive Placebo arm: Date of data snapshot
Patient alive	Censored	Date of last contact when the patient is known to be alive
Unknown	Censored	Date of last contact when the patient is known to be alive

These OS censoring rules will be applied for Phase III only. For Phase II, censoring rules as described in the Phase II TSAP will be used. For the pooled analysis, the censoring rules as described here will be used.

[redacted]

7.5 RANDOMISATION

Permuted block randomisation will be used to randomise patients in 1:1 ratio to nintedanib in combination with pemetrexed and cisplatin or the matching placebo in combination with pemetrexed and cisplatin. In addition, the randomisation was stratified by epithelioid vs. biphasic histology for the Phase II part. No stratification will be used for the Phase III part.

An IVRS/IWRS will be used to perform the randomisation centrally across all study sites. BI will arrange for the randomisation. A randomisation list will be generated by BI using a validated pseudo-random number generator, yielding reproducible and non-predictable results. For the Phase II and Phase III part of this trial, two separate randomisation lists have been generated. The randomisation scheme will not be disclosed to any on site personnel or BI internal trial team members until database lock and unblinding of the trial. For the unblinding of the data of Phase II patients in March 2016, only the randomisation list with regard to the Phase II patients has been unblinded to a limited number of persons, only the Phase II randomisation list will be used for unblinding of the Phase II patients for the primary Phase II OS analysis. The on-site personnel will also be blinded to the block size used in the randomisation. The randomisation scheme will be forwarded via a secure transmission to the CRO that produced the analyses for the DMC.

7.6 DETERMINATION OF SAMPLE SIZE

Phase II

The Phase II part of this randomised, double blind, placebo-controlled trial was carried out as a proof-of-clinical-concept trial to explore the efficacy and safety profiles of the combination regimen of nintedanib 200 mg b.i.d. on top of the standard treatment with pemetrexed and cisplatin in comparison with the matching placebo on top of the standard treatment with pemetrexed and cisplatin. The intent was to provide evidence that will allow informed decision making in terms of the next stages of development. The Phase II part of this trial was therefore sized such that, if the true effect of nintedanib + standard treatment versus the standard treatment alone was a HR of 0.75 (median PFS 8 vs. 6 months), the probability of observing a small HR was sufficiently large. On the other hand, if there was no treatment effect and the true HR was 1, the probability of erroneously observing a small HR was small enough.

Table 7.6: 1 summarizes for different numbers of PFS events the associated probabilities for observing HRs less than some thresholds under two assumptions for the true HR, 0.75 and 1 respectively.

Table 7.6: 1 Number of PFS events and corresponding probability of observing HRs below thresholds

		Probability[1] observing HR of ≤		
PFS Events	True HR	0.8	0.9	1.0
50		0.59	0.74	0.85
65	0.75	0.60	0.77	0.88
80		0.61	0.79	0.90

		Probability[1] observing HR of ≤		
PFS Events	True HR	0.75	0.8	0.9
50		0.15	0.22	0.35
65	1.0	0.12	0.18	0.34
80		0.10	0.16	0.32

[1] Calculation based on the approximate normal distribution of the estimated log HR [R07-4680].

With 65 PFS events, if the true HR was 0.75, the chance of observing a treatment effect with HR ≤ 0.9 was 77%, while the risk of erroneously observing a HR > 1 was 12%. However, if there was no treatment effect, the risk of erroneously observing a HR of ≤ 0.75 was 12%, while the chance of observing a HR > 0.9 was 66%.

Sixty-five PFS events were considered sufficient for the Phase II part of this trial as extra benefit brought in by more events did not justify the cost and effort in the trial conduct.

Assuming the recruitment rate would be 6 patients per month, and 10% of the PFS events would not be observed due to early drop out, with 43 patients per treatment arm, the study duration until 65 observed PFS events was estimated to be approximately 27 months (Table 7.6:2).

Table 7.6: 2 Study duration until 65 observed PFS events for different numbers of randomised patients

Patients randomised	Accrual time [months]	Trial duration until 65 PFS events [months][1]
76	13	38
86	14	27
106	18	22

[1] Assuming a true HR of 0.75 (median PFS 8 vs. 6 months), a recruitment rate of 6 patients per month, and that 10% of the PFS events will not be observed due to early drop out.

