Trial Statistical Analysis Plan

c03766311-01

BI Trial No.:	1199.229
Title:	Investigation of drug-drug interaction between nintedanib and pirfenidone in patients with IPF (an open label, multiple-dose, two group study) Including Amendments 1, 2 & 3 [c03463451-08]
Investigational Product:	Ofev®, nintedanib
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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis data set
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last measured time point
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma over a dosing interval
BI	Boehringer Ingelheim
bid	Bis in die (twice daily dosing)
RPM	Report planning meeting
BSA	Body surface area
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state
CRF	Case Report Form
CT	Concomitant therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Coefficient of variation
DBL(M)	Data Base Lock (Meeting)
DLCO	Diffusing capacity of the Lung for Carbon monoxide
ECG	Electrocardiogram
EMA	European Medicines Agency
EoT	End-of-Text
FU	Follow-up
gCV	Geometric coefficient of variation
gMean	Geometric mean

Term	Definition / description
ICH	International Conference on Harmonisation
IPF	Idiopathic Pulmonary Fibrosis
(I)PV	(Important) Protocol violation
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MQRM	Medical Quality Review Meeting
NA	Not applicable
PK	Pharmacokinetics
PKS	Pharmacokinetic analysis set
PN	Preferred Name
PT	Preferred term
qd	Quaque die (everydDay)
RNA	Ribonucleic acid
SAS	Statistical analyses software
SD	Standard deviation
SOC	System organ class
SSC	Special Search Categories
tid	Ter in die (3 times a day)
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

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.

SAS® Version 9.4 or later version will be used for all analyses.

Pharmacokinetic (PK) parameters will be calculated using WinNonlin™ software (professional Network version 6.3, Pharsight Corporation, Mountain View, CA 94041-1530, USA).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in this TSAP are in accordance with the statistical methods described in the CTP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

The primary endpoints will be used as defined in Section 5.1.1 of the CTP as pharmacokinetic endpoints:

- Group 1
  - $AUC_{0\text{-}tz}$ area under the concentration-time curve of **nintedanib** in plasma over the time interval from 0 to the last measured time point (quantifiable concentration)
  - C_{max} maximum measured concentration of **nintedanib** in plasma after single dose administration
- Group 2
  - $AUC_{\tau,ss}$ area under the concentration-time curve of **pirfenidone** in plasma over a dosing interval
  - $C_{max,ss}$ maximum measured concentration of **pirfenidone** in plasma at steady state

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoint has been specified in the protocol.

5.2.2 Secondary endpoints

Secondary endpoints will be used as defined in Section 5.1.2 of the CTP as pharmacokinetic endpoints:

- Group 1
  - $AUC_{0\text{-}\infty}$ area under the concentration-time curve of **nintedanib** in plasma over the time interval from 0 extrapolated to infinity

5.3 FURTHER ENDPOINTS

[redacted]

5.4 OTHER VARIABLES

5.4.1 Demographics and other baseline characteristics

Demographics and other baseline characteristics will include the following. Baseline is defined in Section 6.7.

5.4.1.1 Demographic data

- Gender
- Ethnicity
- Race
- Age [years] will be calculated as : integer part of [(date of informed consent - date of birth) / 365.25]
- Age by category [years] (<65; ≥65-<75; ≥75 and <65; ≥65-<75; ≥75-<85; ≥85)
- Weight [kg] as continuous variable and by category (<30; ≥30 - <60; ≥60 - <90; ≥90)
- Height [cm]
- Body mass index [kg/m^2]: Weight[kg] / Height [m]*Height[m], as continuous variable and by category (< 18.5; ≥18.5-<25; ≥25-<30, ≥30)
- Body surface area [m^2] (according to Dubois Formula : BSA = 0.007184 * Height[cm]0.725 * Weight[kg]0.425), as continuous variable and by category (<1.73; ≥1.73)

5.4.1.2 Trial indication

- Time elapsed since the first diagnosis of IPF [years] will be calculated as : (date of entry – date of first diagnosis)/365.25
- Time elapsed since the first diagnosis of IPF coded by category (≤ 1 year; > 1 year to ≤ 3 years; > 3 years to ≤ 5 years; > 5 years)

5.4.1.3 Smoking status

- Smoking history (never smoked, ex-smoker, currently smokes)

5.4.1.4 Other baseline characteristics

- Diffusing capacity of the Lung for Carbon monoxide (DLCO) [% predicted] corrected for haemoglobin by the site

5.4.2 Treatment exposure

Treatment exposure will be calculated separately for nintedanib and for pirfenidone.

