Trial Statistical Analysis Plan (Phase II primary OS analysis)

c02218855-03

BI Trial No.:	1199.93
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 Including Protocol amendment 1 c02035745-04 and Protocol amendment 2 c02035745-05
Investigational Product(s):	Nintedanib, BIBF 1120
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Date of statistical analysis plan:	08 DEC 2016 REVISED
Version:	Revised

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
BMI	Body mass index
BRPM	Blinded report planning meeting
BSA	Body surface area
CR	Complete response
CRF	Case report form
CT	Concomitant therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database lock
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DMG	Dictionary Maintenance Group
EoT	End of Text
FVC	Forced vital capacity
ICH	International Conference on Harmonisation
ITT	Intent-to-treat
IPV	Important protocol violation
LLT	Lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model with Repeated Measures
MQRM	Medical Quality Review Meeting
MS	Monotherapy set
NE	Not evaluable
O*C	Oracle Clinical
OS	Overall survival

Term	Definition / description
PD	Progressive disease
PFS	Progression-free survival
PG	Pharmacogenomics
PK	Pharmacokinetics
PPS	Per protocol set
PR	Partial Response
PT	Preferred term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual effect period
RS	Randomised set
SD	Stable Disease
StD	Standard deviation
SFS	Safety set
SMQ	Standardised MedDRA query
SOC	System organ class
ScS	Screened set
TOC	Table of contents
TS	Treated set
TSAP	Trial statistical analysis plan
UDAEC	User-defined AE category

3. INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization. This TSAP follows the Boehringer Ingelheim (BI) internal references (1).

Trial 1199.93 has been changed from an exploratory Phase II trial to a Phase II/III trial by extending the trial with a confirmatory Phase III part.

As described in CTP amendment 2, the primary PFS analysis for the Phase II part has been conducted on 4 March 2016 and the respective analyses are described in the Phase II Interim Analysis TSAP c09088167-01.

This TSAP will describe the analyses conducted for the primary OS analysis of the Phase II part of trial 1199.93. A separate Phase III TSAP will describe the analyses of the Phase III part of this trial.

Study medication will refer to the combination of backbone chemotherapy pemetrexed/cisplatin and/or Nintedanib/placebo, investigational drug will refer to nintedanib/placebo.

SAS® Version 9.2 (or later version) will be used for all analyses, unless stated otherwise.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

[redacted]

4.2 BEST OVERALL RESPONSE

[redacted] The secondary endpoints objective tumour response and disease control as well as the further endpoints time to objective response, duration of objective response, and duration of disease control which are derived from best overall response will be also analysed regardless of confirmation.

4.3 RESIDUAL EFFECT PERIOD

The CTP states that the residual effect period (REP) for the Phase II part of this trial is 28 days. For safety analyses described in this TSAP, a REP of 30 days will be assumed. Thus, all adverse events occurring up to 30 days after the last administration of study medication (pemetrexed/cisplatin and/or nintedanib/placebo) will be considered as "on-treatment" (see Section 7.8.1).

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint of the study 1199.93 is progression-free survival (PFS) by investigator assessment. PFS is defined as the time between the date of randomisation to the date of either progression of disease (based on modified RECIST [R12-1990]), or date of death (from any cause), whichever occurs first.

For each RECIST assessment multiple images may be available, i.e. multiple images may be available for each of the scheduled assessments at week 6, 12, 18 etc. Furthermore, for each RECIST assessment it is possible that scans are performed on more than one day. Therefore, each RECIST assessment is referred to as an imaging time-point in this TSAP.

For each imaging time-point an overall tumour response will be determined according to the modified RECIST criteria. The overall tumour response for each imaging time-point will be selected from the following categories: Complete Response (CR); Partial Response (PR); Stable Disease (SD); Progressive Disease (PD) or Not evaluable (NE).

For details on the imaging process and RECIST evaluation, see Section 5.1.2 of the CTP.

5.1.1 Derivation of endpoint PFS

Derivations below are described in days. However, the endpoints below will be presented in months in the statistical tables produced for the Clinical Trial Report (CTR).

For patients with known date of progression or death:

- PFS = earliest of date of progression or death - date of randomisation + 1.

Patients without any post-baseline imaging will be censored at day 1.

Patients administered a subsequent anti-cancer therapy recorded in the case report form (CRF) but not presenting with PD before the start of this new anti-cancer therapy will be censored at the date of imaging before the new anti-cancer therapy has started.

Patients not administered subsequent anti-cancer therapy and not presenting with PD or death during the trial will be censored at the date of the last evaluable radiological image.

- PFS (censored) = date of last imaging when the patient is known to be progression-free and alive - date of randomisation + 1

It has been observed that patients have their radiological examinations over a number of days, i.e. target lesions assessed on day x and non-target lesions assessed on day y. However, a single date is required for the derivation of PFS for each patient. The following rules will be applied:

- If the overall response is PD, the earliest date of multiple assessments will be taken.

- If the overall response is SD, PR, CR or NE, the latest of multiple assessment dates will be taken, i.e. in the case of SD, PR, CR, the latest of multiple dates will be used to censor the patients.