Based on the recommendation of the DMC to change the trial to a confirmatory trial, and based on the results of the 04-Mar-2016 analysis for Phase II patients, an additional 450 Phase III patients will be randomised into this trial.

The primary PFS analysis of the Phase II part was conducted on 04-Mar-2016 for decision making and sample size estimation for planning of the Phase III part. At this time, 69 PFS and 37 OS events have been observed. The primary OS analysis of the Phase II part of this trial is planned be conducted when approximately 70% of the Phase II patients had an OS event (approximately 61 OS events). This is expected to occur in February 2017. Still, the

analyses might be performed with fewer OS events within the time until March 2017. At this time, assuming a true HR for OS of 0.73, the probability of observing a small HR is considered sufficiently large. On the other hand, if there is no treatment effect and the true HR is 1, the probability of erroneously observing a small HR is small enough. In addition, in an effort to continue to follow up patients on the Phase II part of the study, an analysis of OS data will be performed approximately one year after the primary OS analysis, and at the time of the primary PFS analysis for Phase III.

Table 7.6: 3 summarizes for different numbers of OS events the associated probabilities for observing HRs less than some thresholds under two assumptions for the true HR 0.73 and 1 respectively (further details below).

Table 7.6: 3 Number of OS events and corresponding probability of observing HRs below thresholds

		Probability[1] observing HR of ≤		
OS Events	True HR	0.8	0.9	1.0
50		0.63	0.77	0.87
61	0.73	0.64	0.79	0.89
70		0.65	0.81	0.91

		Probability[1] observing HR of ≤		
PFS Events	True HR	0.75	0.8	0.9
50		0.15	0.22	0.35
61	1.0	0.13	0.19	0.34
70		0.11	0.18	0.33

[1] Calculation based on the approximate normal distribution of the estimated log HR [R07-4680].

Phase III

Based on the observations of the Phase II analysis from March 2016 for patients with epithelioid tumour histology and accounting for a potential selection bias, it is assumed that nintedanib in combination with pemetrexed/cisplatin will increase median PFS by 3.5 months beyond treatment of placebo with pemetrexed/cisplatin when assuming a median PFS of 6 months (HR 0.63). To achieve a power of 90% for the analysis of PFS, 199 PFS events are required. Assuming that 15% of the patients cannot be followed up until progression due to the censoring rules, 199 events are expected at the time of 23 months after start of randomisation into Phase III when assuming a recruitment rate of 18 patients per month (see Table 7.6: 4). According to these assumptions, not all 450 patients will be randomised at the time of the primary PFS analysis. These calculations have been performed with the statistical software Addplan, Version 6.0.4, using Schoenfeld formula for the calculation, and SAS Version 9.4.

Table 7.6: 4 Statistical Power for Progression Free Survival (one-sided alpha 2.5%)

Events	Patients	Median PFS*	Hazard ratio*	Statistical power
199[a]	450	6 vs. 9.5 months	0.63	90%
199[b]	450	6 vs. 9.3 months	0.65	87%
199[c]	450	6 vs. 9.0 months	0.67	82%

* Pemetrexed / cisplatin and placebo versus pemetrexed / cisplatin and nintedanib

a) For accrual rate 18 pts / month, time to events is 23 months. For accrual rate of 14 pts / month, time to events is 27 months. For accrual rate of 22 pts / month, time to events is 20 months (assuming that 15% of PFS events are not observed)

b) For accrual rate 18 pts / month, time to events is 23 months. For accrual rate of 14 pts / month, time to events is 27 months. For accrual rate of 22 pts/month, time to events is 20 months (assuming that 15% of PFS events are not observed)

c) For accrual rate 18 pts / month, time to events is 23 months. For accrual rate of 14 pts / month, time to events is 27 months. For accrual rate of 22 pts / month, time to events is 20 months (assuming that 15% of PFS events are not observed)

Based on the observations of the Phase II analysis from March 2016 for patients of epithelioid tumour histology, and taking into account the selection bias and that the OS results are still considered premature, it is assumed that nintedanib in combination with pemetrexed and cisplatin will increase median OS by approximately 33-40% beyond combination treatment of placebo with pemetrexed and cisplatin assuming a median OS of 14.5 months. Since OS data at the time of the Phase II analysis is considered premature (only 48% of patients with epithelioid tumour histology had an event), an adaptive design with event number reassessment at the interim Phase III OS analysis will be implemented to account for the uncertainty of the OS treatment effect. At the time of the primary PFS analysis, around 140 death events are expected which will be used to analyse OS for the interim OS analysis and to perform an event number reassessment for OS.