Time on drug [days] = date of last administration – date of first administration +1 day

Time on actual drug (150 mg bid for nintedanib; 267 or 534 or 801 mg tid for pirfenidone) [days]: sum of time on-treatment for each dose effectively taken

For group 1, time on drug for pirfenidone whatever the dose is will be displayed.

For group 2, time on drug for nintedanib 150 mg bid will be displayed as well as time on drug for pirfenidone whatever the dose is.

Total dose [mg]: Time on actual drug [days] * actual dose [mg]

For pirfenidone, dose reductions are defined as decreases to either 2*267mg tid or 1*267mg tid.

5.4.3 Treatment compliance

Compliance for nintedanib (group 2 only) and compliance for pirfenidone will be calculated separately over the study as:

$$\text{Compliance [\%]} = \frac{\text{Number of capsules actually taken over the period}}{\text{Number of capsules which should have been taken over the period}} \times 100$$

The number of capsules which should have been taken over the period will be calculated as:

Number of capsules which should have been taken over the period [capsules] = (date of last administration – date of first administration + 1) [days] × (number of capsules which should be taken per day) [1]

[1] The time of first/ last administration are taken into account, so fewer capsules may be expected to be taken on some days.

For nintedanib, the number of capsules which should be taken per day at dose 150 mg qd is 1. The number of capsules which should be taken per day at dose 150 mg bid is 2.

For pirfenidone, the number of capsules which should be taken per day is 3 at dose 267 mg tid, 6 at dose 534 mg tid, and 9 at dose 801 mg tid.

Only treatment interruptions not due to AE will be considered a compliance issue and will be taken into account in the calculation (duration of interruptions due to AE will be subtracted from the duration of the study period).

Compliance will be categorised as follow: <50%, >=50% to <80%, >=80% to <= 120%, > 120%.

5.4.4 Liver enzyme and bilirubin elevations

Liver enzyme and bilirubin elevations will be reported using the two following definitions:

- (ALT ≥ 3xULN and/or AST ≥ 3xULN) AND bilirubin ≥ 2xULN (1)
- ALT ≥ 5xULN and/or AST ≥5xULN

These elevations are defined within a time window of 30 days i.e. the elevation of bilirubin should appear within 30 days of the elevation of AST and/or ALT. Potential Hy's law cases, using the definition (1) above, will be presented using graphs.

Depending on the number of patients experiencing liver enzyme elevations, other cut-offs may be considered.

Maximum individual elevations based on worst value on treatment will be defined as:

- ≥3*ULN; ≥5*ULN; ≥8*ULN for AST and ALT
- ≥1.5*ULN; ≥2*ULN for Bilirubin
- ≥1.5*ULN; ≥2*ULN for alkaline phosphatase
- ≥1*ULN; ≥3*ULN for Gamma-Glutamyl-Transferase

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For treatment specifications, see Section 4 of CTP.

The following trial periods will be defined: screening, post-entry, treatment period, off-treatment, Residual Effect Period, follow-up and post-study as follows:

Note: the last day of each of the following periods is excluded.

- **Screening**: from informed consent to date of entry
- **Post-entry** (if applicable): from entry to first trial drug intake.
- **Treatment period:** from first trial drug intake (or re-start of treatment if interruption) to last trial drug intake (or the day before start date of interruption, if interruption) plus one day
- **Off-treatment** (if applicable): from start date of interruption to re-start of treatment
- **Residual Effect Period**: from the last trial drug intake plus one day to last trial drug intake plus 28 days plus one day.
- **Follow-up** (if applicable): from last trial drug intake plus 29 days up to the beginning of post-study period. This period is only created if last trial drug intake took place more than 28 days before trial completion (i.e. date of the follow-up visit or date where the patient discontinued prematurely the trial).
- **Post-study**: from the latest of last trial drug intake plus 29 days or date of trial completion plus 1 day to database lock

For safety analyses, data up to 28 days after last trial drug intake (inclusive) will be considered on-treatment.