5.1.2 Censoring of PFS

Scans for which NE is assigned as the overall response at an imaging time-point are considered to be missed assessments. It cannot be assumed that NE indicates progression has not occurred. Table 5.1.2:1 describes how patients will be classified for the analysis of PFS.

Table 5.1.2:1 Derivation rules for PFS

Situation	**Outcome (event or censored)**	**Date of PFS or censoring**
No baseline tumour assessment, patient without death or patient with death after second radiological assessment	censored	Date of randomisation
No baseline tumour assessment, patient with death on or before the second scheduled radiological assessment	event	Date of death
Progressed according to investigator (no more than one consecutively missed radiological assessments)	event	Date of PD determined by investigator
Non-PD according to investigator, death before next scheduled assessment	event	Date of death
Non-PD according to investigator[1], one missed assessment, death or progression after date of missed assessment, but before next scheduled assessment	event	Date of PD or death

Table 5.1.2:1 Derivation rules for PFS (cont.)

Situation	**Outcome (event or censored)**	**Date of PFS or censoring**
Non-PD according to investigator[1], more than one consecutively missed assessment	censored	Date of last evaluable imaging before missed assessment
New anti-cancer therapy before PD or death[2]	censored	Date of last evaluable imaging before new anti-cancer therapy
Death before the scheduled date of first imaging	event	Date of death
No imaging performed post-baseline, patient dies between first and second scheduled assessments	event	Date of death
No imaging performed post-baseline, patient dies after second scheduled assessment	censored	Date of randomisation
No imaging performed post-baseline, vital status is unknown or patient is known to be alive	censored	Date of randomisation
Alive and not progressed according to investigator (no missed radiological assessment)	censored	Date of last evaluable imaging

[1]This is from the last assessment at which non-PD (SD or better) was assessed.

[2]Subsequent treatment with pemetrexed/cisplatin/nintedanib will not trigger censoring of PFS.

Patients who are still alive at the time of the analysis without a PFS event will be censored at the time of the last evaluable radiological image. An evaluable radiological image for the censoring of PFS is a scan where an overall response assessment of SD, PR or CR has been assigned. A radiological image where an overall response of NE has been assigned is not

considered evaluable. Patients who have been randomised but never received the investigational drug will be censored on the day of randomisation for PFS.

In order to identify whether consecutive imaging time-points are missing for a given patient, a nominal time point [6, 12, 18, 24, 30 weeks etc.] will be assigned to each and every image. This is achieved by creating windows for every RECIST assessment. The windows are defined in Table 5.1.2:2 below.

Table 5.1.2:2 Nominal time-points and windows for imaging

Nominal time-point [weeks from start of therapy]	**Due date of scans [days]***	**Window [days]**
6	43	1 to =< 64
12	85	65 to =< 106
18	127	107 to =< 148
24	169	149 to =< 190
30	211	191 to =<232
Etc, 6 week interval	etc	etc

*date of first dose of study medication is day 1, for randomised patients that have not been treated, date of randomisation is reference date.

If a patient does not have an image in one of the windows described above, he/she will be said to have 'missed an assessment' for that time-point.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

OS has been changed to the key secondary endpoint in this trial with CTP amendment 1.The analysis of overall survival (OS) is described in Section 5.2.2.

5.2.2 Other Secondary endpoints

The secondary endpoints in this study are overall survival (OS) as key secondary endpoint, objective response and disease control.

5.2.2.1 Overall survival

OS is the time from randomisation to the time of death of any cause. For patients with known date of death (regardless of the cause of death):

- Overall survival = date of death - date of randomisation +1.

Otherwise:

- Overall survival (censored) = date patient last known to be alive - date of randomisation +1.

The date when the patient was last known to be alive will be derived using the following data

- Patient follow-up case report form: date of patient status obtained, last date patient known to be alive (in case patient is lost to follow up), date of refusal (in case the patient actively refused to be followed up)
- Tumour response
- Radiological imaging data
- Administration pages of nintedanib/placebo, pemetrexed, cisplatin (including termination of trial medication page)
- Start date of subsequent anti-cancer therapy.
- Date of FVC assessment

The censoring rules for OS are as in Table 5.2.2:1.

Table 5.2.2.1:1 Derivation rules for OS

Situation	**Outcome (event or censored)**	**Date of death or censoring**
Patient died and the date of death is known	event	Date of death
Patient died and date of death is unknown	censored	Date of last contact when the patient is known to be alive
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

Derivations for OS are performed in days. However, the endpoint will be presented in months in the statistical analysis tables produced for the CTR. Patients who have been randomised but never received the investigational drug will be censored on the day of randomisation for OS.

[redacted]

5.2.2.3 Objective response

Objective response (CR and PR) will be derived from patients best overall response (see Section 5.3), and analysed via objective response rate, regardless of confirmation.

5.2.2.4 Disease control

Disease control (CR and PR and SD) will be derived from patients best overall response (see Section 5.3), and analysed via disease control rate, regardless of confirmation.

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

Two treatment groups will be compared in the analyses; these will be the treatments nintedanib plus pemetrexed /cisplatin followed by nintedanib monotherapy versus placebo plus pemetrexed/cisplatin followed by placebo monotherapy. For efficacy analyses, patients will be analysed as randomised. For safety analyses, patients will be analysed as treated.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Even though all treated patients will be included in the safety and all randomised patients in the efficacy analyses, patients with potentially important protocol violations (IPV) will be documented.