Depending on the event number reassessment of OS at the time of the interim Phase III OS analysis, the final number of OS events needed for the primary Phase III OS analysis can be increased from approximately 279 OS events up to a maximum of approximately 346 OS events. Details about the adaptive design and the event number reassessment will be described in the DMC charter.

Table 7.6: 5 indicates that with 450 patients 279 death events would provide 80% power % power for OS if the underlying treatment difference were 5.8 months (HR=0.71). Assuming an underlying treatment difference of 5.1 months (HR 0.74), 346 death events would provide 80% power for OS. With the event number reassessment, the Phase III part of this trial is designed to provide 80% power for OS for a treatment effect within the range of 0.71 – 0.74. 279-346 OS events would be expected to occur within approximately 38-50 months if 450 patients were randomised at a rate of approximately 18 patients per month. These calculations have been performed with the statistical software Addplan, Version 6.0.4, using Schoenfeld formula for the calculation, and an O'Brien and Fleming class spending function for an overall alpha of 0.025 (one-sided) for OS when adjusting for the interim look at the time of the primary analysis for PFS.

Table 7.6: 5 Statistical Power for Overall Survival

Events	Patients	Median OS*	Hazard ratio*	Statistical power
346[a]	450	14.5 vs. 19.6 months	0.74	80%
305[b]	450	14.5 vs 20 months	0.73	80%
279[c]	450	14.5 vs 20.3months	0.71	80%

* Pemetrexed/Cisplatin and placebo versus Pemetrexed/Cisplatin and nintedanib

a) For accrual rate 18 pts / month (accrual time 25 months), time to events is 50 months. For accrual rate 14 pts / month (accrual time 32 months), time to events is 54 months. For accrual rate of 22 pts/month (accrual time 21 months), time to events is 47 months

b) For accrual rate 18 pts / month (accrual time 25 months), time to events is 42 months. For accrual rate 14 pts / month (accrual time 32 months), time to events is 46 months. For accrual rate of 22 pts/month (accrual time 21 months), time to events is 39 months.

c) For accrual rate 18 pts / month (accrual time 25 months), time to events is 38 months. For accrual rate 14 pts / month (accrual time 32 months), time to events is 42 months. For accrual rate 22 pts / months (accrual time 21 months), time to event is 35 months.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP and relevant BI SOPs. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH-GCP.

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 general rule, no trial results should be published prior to finalisation of the CTR. Interim trial related information (e.g. trial design, blinded safety data) may be presented in abstract form at medical congresses if agreed to by the co-ordinating investigator and BI.

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / Independent Ethics Committee (IEC) and 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 ICF and any additional patient information form retained by the investigator as part of the trial records. A signed copy of the ICF and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal trial-related data will be used by BI in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by BI, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs 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 ICF documentation of this clinical trial.

8.3 RECORDS

Electronic Case Report Forms (eCRFs) for individual patients will be provided by the sponsor via remote data capture. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

The investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The CRA / on site monitor and auditor may review all eCRFs, and ICFs. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular AE is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For nintedanib (BIBF 1120), this is the current version of the IB (c01632700).

For Pemetrexed and Cisplatin this is the current, local SPC. The current versions of these reference documents are to be provided in the ISF. No AEs are classified as listed for matching placebo, study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of SAEs, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

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.

8.6 COMPLETION OF TRIAL

The IEC/CA in each participating European Union member state needs to be notified about the end of the trial (last patient/patient out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

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10. APPENDICES

10.1 CLINICAL EVALUATION OF LIVER INJURY

Alterations of liver laboratory parameters, as described in Section 5.2.2.2 (Protocol-Specified Significant Events), are to be further evaluated using the procedures specified in the "DILI checklist" provided in the ISF.