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table defines the different categories of important PVs. The final column describes which PVs will be used to exclude patients from the PKS. If the data show other important PVs, this table will be supplemented accordingly by the time of the MQRM/RPM/DBLM.

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from
A		**Entrance criteria not met**		
	A1	Inclusion criteria not met	Inclusion criteria 2 to 6 Automatic IPV	None
	A2	Exclusion criteria met	Exclusion criteria 1 to 21 Automatic IPV and Medical review of MQRM listings	None
B		**Informed consent**		
	B1	Informed consent not given or given too late	Inclusion criteria 1 Automatic IPV	None
	B2	Informed consent not given for pharmacogenetics samples (unspecified part) but pharmacogenetics test done	According to pharmacogenetics database and CRF Automatic IPV	None
	B3	Informed consent not given for [redacted] but [redacted] test done	According to [redacted] and CRF Automatic IPV	None
C		**Trial medication and randomisation**		
	C1	Incorrect trial medication taken	Manual IPV (see monitoring manual) and Medical review of MQRM listings	None
	C2	Drug not permanently discontinued despite criteria of Section 3.8.1 of CTP met	Medical review of MQRM listings	None
D		**Concomitant medication**		
	D1	Patient received restricted concomitant therapies during treatment phase	Medical review of MQRM listings.	PKS
E		**Missing data**		
	E4	Certain violations of procedures used to measure primary data	Medical review of MQRM listings, to be decided no later than RPM.	PKS
F		**Incorrect timing**		
	F5	Certain violations of time schedule used to measure primary data[1].	Medical review of MQRM listings, to be decided no later than RPM.	PKS

[1] Time deviations will only be flagged as important PV, when leading to exclusion of the entire subject from an analysis set
Source: BI reference document "Protocol Violation Handling Definitions" (001-MCS-50-413_RD-01) (1)

6.3 PATIENT SETS ANALYSED

- **Screened set**
  This patient set includes all patients having signed informed consent and performed visit 1.

- **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 investigational treatment.

- **Pharmacokinetic analysis set (PKS)**
  The PKS will be used as defined in section 7.3 of the CTP.

The following table shows which patient set will be used for which study period and which class of endpoints.

Table 6.3: 1 Patient sets analysed

	Patient set		
Class of endpoint	Screened set	TS	PKS
Primary endpoint			X
Secondary endpoints			X
Further endpoints			X
Safety analyses		X	
Demographic/baseline characteristics / extent of exposure	X	X	

Note that the number of patients with available data for an endpoint may differ.

6.4 SUBGROUPS

This section is not applicable.

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

The endpoints will be used as defined in Section 7.5 of the CTP.

Data of treated subjects who failed to complete all stages of the study (subjects who withdraw consent or are removed from the trial) will be reported as far as data are available. It is not planned to impute missing values.

For previous/concomitant therapies, in case of (partially) missing start and end dates of concomitant therapies, the dates will be imputed so that the extent of exposure to the concomitant therapy is maximal, i.e. the first day (month) of the month (year) for incomplete start dates and the last day (month) of the month (year) for incomplete end dates.

Missing or incomplete AE dates will be imputed according to BI standards (see "Handling of missing and incomplete AE dates") (3).

Handling of missing PK data will be performed according to the BI standard procedure "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (001-MCS-36-472_RD-01) (2).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

As a general rule, last assessment before first trial drug intake (included) will be used as baseline. If the baseline value is missing and the screening value is available, then the baseline value will be defined as the screening value taken closest to baseline date.

A windowing will be performed as described in Tables 6.7: 1, 6.7: 2, 6.7: 3 and 6.7: 4, in order to assign data to the relevant study visit based on the actual day of the assessment. Data will be analysed using the re-calculated visits in the statistical tables. However, in the listings, all visits performed will be displayed (even if outside time-window), along with the re-calculated visit.