Potentially important protocol violations are described as in Table 6.2:1 below. The final list of important PVs will be confirmed at the last blinded report planning meeting (BRPM) before the database lock at the time of the CTR.

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from
A		**Entrance criteria not met**		
	A1[1]	Patient has condition that may cause additional risk from study medication	In 4, Ex 4-7, 18-20, 31-36.	None
	A2[1]	Patient has laboratory assessment that may cause additional risk	Ex 21-29	None
	A3[1]	Patient is unable to comply with the protocol	Ex 37-38	None
	A4[1]	Patient does not have trial diagnosis or is not part of the target population	In 2, 5, Ex 3	None
B		**Informed consent**		
	B1[1]	Informed consent not given or too late	In 6	All
	B2[1]	Patient less than 18 years old	In 1	None
	B3[1]	Pharmacogenomic investigation performed without prior separate informed consent	CTP Section 5.3.3	None

Table 6.2: 1 Important protocol violations (cont.)

Category/ Code		Description	Example/Comment	Excluded from
C		**Trial medication and randomisation**		
	C1[2]	Incorrect investigational drug taken	Medication kit assigned not matching treatment patient was randomised to (cross-treatment) and/or not matching IXRS assignment. During trial conduct, this will be monitored via IXRS reports manually. At final analysis, this will be programmed.	None
	C2[1]	Patient treated but not randomized by IXRS or treated before randomized by IXRS		None
	C3[2]	Administration of Pemetrexed and Cisplatin not according to protocol	Drug administration according to protocol = "no" and medical review of data by the trial team (decision will be made at MQRM/BRPM/DBL meeting)	None

[1]IPV will be derived automatically

[2]IPV will be identified via individual review at MQRM/BRPM/DBL

6.3 PATIENT SETS ANALYSED

- Screened set (ScS)

  This patient set includes all patients who have signed the informed consent. The ScS will be used for patient disposition tables.

- Randomised set (RS)

  This patient set includes all randomised patients, regardless of whether or not they have received treatment. Patients are assigned to nintedanib or placebo as randomised. The randomised set will be used for the efficacy analyses. This patient set reflects the Intent-to-treat (ITT) population.

  Remark on the randomised set:

  With respect to those patients who were incorrectly randomised and must be included in the ITT analysis: such patients should continue in the trial and participate in all aspects of the trial other than taking study medication. From previous experience, it was observed that many of these patients will agree to continue in the trial. However some patients could withdraw consent for further participation. If a patient was not

willing to participate in the imaging component of the study design, the patient should be encouraged to at least participate in follow-up visits in order to document as much as possible, and at a minimum with vital status and cause of death.

Only in exceptional cases where randomisation has been performed by error, e.g., a patient did not exist, or typing error, etc. a randomisation by mistake may be accepted. Such patients will be flagged in the IVRS system as non-randomised. For such exceptional cases an immediate information is needed providing all information that would clearly outline the exceptional reason to a potential external auditor. Note that this should be the exception and should be avoided if possible.

- Treated set (TS)

  This patient set includes all patients who were dispensed study medication and were documented to have taken at least one dose of study medication. Patients are assigned to Nintedanib or placebo according to actual treatment received during the whole treatment period. The TS will be used for safety analyses.

  In the BRPM a decision will be made how to assign patients who have received the incorrect treatment for only a limited time during their participation in the trial depending on the amount of incorrect treatment they received. Patients who received pemetrexed/cisplatin only will be assigned to their randomised treatment.

- Safety set (SFS)

  This patient set includes all patients who were documented to have received at least one dose of investigational treatment (nintedanib/placebo). Patients are assigned to nintedanib or placebo as actually treated. In the BRPM a decision will be made how to assign patients who have received the incorrect treatment for only a limited time during their participation in the trial depending on the amount of incorrect treatment they received.

  The difference in the number of patients included in the TS and the SFS will be used to assess the number of patients who have received pemetrexed/cisplatin only. If the TS and the SFS differ by a high number of patients, then additional safety tables and listings should be provided in the CTR to illustrate and summarize the differences.

- Monotherapy set (MS)

  The MS will include all patients who were documented to have received at least 1 dose of investigational drug during monotherapy phase. This set will be used for particular safety analyses during the monotherapy phase (see Section 7. 8.1).

No per protocol population will be used for analyses.

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates are imputed according to BI standards (2).

The handling of missing data for the FVC analysis is described in Section 7.5.2.

In general, missing data not discussed in this section or Section 7.5.2 will not be imputed, unless required for the following analyses and definitions. Then the rules as described below apply.

1) Change of laboratory values from baseline

Laboratory values at baseline: For missing laboratory data at visit 1 (before the very first administration of study medication) the data of preceding visits will be used. Refer also to Section 7.8.2 where the determination of possible clinically significant laboratory values in case of missing baseline values is described.

2) Definition of on-treatment period and actual treatment

Date of permanent discontinuation of last study medication: All reasonable efforts should be undertaken during the study to obtain the dates of permanent discontinuation of last study medication. However, if the date of the very last nintedanib/placebo intake is missing this will be imputed with the date of first investigational drug intake in the last cycle + 21 days for monotherapy cycles or the date of first investigational drug intake in the last cycle + 20 days for combination therapy cycles. If also the first investigational drug intake in the last cycle is unknown, then the date of last drug intake of the second last cycle + 22 days will be imputed. If the imputed date leads to a date that is later than the death date, then the imputed date will be the date of death.