10.2 ECOG PERFORMANCE STATUS

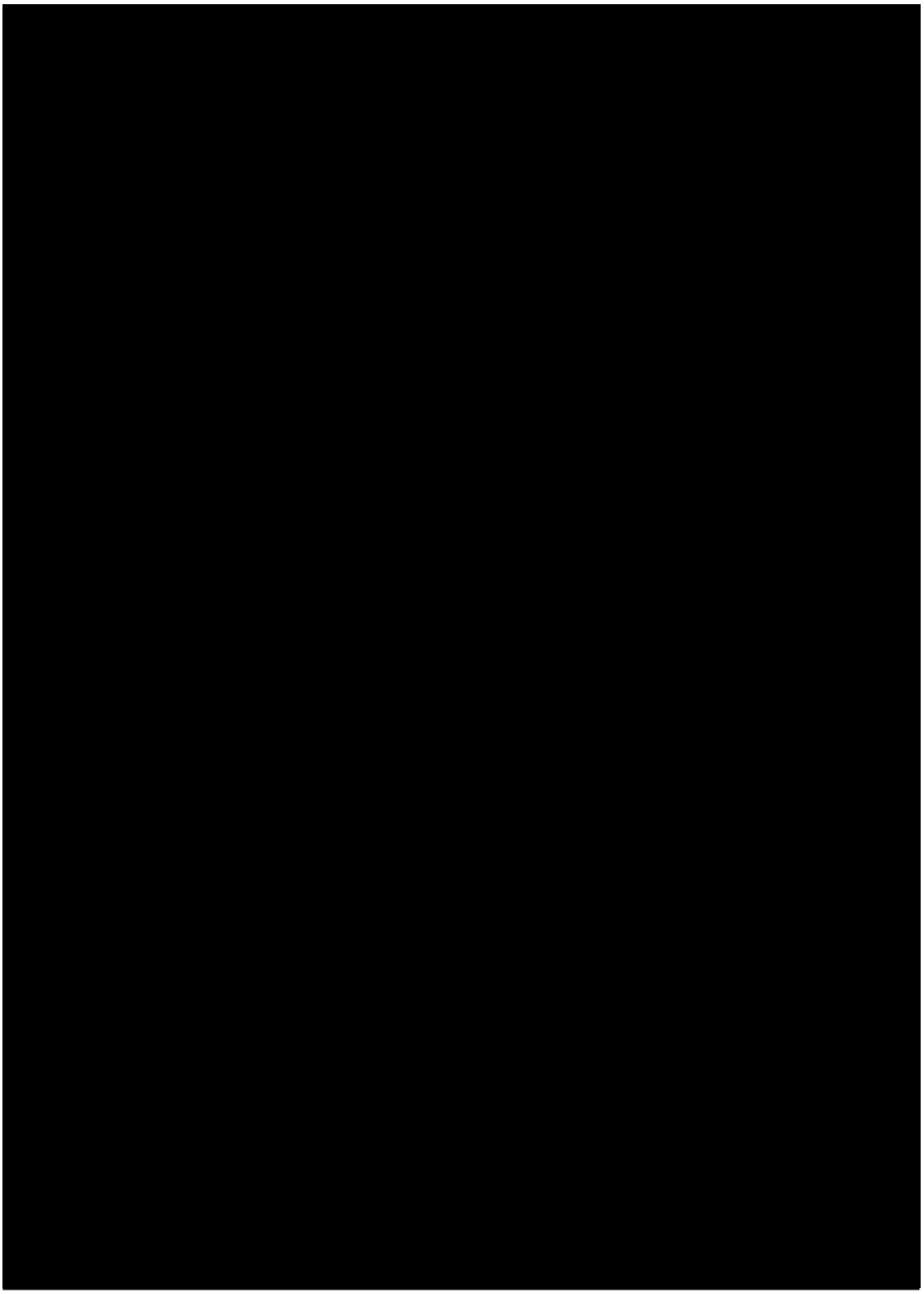
Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up to about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Dead