Table 6.7: 1 Time windowing rules for physical examination, vital signs - Group 1

Time window of actual day [1]			Allocated to		
Start day	End day (included)	Length of the time-window [days]	Visit number	Visit name	Planned day of the visit
1	1	1	1, or 2[2]	Baseline	1
2	29	28	3	3 weeks	23
30	Last treatment intake + 27 [3]	variable	NA	Between 3 weeks - FU	NA
Last treatment intake + 28	Last treatment intake + 31	4	4	Follow-up	52

[1] First trial drug intake date is taken into account as a reference to calculate time windows
[2] Depending on the last assessment before first trial drug intake (included), refer to Section 6.7 for baseline definition
[3] This period only exists if last treatment intake occurs after 2 days (later than 28 days before 30 days)

Table 6.7: 2 Time windowing rules for physical examination, vital signs - Group 2

Time window of actual day [1]			Allocated to		
Start day	End day (included)	Length of the time-window [days]	Visit number	Visit name	Planned day of the visit
1	1	1	1, or 2[2]	Baseline	1
2	12	11	3a	1 week	8
13	19	7	3b	2 weeks	16
20	Last treatment intake + 27 [3]	variable	NA	Between 2 weeks - FU	NA
Last treatment intake + 28	Last treatment intake + 31	4	4	Follow-up	44

[1] First trial drug intake date is taken into account as a reference to calculate time windows
[2] Depending on the last assessment before first trial drug intake (included), refer to Section 6.7 for baseline definition
[3] This period only exists if last treatment intake occurs after 6 days (later than 28 days before 20 days)

Table 6.7: 3 Time windowing rules for laboratory measurements – Group 1

Time window of actual day [1]			Allocated to		
Start day	End day (included)	Length of the time-window [days]	Visit number	Visit name	Planned day of the visit
1	1	1	1	Baseline	1
2	38	37	3	3 weeks	23
39	No upper limit	NA	4	Follow-up	52

[1] First trial drug intake date is taken into account as a reference to calculate time windows

Table 6.7: 4 Time windowing rules for laboratory measurements – Group 2

Time window of actual day [1]			Allocated to		
Start day	End day (included)	Length of the time-window [days]	Visit number	Visit name	Planned day of the visit
1	1	1	1	Baseline	1
2	12	11	3a	1 week	8
13	30	18	3b	2 weeks	16
31	No upper limit	NA	4	Follow-up	44

[1] First trial drug intake date is taken into account as a reference to calculate time windows

If after windowing of visits at baseline, two values fall within the same baseline interval, then the last value will be taken into account. If after windowing of post-baseline visits, two visits fall in the same interval, then the measurement closest to the planned visit will be taken into account. In case two measurements are equidistant from the planned visit, then the last one will be picked. The same rules will be applied for laboratory measurements.

For physical examination and vital signs only, if after windowing of post-baseline visits, two values fall within the same interval “Follow-up” then only the first value will be taken into account.

7. PLANNED ANALYSIS

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

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 group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to the nearest integer. The category missing will be displayed only if there are actually missing values.

For PK analysis, continuous data will be summarised by the following statistics: N/ gMean / gCV / Mean / CV / SD / Min / 10^{th} percentile / 25^{th} percentile / Median / 75^{th} percentile / 90^{th} percentile / Max.

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.

7.2.1 Baseline conditions

A summary of baseline conditions will be provided by group, System Organ Class (SOC) and Preferred Term (PT). SOC will be sorted according to the standard sort order specified by EMA and PT by descending frequency over both groups.

7.2.2 Concomitant therapies

Concomitant therapies will be described over several study periods:

Previous therapies will be defined as treatments with an end date before first trial drug intake.

Baseline therapies will be defined as treatments with a start date before first trial drug intake and a stop date after or on the day of the first trial drug intake.

On-treatment concomitant therapies are defined as treatments with a start date after or on the day of first trial drug intake and before or on the day of last drug intake.

The following concomitant therapies categories have been created:

- Previous concomitant therapies
- Baseline concomitant therapies
- All on-treatment concomitant therapies (including baseline CTs)

Summaries of the CT categories will be provided by treatment group, ATC3 codes and Preferred Name (PN) (sorted by alphabetical ATC class and decreasing frequency of preferred names in group 1 within ATC class).

Relevant groups of therapies have been defined as Special Search Categories (SSC). These are listed in Section 9.2.

Summaries of baseline CTs and all on-treatment CTs (including baseline CTs) will also be performed by SSC and PN (sorted by alphabetical SSC and decreasing frequency of preferred names within SSC).

