TRIAL STATISTICAL ANALYSIS PLAN c15128276-02

BI Trial No.:	1386-0004
Title:	A multi-centre, double-blind, parallel-group, randomised, placebo controlled phase II a study to investigate safety, tolerability, pharmacodynamics, and pharmacokinetics of different doses of orally administered BI 1467335 during a 12-week treatment period compared to placebo in patients with clinical evidence of NASH. Including Protocol Amendment 1 [c08980589-01], amendment 2 [c08980589-03-02], amendment 3 [c08980589-03], amendment 4 [c08980589-04]
Investigational Product(s):	BI 1467335
Responsible trial statistician(s):	Phone: Fax:
Date of statistical analysis plan:	10 AUG SIGNED
Version:	FINAL

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2. LIST OF ABBREVIATIONS

Term	Definition / description
γ-GT	Gamma-Glutamyltransferase
AE	Adverse event
ALT	Alanine Aminotransferase
AOC3	Amine oxidase copper-containing 3
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
BP	Blood pressure
BRPM	Blinded report planning meeting
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV [%]	Arithmetic coefficient of variation in %
DBLM	Data base lock meeting
DBP	Diastolic blood pressure
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DRA	Drug Regulatory Affairs
DMG	Dictionary Maintenance Group
ECG	Electrocardiogram
ECGS	ECG analysis set
ELF	Enhanced Liver Fibrosis
EMEA	European Agency for the Evaluation of Medicinal Products
FAS	Full Analysis Set
HDL	High Density Lipoprotein
HR [beats/min]	Heart rate in beats per minute

Term	Definition / description
HV	Healthy volunteer
ICH	International Conference on Harmonisation
IPV	Important Protocol Violation
LDL	Low Density Lipoprotein
MCPMod	Multiple Comparison Procedure Modelling
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effect Model Repeated Measurement
MQRM	Medical Quality Review Meeting
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PK	Pharmacokinetics
PKECGS	PK ECG set
PPS	Per protocol set
PR interval	ECG interval from the onset of P wave to the beginning of the QRS
PSTAT	Project Statistician
PT	Preferred term
PV	Protocol violation
QD	quaque die (once a day)
QRS complex	Combination of the Q, R, and S waves
QT interval	ECG interval from the beginning of the QRS complex to the end of the T wave
QTcB [msec]	QT interval, heart rate corrected according to Bazetts formula
QTcF [msec]	QT interval, heart rate corrected according to Fridericias formula
QTcN [msec]	QT interval, heart rate corrected according to study population formula
REP	Residual effect period
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
RPM	Report Planning Meeting

Term	Definition / description
RS	Randomised set
SA	Statistical analysis
SBP	Systolic blood pressure
SD	Standard deviation
SMQ	Standardised MedDRA query
SOC	System organ class
TCM	Trial Clinical Monitor
ToC	Table of contents
TMW	Trial Medical Writer
TS	Treated set
TSAP	Trial statistical analysis plan

3. INTRODUCTION

As per ICH E9 (1), 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, randomisation.

Study data will be stored in a trial database within the medidata RAVE (BRAVE) system.

The statistical analyses will be performed within the validated working environment CARE (Clinical data Analysis and Reporting Environment), including SAS_{TM} (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SAS_{TM}-based tools (e.g., macros for the analyses of adverse event (AE) data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the clinical trial report (CTR) appendices). R version 3.3.2 or later with “DoseFinding” package [R15-2001] will be used for analysis based on MCPMod.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

No changes to the planned analysis according to the CTP have been made.

5. ENDPOINTS

General remarks with regard to naming convention and its derivation:

- Absolute value: $X_{on-treatment}$ or $X_{baseline}$
- Absolute change from baseline: $X_{on-treatment} - X_{baseline}$
- Change from baseline in %: $\frac{X_{on-treatment} - X_{baseline}}{X_{baseline}} * 100$
- Relative to baseline in %: $\frac{X_{on-treatment}}{X_{baseline}} * 100$

5.1 PRIMARY ENDPOINT

CTP Section 5.1.1:
The primary endpoint is the plasma amine oxidase copper-containing 3 (AOC3) activity relative to baseline in %, 24 h post dose, after 12 weeks of treatment. The baseline is defined as the last AOC3 activity measurement prior to administration of any randomised study medication.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

There are no key secondary endpoints in this trial.

5.2.2 Secondary endpoints

CTP Section 5.1.2:
Safety and tolerability will be assessed based on the number (%) of subjects with adverse reactions[displayed as drug-related adverse events].

The secondary biomarker endpoints will be assessed based on the

- *relative ALT change from baseline after 12 weeks of treatment*
- *relative AST change from baseline after 12 weeks of treatment*
- *relative AP change from baseline after 12 weeks of treatment*
- *relative γ-GT change from baseline after 12 weeks of treatment (GGT)*
- *relative caspase cleaved cytokeratin 18 (M30) change from baseline after 12 weeks of treatment (CK-18 Caspase)*
- *relative total cytokeratin 18 (M65) change from baseline after 12 weeks of treatment (CK-18 Total)*

The relative change from baseline in % will be described as “relative to baseline in %” or in short as “R2Base %”.