Missing infusion time: If the time of infusion is missing, then the start time of the infusion will be imputed as "0:00".

3) Randomisation and stratification

IVRS/IWRS (IXRS) versus eCRF data: In general, the data as reported in the eCRF will be used for analyses. If data are missing in the eCRF (e.g. stratification factors) or unknown they will be imputed with the data from IXRS. If the date of randomisation differs between IXRS and eCRF, the randomisation date as in IXRS will be used.

4) Partial death dates

If a partial (year and month) death date is reported, the date will be imputed with the end of the month for the analysis of PFS and OS. This is in line with the imputation of partial dates for the analysis of adverse events.

5) Partial or missing start date of subsequent anti-cancer therapy

If the day of the start date of subsequent anti-cancer therapy is missing, then the 1th of the months will be imputed unless the first day leads to a date before the stop date of study medication, then the study medication stop date + 1 day will be imputed. If “day and month” or “day and month and year” are missing, it will be distinguished whether the start date of new anti-cancer therapy is required for censoring of PFS or for other descriptive statistics (e.g. duration of subsequent therapy). For censoring of PFS: If only the year is reported, January, 1st will be imputed unless this leads to a date before the stop date of study drug, then the study drug stop date + 1 day will be imputed. In case of completely missing start date of subsequent anti-cancer therapy and the patient did not have any post-baseline tumor assessment and did not progress or die, the PFS of this patient will be censored at the day of randomisation / start date of study medication. Additionally, all imputed start dates of subsequent anti-cancer therapy should be before death date if available. For descriptive statistics, dates will not be imputed if more than only the day of the date is missing. Missing stop date of subsequent anti-cancer therapies will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study days and visits will be labelled according to the flow chart of the CTP.

Unless otherwise specified, baseline is defined as the latest time-point before the very first administration of study medication. If there is no measurement earlier than the very first administration of study medication no baseline will be derived. For nominal timepoints and windows of tumour imaging, see Table 5.1.2:2.

For patients randomised but not treated, the last screening value will be used as baseline.

[redacted]

[redacted]

[redacted]

2) Change of laboratory values from baseline

Laboratory values: Baseline is defined as the latest time-point before the very first administration of study medication. As for laboratories not only the examination date but also time is recorded, examination time has to be taken into account when defining baseline. That is, a laboratory value on the same date as the first study drug administration is considered as baseline value if and only if the time of laboratory value is before or the same as the time of first study drug administration.

If any of these times are missing and the date of laboratory is equal to the date of first study drug administration, then the laboratory assessment will be considered as according to protocol, i.e. as prior to first administration of study medication.

7. PLANNED ANALYSIS

The labelling and display format of statistical parameters will follow the BI guideline (3).

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / Standard deviation (Std)/ Min / Median / Max.

For time-to-event analysis tables, the set of statistics is: number of patients [N(%)], Number of patients with event [N(%)], <Time to event> [months] followed by P25 (25^{th} percentile), Median, P75 (75^{th} percentile), Number of patients censored [N(%)]. If not specified otherwise, the duration as well as time to event will be displayed in months and a final decision will be made at the last BRPM.

For appendix tables, the set of summary statistics is: N / Mean / SD / Min / P25 / Median / P75 / Max / Missing.

If not otherwise specified, the abbreviation Pxx should be used for displaying the xxth percentiles.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

Two-sided p-values and confidence intervals will be displayed.

Sort order for general categorical variables: If categories correspond to the collected categories on the eCRF and the table shells do not explicitly specify the ordering, the “default ordering” defined by the eCRF is to be used in such cases. If categories are derived, the ordering as specified in the table shell document should be used; in general ordinal data (e.g. categorised continuous data) are to be displayed in ascending order.

The denominator of the main categories is defined by the number of patients in the used patient set. The main categories define the denominators of the subcategories. Subcategories should be intended and "[N(%)]" to be displayed only for the main category.

If a table includes only categorical data, "N[(%)]" is to be displayed in the column header.

Abbreviations (e.g. Wors.) should not be displayed without any explanations. They will be either spelled out in the table or explained in footnotes (whatever is more reasonable from the programming point of view).

If applicable, conversion from days to weeks, months and years will be as follows:

- Weeks = Days/7
- Months = (Days ×12)/365.25

- Years = Days/365.25.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. Concomitant diseases will be coded similarly as adverse events based on the most current Medical Dictionary for Regulary Activities (MedDRA) version. Concomitant therapies will be coded according to World Health Organization Drug Dictionary (WHO DD). Concomitant therapies (CT) will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The third ATC level will be used to categorise CTs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, patients receiving CTs with more than one possible ATC level 3 category will be counted more than once; footnotes will clarify this possible double counting in tables.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this part of the report. The amount and time for which nintedanib/placebo and pemetrexed/cisplatin therapy is taken will be interpreted in light of treatment exposure, efficacy and safety.