Finally, a specific table for all on-treatment concomitant therapies (including baseline CTs) that were restricted during the study will be provided (by PN).

Treatments that were restricted during the treatment period and that will be presented in this specific table are described in section 4.2.2.1 of the CTP.

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINTS

The analysis will be performed as defined in Section 7.3.1 of the CTP.

Table 7.4: 1: Primary and secondary endpoints for inferential PK analysis

Treatment group	Analyte	Parameter	Test treatment (T)	Reference treatment (R)
Group 1	Nintedanib	$AUC_{0\text{-}tz}$, C_{max}, $AUC_{0\text{-}\infty}$	Nintedanib + Pirfenidone	Nintedanib alone
Group 2	Pirfenidone	$AUC_{\tau,ss}$, $C_{max,ss}$	Pirfenidone + Nintedanib	Pirfenidone alone

The inferential statistical analysis of the endpoints above will be performed by use of the macro XPKISTAT and the option BWU (Bioavailability/Bioequivalence, within-subject design, uncontrolled for time). The SAS code is done in Section 9.1.

Descriptive statistics of plasma concentrations and PK endpoints will be done by the department of Translational Medicine and Clin. Pharmacology at BI and will be presented in Section 15.6 of the CTR.

The analysis of PK parameters, as well as the tables and graphs for the pharmacokinetic non-compartmental analyses will follow specific definitions of this TSAP or, otherwise, the BI standard procedure "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics" (001-MCS-36-472) (7).

Exclusion of PK parameters

The analysis data set (ADS) PK6+ contains column variables KPEXC and KPEXCX indicating inclusion/exclusion (KPEXC) of a PK parameter and an analysis flag comment (KPEXCX). All analyses based on the PKS will include parameters if they are not flagged for exclusion, that is KPEXC is equal to “Included”.

Exclusion of PK concentrations

The ADS PK4+ (PK concentrations per time-point) contains column variables PKEXC or PKEXCX indicating inclusion/exclusion (PKEXC) of a concentration and an analysis flag comment (PKEXCX). Exclusion of a concentration depends on the analysis flag comment PKEXCX. For example, if PKEXCX is set to ‘ALL CALC’, the value will be excluded for all types of analyses based on concentrations. If PKEXCX is set to ‘DESC STATS’, the value will be excluded from descriptive evaluations per planned time point/ time interval. If PKEXCX contains the addition ‘TIME VIOLATION’ or ‘TIME DEVIATION’, the value can be used for further analyses based on actual times. If PKEXCX is set to ‘HALF LIFE’, the value will be excluded from half-life calculation only; the value is included for all other analyses.

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (001-MCS-36-472_RD-01) (2) and "Description of Analytical Transfer Files and PK/PD Data Files" (001-MCS-36-472_RD-03) (8).

7.5 SECONDARY AND FURTHER ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary endpoints

The analysis will be performed as defined in Section 7.3.2 of the CTP and as described above for primary endpoints.

Descriptive statistics of plasma concentrations and PK endpoints will be done by the department of Translational Medicine and Clin. Pharmacology at BI and will be presented in Section 15.6 of the CTR.

7.6 FURTHER ENDPOINTS

7.7 EXTENT OF EXPOSURE

A table displaying the disposition of patients and the conclusion of patients' participation, and a table displaying the primary reason for non-inclusion/entry will be provided.

Summary tables showing the duration on treatment, the total dose of nintedanib and pirfenidone and the duration on actual treatment dose (see Section 5.4.2) will be performed for nintedanib and for pirfenidone on the TS.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

7.8.1 Adverse events

Unless otherwise specified, the analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

Furthermore, for analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

For further details on summarization of AE data, please refer to the guidelines "Handling of missing and incomplete AE dates" (3) and "Analysis and presentation of adverse event data from clinical trials" (4).

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake till 28 days after last drug intake (inclusive) will be assigned to the treatment. All adverse events occurring before first drug intake will be assigned to 'screening' and all adverse events occurring after last drug intake + 28 days will be assigned to 'post-treatment', 'follow-up' or 'post-study' (for listings only). Also, all AEs occurring between the start of an interruption and the end of interruption will be assigned to 'off-treatment' period in the listings. For details on the treatment definition, see Section 6.1.