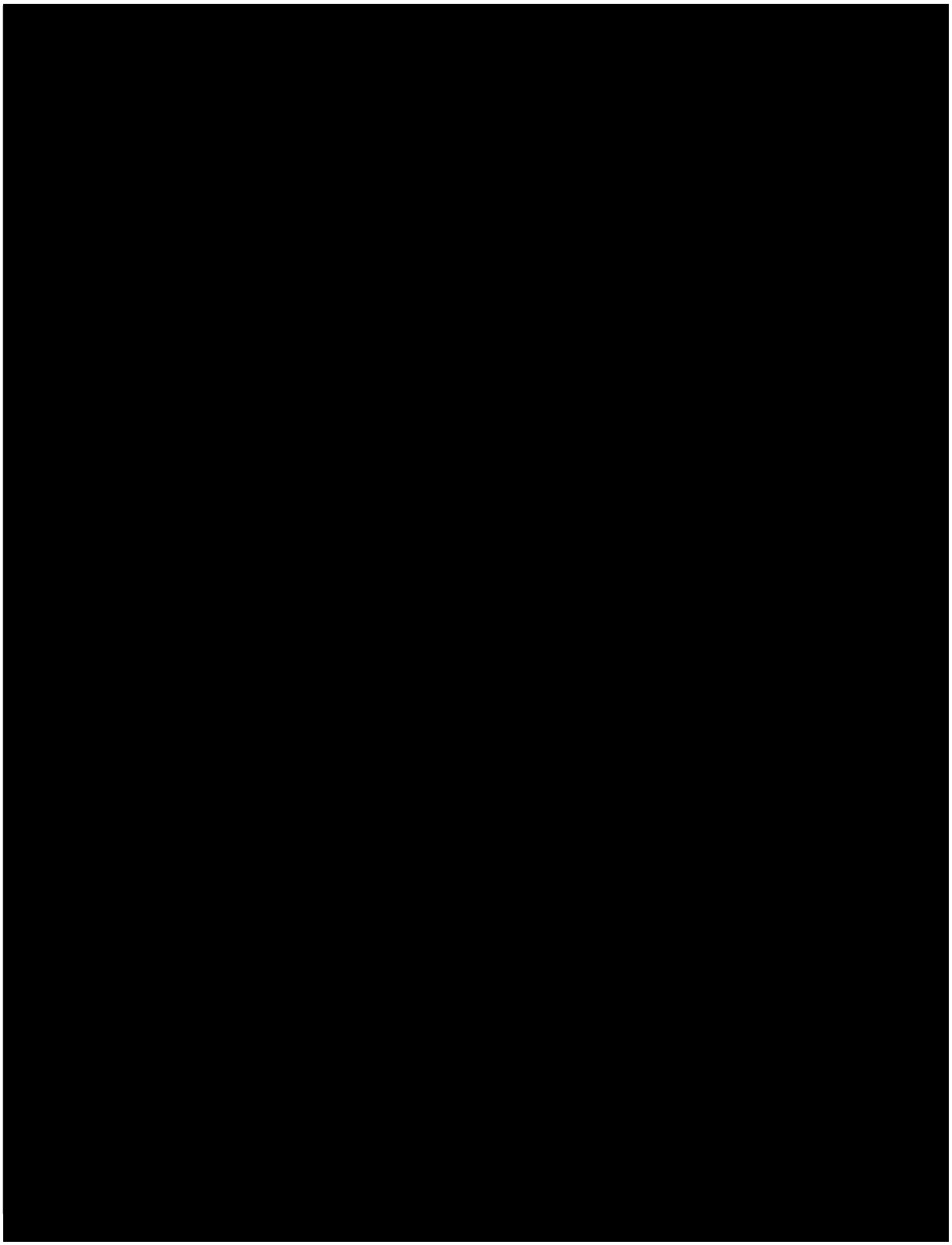
[redacted]

[redacted]

[redacted]

[redacted]