7.4 PRIMARY ENDPOINT

The analysis for the primary endpoint PFS will be conducted for all patients of the randomised set. The primary analysis of the primary endpoint PFS was conducted on 4 March 2016 according to an authority request. Still, an update of this analysis will be done at the time of the primary OS analysis. PFS will be assessed based on the Kaplan-Meier method for each treatment arm separately. Point estimates together with confidence intervals (based on Greenwood`s method) will be provided for median PFS. An estimation of nintedanib treatment effect on PFS compared to placebo treatment will be given by the hazard ratio and its 95% confidence interval using a Cox proportional hazards model. The Cox proportional hazards model will be stratified by the stratification factor tumour histology (epithelioid vs. biphasic) used at randomisation. Hazard ratios < 1 will favour treatment with nintedanib.

Furthermore, the stratified log-rank test will be used to test for the treatment effect of nintedanib. The log-rank test will include the stratification factor tumour histology (epithelioid vs. biphasic). The two-sided stratified log-rank test p-value will be obtained by fitting a stratified survival model using PROC PHREG in SAS. The model will be fitted using the default method for handling ties (Breslow`s method) and the p-value presented will be that from the score test. It should be emphasised here that the p-value is only to be understood in an exploratory way. The censoring rules for PFS are as stated in Section 5.1.2. The Brookmeyer and Crowley method ([R09-6372]) with a linear transformation, which

incorporates the Greenwood variance formula will be used to produce 95% confidence intervals for the median PFS in each treatment arm.

[redacted]

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

OS has been changed to the key secondary endpoint in this trial with CTP amendment 1. The analysis of OS is described below in Section 7.5.2.1.

7.5.2 Other Secondary endpoints

7.5.2.1 Overall survival

The key secondary endpoint OS will be analysed for all patients of the randomised set. As described in CTP amendment 2, the primary OS analysis of Phase II will be conducted when approximately 70% of the Phase II patients had an OS event (approximately 61 OS events). The analysis might be performed with fewer OS events but no later than March 2017.

OS will be assessed based on the Kaplan-Meier method for each treatment arm separately. Point estimates together with confidence intervals (based on Greenwood`s method) will be provided for median OS. An estimation of nintedanib treatment effect on OS compared to placebo treatment will be given by the hazard ratio and its 95% confidence interval using a Cox proportional hazards model. The Cox proportional hazards model will be stratified by the stratification factor tumour histology (epithelioid vs. biphasic) used at randomisation. Hazard ratios < 1 will favour treatment with nintedanib.

Furthermore, the stratified log-rank test will be used to test for the treatment effect of Nintedanib. The log-rank test will include the stratification factor tumour histology (epithelioid vs. biphasic). The two-sided stratified log-rank test p-value will be obtained by fitting a stratified survival model using PROC PHREG in SAS. The model will be fitted using the default method for handling ties (Breslow`s method) and the p-value presented will be that from the score test. It should be emphasised here that the p-value is only to be understood in an exploratory way. The censoring rules for OS are as stated in Section 5.2.2.1. The Brookmeyer and Crowley method ([R09-6372]) with a linear transformation, which incorporates the Greenwood variance formula, will be used to produce 95% confidence intervals for the median OS in each treatment arm.

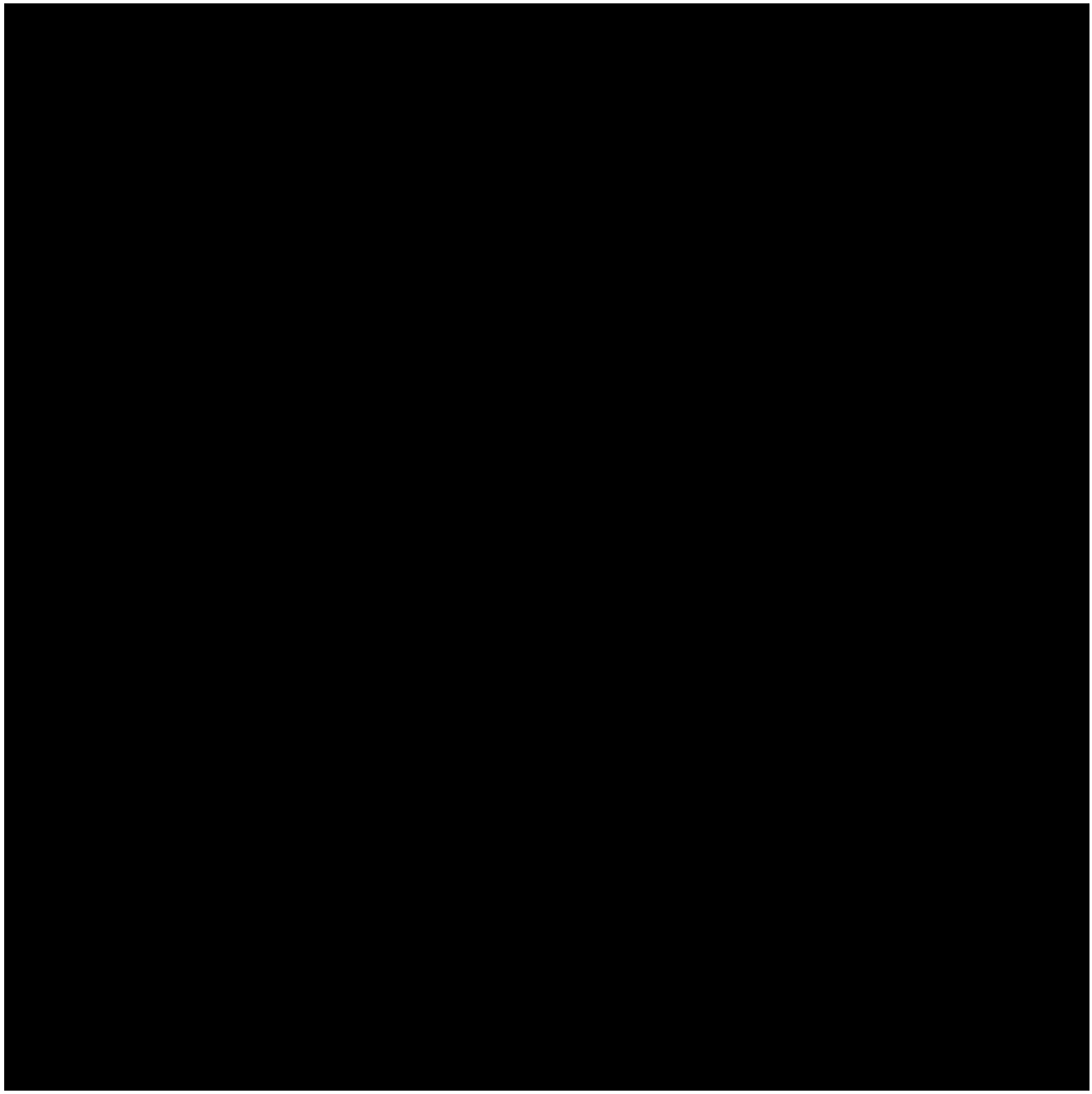
[redacted]