According to ICH E3 (5), AEs classified as 'other significant' will include those non-serious and non-significant adverse events with
(i) 'action taken = discontinuation' or 'action taken = reduced', or

(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Report Planning Meeting.

An overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarised by treatment group, primary system organ class and preferred term (mention MedDRA levels to be displayed in the tables). Separate tables will be provided for

- patients with serious adverse events
- patients with other significant adverse events according to ICH E3 (5)
- patients with investigator defined drug related adverse events
- patients with adverse events of special interest
- patients with adverse events leading to permanent dose reduction of pirfenidone
- patients with adverse events leading to premature discontinuation from nintedanib or pirfenidone
- for patients with adverse events leading to death

The system organ classes will be sorted according to the standard sort order specified by EMA, preferred terms will be sorted by frequency in group 2 (within system organ class).

Specific tables will be created in order to describe the adverse events of particular note diarrhea, nausea and vomiting:

- Summary of adverse events including number and duration of episodes

- Summary of adverse events including seriousness, clinical consequences (dose reduction, drug discontinuation or drug interruption) , intensity, drug relationship and outcome

Specific tables will be created to summarise the diarrhea and bleeding specific items of the CRF.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (6).

Please refer to Section 7.3.4 of the CTP.

Specific tables will be presented to describe liver enzyme elevations as defined in Section 5.4.4:

- Summary table of liver enzyme elevation including number of patients with liver enzyme elevation
- Summary table of individual maximum liver enzyme and bilirubin elevations

7.8.3 Vital signs

Only descriptive statistics (by visit and change from baseline) are planned for this section of the report.

7.8.4 ECG

Not applicable, relevant ECG findings are recorded as baseline condition or AEs.

7.8.5 Others

Not applicable, relevant physical examinations and spirometry findings are recorded as baseline condition or AEs.

8. REFERENCES

R08-2251 European Medicines Agency (EMEA). ICH topic E 9: statistical principles for clinical trials: step 5: note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96). London: EMEA 1998

1 *001-MCS-50-413_RD-01*: "Protocol Violation Handling Definitions", current version, IDEA for CON.

2 *001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version, IDEA for CON.

3 *001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version, IDEA for CON.

4 *001-MCG-156_RD-02:* "Analysis and presentation of adverse event data from clinical trials", current version, IDEA for CON.

5 *CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version.

6 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

7 *001-MCS-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, IDEA for CON.

8 *001-MCS-36-472_RD-03*: "Description of Analytical Transfer Files and PK/PD Data Files", current version, IDEA for CON.

[redacted]

9.1 STATISTICAL ANALYSES SOFTWARE (SAS) CODE FOR PK ANALYSES

Model for inferential analysis on PK endpoints

For the primary and secondary PK endpoints, inferential analyses will use. The XPKISTAT macro will be used for the analyses. The following parameters will have to be used:

```
%xpkistat  (design = bwu,
            disptab = #DISP = BAGM,
            rage = YES,
            dispnum = ,        /* output number or prefix */
            runtype = report,
            listlog = YES,
            smatrix = 'plasma EDTA',
            sanalyte = 'BIBF 1120 BS', /*PIRFENIDONE*/
            skpnm = 'AUClast'
               /* 'Cmax' 'AUCINF_pred' 'AUC_TAU_ss' or 'Cmax_ss' */
            spairtrt = ,
              /* nintedanib + pirfenidone / nintedanib alone =>for group 1
               pirfenidone + nintedanib / pirfenidone alone =>for group 2*/
            anaset = 'PKS',
            limitp = no
            );
```

The SAS model behind is the following:

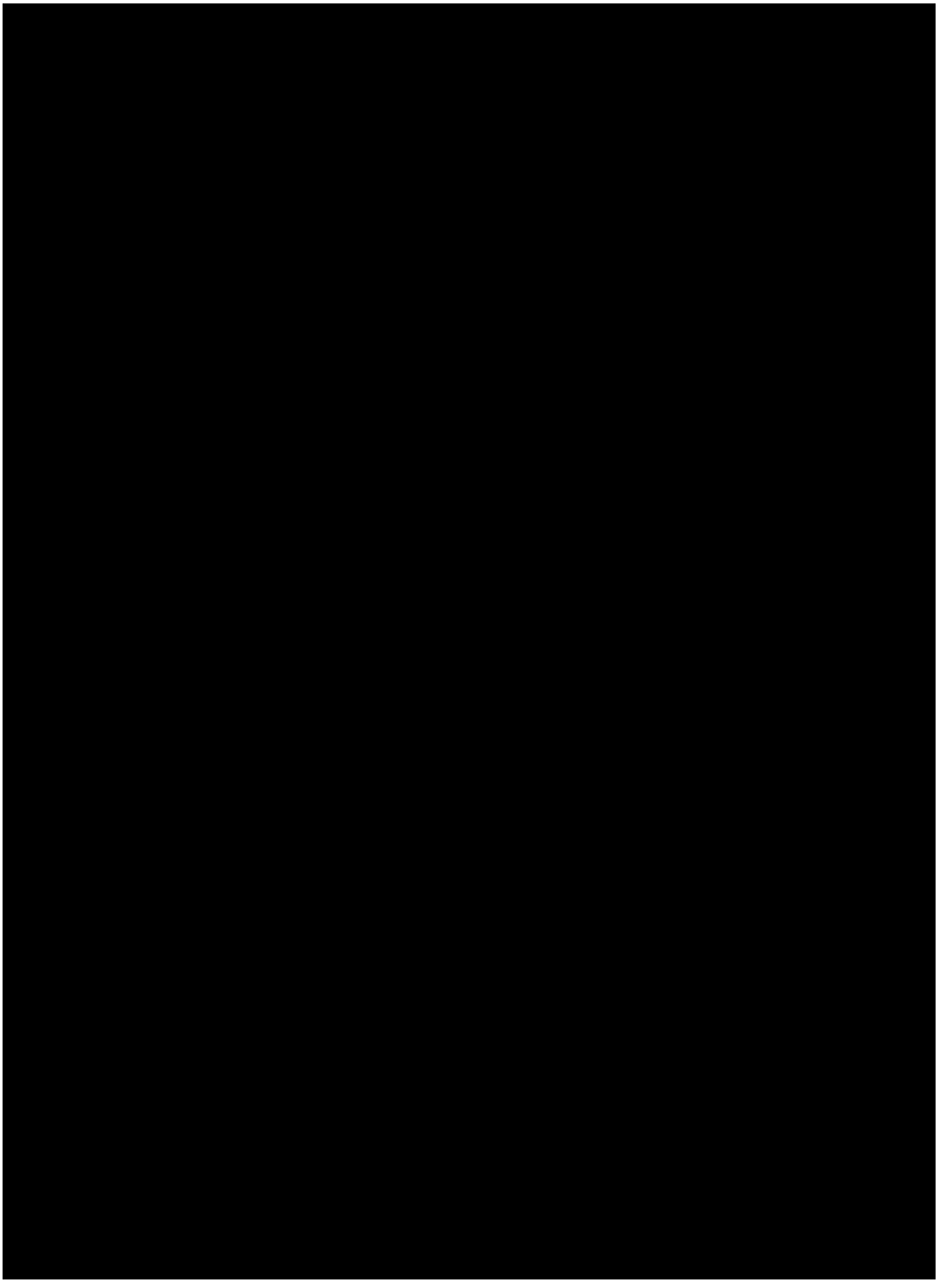
```
PROC MIXED;
      CLASS ptno pktrt;
      MODEL <PKendpoint> = pktrt / HTYPE=2 SOLUTION;
      RANDOM ptno;
RUN;
```

Where

- ptno = unique number of the subject
- pktrt = treatment ie nintedanib alone or nintedanib + pirfenidone for patients in group 1 and pirfenidone alone or pirfenidone + nintedanib for patients in group 2
- <PKendpoint> = $AUC_{0\text{-}tz}$, C_{max} and $AUC_{0\text{-}\infty}$ for group 1 and $AUC_{\tau,ss}$ and $C_{max,ss}$ for group 2

For sensitivity analysis, the SAS model is the following:

```
PROC MIXED;
      CLASS ptno pktrt;
      MODEL <PKendpoint> = pktrt ptno / HTYPE=2 SOLUTION;
RUN;
```



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	**09-Mar-17**	[redacted]	None	This is the final TSAP without any modification