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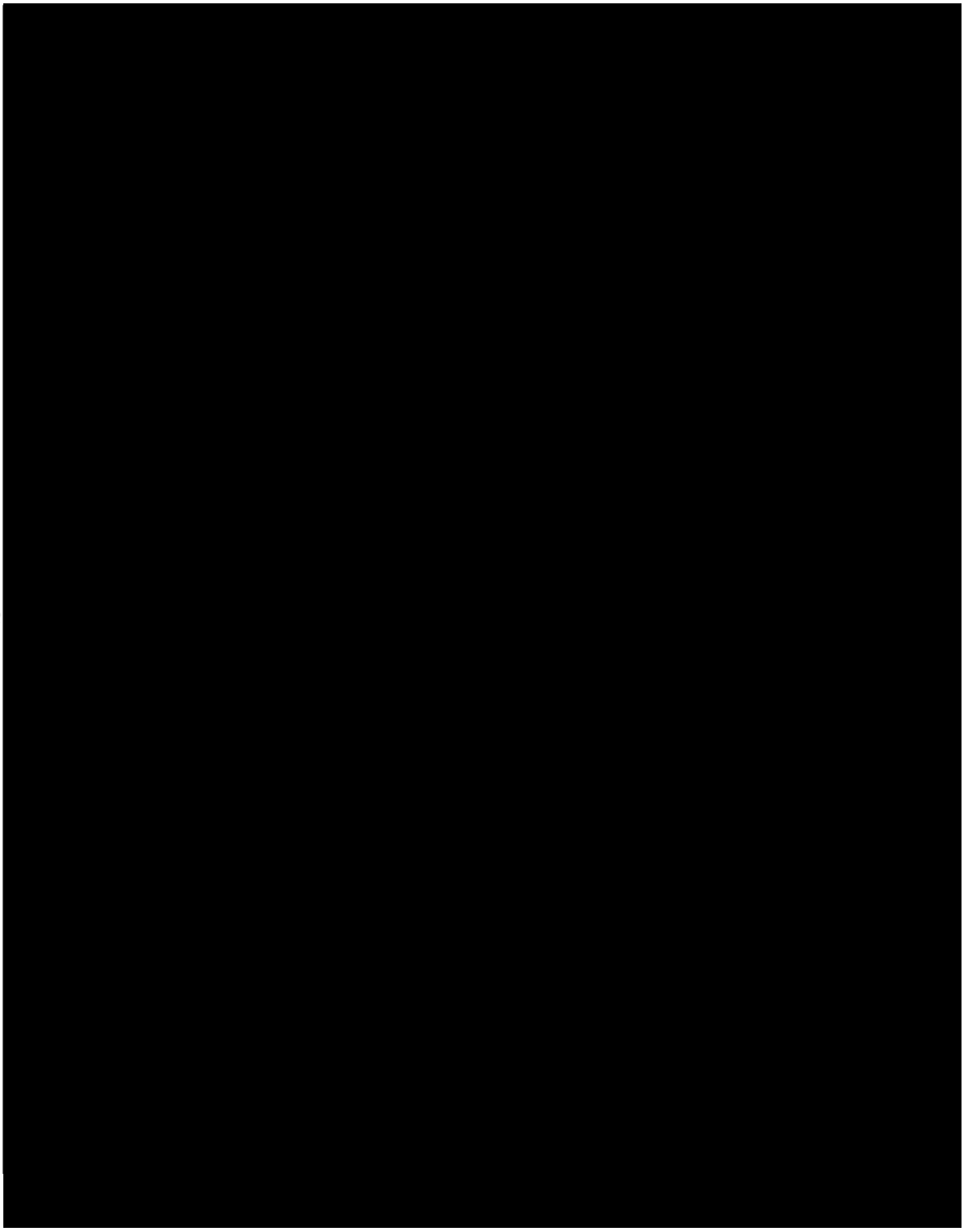

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		1
Date of CTP revision		21 Sep 2015
EudraCT number		2012-005201-48
BI Trial number		1199.93
BI Investigational Product		Nintedanib, BIBF 1120
Title of protocol		Double blind, randomised, multicentre, phase II/III study of nintedanib in combination with pemetrexed / cisplatin followed by continuing nintedanib monotherapy versus placebo in combination with pemetrexed / cisplatin followed by continuing placebo monotherapy for the treatment of patients with unresectable malignant pleural mesothelioma
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
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		Throughout document
Description of change		Administrative changes
Rationale for change		Updates including terminology, abbreviations and references
Section to be changed		Title Page
Description of change		Sponsor contact change
Rationale for change		To provide updated sponsor contact information
Section to be changed		Protocol Synopsis
Description of change		Several sections, including the title, objectives, main criteria for inclusion, number of patients, endpoints and statistical method
Rationale for change		Updated per DMC recommendation
Section to be changed		Flowcharts