7.5.2.3 Objective response

Logistic regression will be used to test for a difference between the two arms for objective response rate. The model will be adjusted for the stratification factor tumour histology. The exploratory p-value will be generated from the likelihood ratio test statistic. An odds ratio and corresponding 95% CI will be generated using the likelihood ratio confidence interval in order to obtain a direct correspondence between the p-value and the odds ratio confidence interval. Odds ratios >1 will favour nintedanib.

7.5.2.4 Disease control

Logistic regression will be used to test for a difference between the two arms for disease control rate. The model will be adjusted for the stratification factor tumour histology. The exploratory p-value will be generated from the likelihood ratio test statistic. An odds ratio and corresponding 95% CI will be generated using the likelihood ratio confidence interval in order to obtain a direct correspondence between the p-value and the odds ratio confidence interval. Odds ratios >1 will favour nintedanib.



7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse events

The analyses of adverse events (AEs) will be descriptive in nature. All analyses will be based on the number of patients with AEs (not the number of AEs).

The analyses will be based on BI standards (3). Adverse events will be coded with the most recent version of MedDRA. The severity of AEs will be scaled according to common terminology criteria of adverse events (CTCAE) version 3.0 ([R04-0474]).

According to the BI standards, first, multiple occurrences of AEs, i.e. AE entries on the eCRF, will be collapsed to episodes on the lowest level term (LLT) provided that the occurrences were time-overlapping or time-adjacent (the second occurrence started before or

one day after the end of the first occurrence) and provided that the treatment did not change between the onset of the occurrences or treatment changed but no deterioration was observed for the later occurrence. Second, for each patient, all episodes with the same preferred term (PT) will be condensed to one AE record on the PT and System organ class (SOC) level using a worst case approach for all AE attributes including CTCAE version 3.0 grading.

The analyses of adverse events will be based on the concept of treatment-emergent adverse events, where a treatment emergent AE has an onset in the analysing treatment period. The main AE analysis will be based on the "on-treatment period", which starts with the date of first administration of any study medication (pemetrexed/cisplatin and/or nintedanib/placebo) and ends 30 days after the last administration of study medication (pemetrexed/cisplatin and/or nintedanib/placebo).

AEs with onset date in the screening-period (time between informed consent date and date of first administration of study medication) or post-study-period (time after the on-treatment-period) will be tabulated and listed separately.

Sorting order: In tables presenting PTs only, PTs will be sorted by descending frequency of the nintedanib arm. In tables presenting SOCs and PTs, SOCs will be sorted alphabetically and PTs (within SOC) by descending frequency of AEs in the nintedanib arm.

Reporting of CTCAE grades in tables: Displaying of CTCAE grades in AE tables (Section 15) will be "All grades", "Grade 1/2" and "Grade 3/4/5". A separate table will show AEs leading to death. AEs with missing CTCAE grade or CTCAE grades not equal to 1 to 5 will be displayed in the column "All grades". A separate table/listing will be created showing AEs either without a CTCAE grade definition or with a definition but with CTCAE grade missing or CTCAE grades not equal to 1 to 5.

In the appendix (Section 16), the categorization "All grades", "Grade 1", "Grade 2"; "Grade 3", "Grade 4" and "Grade 5" will be used.

Listings of adverse events will be displayed by patients. The actual planned dose of nintedanib/placebo and/or pemetrexed/cisplatin administered at the day of AE onset will be derived and included in the listings. Adverse events will be reported with start day and end day as calculated from the first day of treatment with study medication.

Incidence and severity of adverse events

The incidence of AEs overall (irrespective of relatedness to study medication), related AEs, and of serious AEs (SAE) will be reported by severity according to CTCAE grades version 3.0 ([R04-0474]).

Other significant adverse events

Other significant AEs are defined as serious and non-serious AEs that lead to dose reduction or permanent discontinuation of study medication. Their incidence will be reported by severity according to CTCAE grades.

A listing of patients who developed 'other significant' AEs will be provided and a flag for serious and non-serious will be included.

AEs leading to dose reduction of any study medication (cisplatin or pemetrexed or nintedanib/placebo); cisplatin or pemetrexed and nintedanib/placebo; cisplatin; pemetrexed; nintedanib/placebo; cisplatin or pemetrexed will be tabulated.

AEs leading to permanent discontinuation of last study medication, i.e. leading to discontinuation of the last administered study medication will be reported.

In addition, AEs leading to discontinuation of any study medication (cisplatin or pemetrexed or nintedanib/placebo); cisplatin or pemetrexed and nintedanib/placebo; cisplatin; pemetrexed; nintedanib/placebo; cisplatin or pemetrexed will be tabulated.

Adverse events leading to death

AEs leading to death during the on-treatment period will be tabulated. Reported fatal AEs that occurred in the post-study phase will be listed.

Protocol-specified adverse events of special interest (AESI)

Protocol-specified AEs of special interest (AESI) as defined in the CTP will be analysed.

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

AE tables separated for the combination and monotherapy phase

In addition to the on-treatment period, AEs will be analysed separately for the combination and the monotherapy phase. The end of the combination phase will be defined as the date of the last administration of last study medication + 30 days for patients not continuing to monotherapy; for patients continuing to monotherapy, the end of the combination phase is the last day before the start of the monotherapy phase. The start of the monotherapy phase is the day of first administration of nintedanib/placebo during monotherapy. The monotherapy phase ends with last intake of nintedanib/placebo + 30 days. This way, combination therapy phase and monotherapy phase sum up to the on-treatment period. In case of an off-treatment

period in-between the combination therapy and the monotherapy phase, the off-treatment period is assigned to the combination therapy phase.

Patients receiving only one of the two chemotherapies; or patients only receiving chemotherapy but no nintedanib/placebo will be counted to combination therapy. The AEs during monotherapy will be displayed for the monotherapy set.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (4). The same on-treatment periods as considered for the analysis of adverse events will be applied for laboratory values except for that the baseline laboratory value will be included in the on-treatment period. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses. Patients with missing CTCAE grade at baseline or no baseline value but with post-baseline values will be displayed in a new category “missing CTCAE grade at baseline”.

Descriptive statistics, including change from baseline and frequency of patients with transitions relative to the reference range, will be provided. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE v3.0 ([R04-0474]). The following outputs will be presented:

Worst CTCAE grade experienced during the on-treatment phase.

Transitions of CTCAE grade from baseline to worst laboratory value, from worst to last laboratory value on treatment and from baseline to last laboratory value during the on-treatment phase.

Worst laboratory value and its CTCAE grade (highest CTCAE grade) over all courses will be calculated for each laboratory parameter specified above.

The last laboratory value on treatment is the last laboratory value during the on-treatment period.

Note: Patients with a CTCAE grade of -9 (no CTCAE grade defined) will be automatically treated as CTCAE grade 0 for all analyses. In laboratory listings, the CTCAE grade will be displayed as -9.

Patients with a CTCAE grade of -1 will be treated as Grade 1 for Uric Acid for all analyses. In laboratory listings, the CTCAE grade will be displayed as -1.

Possible clinically significant abnormal laboratory values are defined as those laboratory values that are of CTCAE grade ≥ 2 and show an increase from baseline value by at least one CTCAE grade. For those parameters for which no CTCAE has been defined, BI standard definition will be used to determine possible clinical significance. Frequency of patients with possible clinically significant abnormal laboratory values will be provided whenever applicable. If no baseline value is available but the patient has a post-baseline laboratory

value of CTCAE grade ≥2, an increase from baseline is assumed, i.e. the laboratory value considered as possible clinically significant.

In Section 15 of the CTR, the analysis will focus on the following laboratory parameters (low/high values define the 'worsening' direction), ie the primary laboratory values are the following:

Low values (-): Haemoglobin (HGB), White blood cell count (WBC, total leukocyte count), Neutrophils (NEUT), Platelets (PLTCT, Thrombocytes), Total protein (TPRO).

High values (+): Creatinine (CRE), SGOT-AST (SGOT), SGPT-ALT (SGPT), Alkaline phosphatase (ALKP), Total Bilirubin (TBILI), International normalised ratio of pro-thrombin time (INR), Partial thromboplastin time (PTT), Urea (UREA), Uric acid (URIC), urine protein (UPROZ).

High and low values (+ and -): Thyroid stimulating hormone (TSH), free Triiodothyronine (FT3), free Thyroxine (FT4), Potassium (K), Magnesium (MG), Sodium (NA).

All laboratory values other than those in the primary list will be considered as secondary, including but not limited to the parameters listed in the following. Secondary laboratory values will be displayed in Appendix 16.1.9.2 of the CTR.