Number of global amendment		1
Description of change		Changes in the procedures and timing of assessments for patients in combination therapy and monotherapy
Rationale for change		The flowcharts are updated to clarify the changes in assessments and timing of added assessments
Section to be changed		Section 1 – Introduction
Description of change		Updated research results and details regarding safety and efficacy of nintedanib, pemetrexed and cisplatin
Rationale for change		Updated results became available for studies with nintedanib alone and in combination with pemetrexed/cisplatin and other combination therapies for multiple indications
Section to be changed		Section 2 – Rationale, Objectives, and Benefit – Risk Assessment
Description of change		Updated research results and details regarding treatment for mesothelioma.
Rationale for change		Revised based on updated data
Section to be changed		Section 3 – Description of Design and Trial Population
Description of change		1. a) Changed from an exploratory Phase II study to a confirmatory Phase II/III study b) Increased sample size c) Plan for adaptive design is described d) Internal DMC replaced by external DMC [redacted] 3. Continuation of study treatment beyond progression permitted
Rationale for change		1. Changes made to reflect transition to a confirmatory Phase II/III study as per DMC recommendations. Adaptive design will be further described based on feedback from regulatory authorities. [redacted] 3. Revised to allow patients that are benefitting to remain on study treatment
Section to be changed		Section 4 – Treatments
Description of change		1. a) Hydration added as pre-medication regimen b) Study treatment interruption and stopping criteria clarified c) Management of adverse events clarified 2. Timing of patient data unblinding revised
Rationale for change		1. Updates made based on guidance available in cisplatin SPC and updated safety information in the IB (c01632700).

Number of global amendment		1
		2. The timing of data unblinding will be determined based on later analyses
Section to be changed		Section 5 – Variables and Their Assessment
Description of change		1. a) Efficacy endpoints revised [redacted] 2. a) Evaluation of lesions clarified b) Assessment of adverse events clarified c) Timing of labs and required lab parameters revised d) Management of proteinuria clarified [redacted]
Rationale for change		1. Endpoints, procedures and assessments revised/added to support confirmatory study design 2. Clarifications and allowance for optional on-site visits during the combination treatment period [redacted]
Section to be changed		Section 6 – Investigational Plan
Description of change		• Clarified the timing of the run-in and screening period • Continuation of study treatment beyond progression permitted • Specified procedures performed at FU1 and at further follow up visits • Updated the definition of the end of trial
Rationale for change		Clarified timing of procedures and assessments throughout the study and the definition of the end of trial to ensure consistency throughout protocol
Section to be changed		Section 7 – Statistical Methods and Determination of Sample Size
Description of change		Revised the planned statistical analysis of all endpoints
Rationale for change		Changes made to reflect transition to a confirmatory Phase II/III study as per DMC recommendations
Section to be changed		Section 10 – Appendices
Description of change		[redacted]

Number of global amendment		1
Rationale for change		Detailed procedure is described in the "DILI checklist" provided in the ISF and [redacted]

Number of global amendment		2
Date of CTP revision		22 Jun 2016
EudraCT number		2012-005201-48
BI Trial number		1199.93
BI Investigational Product		Nintedanib, BIBF 1120
Title of protocol		Double blind, randomised, multicentre, phase II/III study of nintedanib in combination with pemetrexed / cisplatin followed by continuing nintedanib monotherapy versus placebo in combination with pemetrexed / cisplatin followed by continuing placebo monotherapy for the treatment of patients with unresectable malignant pleural mesothelioma
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
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		Throughout document
Description of change		Administrative changes
Rationale for change		Updates including terminology and references
Section to be changed		Protocol Title
Description of change		Abbreviated study name added
Rationale for change		Clarified reference
Section to be changed		Protocol Synopsis
Description of change		Several sections including the title, main criteria for inclusion, number of patients, criteria for safety, and statistical methods
Rationale for change		Updated per regulatory authority (EMA/FDA)