Low values (-): not applicable

High values (+): Prothrombin time (PRT, PRT_SEC), Lactate dehydrogenase (LDH), Direct bilirubin (BILID), Indirect bilirubin (BILII).

High and low values (+ and -): Calcium (CA), Glucose (GLU), Phosphorus (P).

Urine analysis: semi quantitative; based on dipsticks with 0, +, ++, and +++; the more + the worse, Urine glucose (UGLU), Urine erythrocytes (URBCZ), Urine leucocytes (UWBCZ), Urine nitrite (UNIT), Urine pH (UPH).

For urine measurement based on dipsticks the indicated results will be converted as follows for the analysis:

Table 7.8.2: 1 Conversion of urine measurements based on dipsticks

Original dipstick measurement	Converted dipstick measurement
"-" ; "NEG" ; "NEGATIVE" ; "NORMAL"	0.0
"0.5" ; "TRACES" ; "TRACE" ; "+/-" ; "+-" ; "-/+"	0.5
"+" ; "1+"	1.0
"++" ; "2+"	2.0
"+++" ; "3+"	3.0
"++++" ; "4+"	4.0

Laboratory values of special interest (LVSI)

Hepatic enzyme elevations (potential Hy's law cases): These are defined as those cases where a combination of all of the following events occurred: any on-treatment value of ALT and/or AST > 3ULN with total bilirubin ≥ 2ULN and ALKP < 2ULN. The events can occur in any order, but must occur within 14 days of the previous event, i.e. the second event must occur within 14 days of the first event, and the third event must occur within 14 days of the second event, etc. Patients with missing laboratory values for liver enzymes will be excluded from these analyses, but presented separately.

Tabulations of hepatic enzyme elevations and liver laboratory values will be done according to the FDA Drug Induced Liver Injury (DILI) guidance (5).

Neutropenia evaluation based on neutrophil counts: since Pemetrexed and Cisplatin induce neutropenia, it is important to elucidate whether the addition of Nintedanib increases the frequency and intensity of neutropenia. In addition, platelet count and haemoglobin count will be evaluated. For this, the laboratory values over time for patients with laboratory CTCAE grade 3 or 4 will be plotted, and the occurrence of laboratory values of grade 3 or 4 with regard to the administration of chemotherapy will be shown.

In addition, serum creatinine will be analysed in detail to evaluate kidney function of patients.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report.

7.8.4 ECG

Newly emergent abnormalities will be recorded and analysed as adverse events.

7.8.5 Others

PK – not applicable.

8. REFERENCES

1 *001-MCG-160_RD-01*: "TSAP annotations", current version; IDEA for CON.

2 *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.

3 *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.

4 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

5 Guidance for Industry. Drug Induced Liver Injury: Premarketing Clinical Evaluation. U.S. Department of Health and Human Services Food and Drug Administration, 2009. website:fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

[R12-1990] Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol (15): 257-260, 2004.

[R09-6372] Brookmeyer R, Crowley JA. Confidence interval for the median survival time. Biometrics (38):29-41, 1982.

[R04-0474] Common terminology criteria for adverse events (CTCAE) (publish date: December 12, 2003). Weblink ctep.cancer.gov/forms/CTCAEv3.pdf ; Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, March 31, 2003, Publish Date: December 12, 2003

[R10-4485] Hertz-Picciotto I, Rockhill B. Validity and efficiency of approximation methods for tied survival times in Cox regression. Biometrics (53):1151-1156, 1997.

10. HISTORY TABLE

This is a revised TSAP including the following modifications to the final TSAP.

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	**12-Mar-15**	[redacted]	None	This is the final TSAP without any modification
Revised	**08-Dec-16**		All	Correction of spelling and grammar mistakes
			3	Explanation about different TSAPs to be used in this Phase II/III trial added
			[redacted]	[redacted]
			[redacted]	[redacted]
			4.3	Clarification that a REP of 30 days will be considered for safety analyses
			5	Revision of endpoints for the Phase II part according to CTP amendment 1 The definition and derivation of new endpoints has been added
			5.2.2.1	Clarification about eCRF data from follow-up page to be used to derive patients last day known to be alive Date of FVC assessment added to derive patient last known to be alive
			[redacted]	[redacted]
			6.3	The monotherapy set added for safety analyses during the monotherapy phase
			[redacted]	[redacted]
			6.6	Clarification that date patient last known to be alive will not be used for derivation of date of discontinuation of last study medication
			6.7	Derivation of baseline for randomised but not treated patients was added
			7	Revision of the endpoints for the Phase II part as introduced by CTP amendment 1 The definition and derivation of new endpoints has been added
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
				[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted] with these AEs have been observed.
			7.8.1	AE analyses separated for the combination and the monotherapy phase have been added
			7.8.2	Correction of definition of last laboratory value for analyses
			7.8.2	Correction of analysing patients with a CTCAE lab value of -1
			7.8.2	Clarification how patients without baseline laboratory value will be treated for analyses of possible clinically significant
			7.8.2	Correcting for missing laboratory value urine protein
			7.8.2	Conversion of urine measurements based on dipstick added
			7.8.2	Analyses with regard to neutrophil haemoglobin and platelet count added
			8	Additional reference added