Number of global amendment		2
		recommendation and Phase II analysis
Section to be changed		Flowcharts
Description of change		Separate flow charts for Phase II and III. Changes in the procedures and timing of assessments for patients in combination therapy and monotherapy in Phase III
Rationale for change		Updated to clarify the changes in assessments and timing of assessments in separate Phases
Section to be changed		Section 1 - Introduction
Description of change		Updated research results and details regarding safety of nintedanib in combination with pemetrexed and cisplatin
Rationale for change		Updated results became available from the Phase II part of the study
Section to be changed		Section 2 – Rationale, Objectives, and Benefit – Risk Assessment
Description of change		1. Updated research results regarding treatment for mesothelioma and limitation of Phase III patients to epithelioid histology 2. Corrected primary objectives
Rationale for change		1. Revised results based on updated data available from the Phase II part of the study 2. OS was incorrectly listed as a primary objective
Section to be changed		Section 3 – Description of Design and Trial Population
Description of change		1. Limit Phase III to epithelioid histology 2. Describe the time of the primary OS analysis for Phase II 3. Describe the time of the primary PFS and the interim and primary OS analyses for Phase III 4. Increase sample size to 450 Phase III patients 5. Describe adaptive design with OS event number adjustment 6. Revise inclusion and exclusion criteria a) Limit Phase III enrollment to epithelioid histology only b) Adjust creatinine clearance value
Rationale for change		1. Updated data available from the Phase II part of the study 2. Separate time point for Phase II primary OS analysis since Phase II data will not be included in confirmatory analyses 3. Clarification of time point for primary analyses for Phase III 4. Sample size for Phase III confirmatory trial

Number of global amendment		2
		5. Adaptive design implemented to account for the uncertainty of the OS treatment effect 6. a) Updated data available from the Phase II part of the study b) Updated to adjust for starting dose of cisplatin and to fulfill SmPC criteria
Section to be changed		Section 4 – Treatments
Description of change		1. Update dose reduction and retreatment criteria 2. Update criteria for liver enzyme elevations 3. Describe the unblinding of Phase II and Phase III patients 4. Describe unblinding of independent team from sponsor with regard to primary PFS analysis/interim OS analysis of Phase III 5. Update procedures for emergency unblinding 6. Remove lifestyle restriction to UV exposure
Rationale for change		1. Updates based on CTCAE version 4.03 and nintedanib standard 2. Updated per nintedanib standard 3. Phase II patients will be unblinded independent of Phase III patients 4. Independent team needed to maintain blind 5. Clarification 6. UV exposure no longer listed as a risk per the investigator brochure
Section to be changed		Section 5 – Variables and Their Assessment
Description of change		1. Observation period for primary and secondary endpoints updated [redacted] 4. Collection of bone scans clarified 5. Criteria for continuing study treatment beyond progression added 6. Change CTCAE from version 3.0 to 4.03 for Phase III patients 7. Exemption for reporting of (S)AEs added 8. Residual effect period prolonged for Phase III 9. Study procedures changed for Phase III patients 10. [redacted] b) Weekly on-site visits removed c) Timing of ECG procedure revised for Phase III patients [redacted]

Number of global amendment		2
		for Phase III patients [redacted]
Rationale for change		1. Clarification with regard to different phases of the trial 2. Clarification 3. Clarification 4. Clarification 5. Updated as per FDA request 6. Update based on feedback from regulatory authorities 7. Updated per sponsor standard 8. Updated to fulfill FDA requirements 9. To reduce complexity and to reduce burden to patients
Section to be changed		Section 6 – Investigational Plan
Description of change		1. Follow up for PD and follow up for OS clarified for separate trial phases described 2. Updated the definition of the end of the whole trial and reporting of the trial
Rationale for change		1. Clarification 2. Clarification
Section to be changed		Section 7 – Statistical Methods and Determination of Sample Size
Description of change		1. Revised description of analyses for Phase II and Phase III part a) Change hypotheses for Phase III part to one-sided b) Change the alpha level from two-sided 0.1 to one-sided 0.025 c) Describe analyses method for adaptive design with OS event number reassessment [redacted] e) Change of the OS censoring rule if patient died with death date unknown [redacted] g) Revise sample size section for Phase II and Phase III
Rationale for change		1. Clarification of adaptive design and adjustment of sample size based on regulatory authority feedback and on results of Phase II analysis

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Pharmacokinetics	[redacted]	23 Jun 2016 14:52 CEST
Approval-Trial Clinical Monitor	[redacted]	23 Jun 2016 14:52 CEST
Approval-Team Member Medicine	[redacted]	23 Jun 2016 14:56 CEST
Approval-Therapeutic Area [redacted]	[redacted]	23 Jun 2016 15:01 CEST
Author-Trial Statistician	[redacted]	27 Jun 2016 09:25 CEST
Approval-Other	[redacted]	29 Jun 2016 16:03 CEST

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