5.3.2 Safety endpoints

12-lead ECG endpoints

For the definition of baseline and a summary of time points please refer to Section 6.7.

Quantitative ECG endpoints:

The following quantitative ECG endpoints will be determined for the ECG variables QTcF, QT, HR, PR, QRS, RR and QTcB derived as described in Additional Section 9.1:

- absolute values (per time point)
- changes from baseline (per time point)
- percent changes from baseline (per time point; for HR, PR, QRS)

Categorical ECG endpoints

The following categorical ECG endpoints will be determined based on the quantitative ECG endpoints:

- New onset (meaning that this or a higher category was not present any time at baseline) of maximum QTcF interval > 450 to 480 msec, > 480 to 500 msec, or > 500 msec on treatment. For assignment of a particular patient to one of the above categories, all time points on-treatment (refer to Table 6.7: 1) will be considered.
- Maximum change from baseline in QT interval ≤ 60 msec, or > 60 msec on treatment
- Maximum change from baseline in QTcF interval ≤ 30 msec, > 30 to ≤ 60 msec, or > 60 msec on treatment

The occurrence of any of the following will be viewed as “notable findings”:

- New onset (not present any time at baseline) of uncorrected QT interval > 500 msec at any time on treatment

If baseline is missing, any occurrence of QT interval > 500 msec at any time on treatment will be a notable finding

- New onset of QTcF interval > 500 msec at any time on treatment
  If baseline is missing, any occurrence of QTcF interval > 500 msec at any time on treatment will be a notable finding
- Increase in QTcF interval from baseline by > 60 msec at any time on treatment
- Increase in HR from baseline by ≥ 25%, when corresponding on-treatment value of HR is > 100 bpm, or decrease in HR by ≥ 25%, when corresponding on-treatment value of HR is < 50 bpm, at any time on treatment
- Increase in the PR interval from baseline by ≥ 25%, when corresponding on-treatment value of PR interval is > 200 msec, at any time on treatment
- Increase in the QRS complex from baseline by ≥ 10%, when corresponding on-treatment value of QRS complex is > 110 msec, at any time on treatment

Categorical endpoints will also include morphological (i.e. qualitative) findings that might be attributable to treatment. In particular, new onset of findings not present at baseline with regard to e.g. rhythm, conduction, ST segment changes, T and U wave abnormalities and myocardial infarction will be explored.

Vital signs and body weight

For the Vital Signs variables:

- Systolic blood pressure
- Diastolic blood pressure
- Pulse rate
- Respiratory rate

And the body weight variables:

- BMI
- Body weight
- Waist circumference
- Hip circumference
- Hip/Waist ratio

The following quantitative vital signs and body weight endpoints will be determined

- absolute values (per time point)
- changes from baseline (per time point)

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic trial information on treatments to be administered, assignment of a dose group, and selection of doses, see CTP Section 4.

Table 6.1: 1 Treatment descriptions

Long Name	Short Name
Placebo	Placebo
BI 1467335 1 mg QD	1 mg QD
BI 1467335 3 mg QD	3 mg QD
BI 1467335 6 mg QD	6 mg QD
BI 1467335 10 mg QD	10 mg QD

Patients will be analysed as randomised for safety and efficacy analyses.

Table 6.1: 2 Analysing periods (same for all treatment groups)

Analysing Treatment Period	Start time	Stop time
Screening	0:00 h on day of informed consent	first treatment administration
On-treatment	first treatment administration	Individual trial termination date

Displays of AEs, laboratory tests and vital signs will be presented separately for the following treatments during the "On-treatment" phase:

- Placebo
- BI 1467335 1 mg QD
- BI 1467335 3 mg QD
- BI 1467335 6 mg QD
- BI 1467335 10 mg QD

AEs:
Two types of AE displays will be provided in the report:

A) Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT only) of the CTR displays:

In these displays, the on-treatment phase will be analysed (labelled with the name of the study treatment (short name)). Screening period will not be included in this analysis.

B) Section 15.4 and Appendix 16.1.13.1.8 (except for ClinicalTrials.gov and EudraCT) of the CTR displays:

- Screening (labelled "**Screening**")
- On-treatment (labelled with the name of the study treatment (label with short name))

In Section 16.1.13.1.8 AE tables, the following totals will be provided in addition:

- a total over all active treatments during on-treatment ("**Total BI**")

Laboratory tests:
Laboratory values are displayed for

- Baseline
- On-treatment

Vital signs:
Vital signs and 12-lead ECG values are displayed for

- Baseline
- On-treatment

For more details refer to Section 6.7.

More details on the technical implementation of these analyses are provided in the Analysis Data Set Plan (ADS Plan) of this TSAP.

6.2 IMPORTANT PROTOCOL VIOLATIONS

A protocol violation (PV) is important if it affects the rights or safety of the study patients, or if it can potentially influence the primary outcome measurement(s) in a non-negligible way.

A list of important PVs (IPVs) is given in Table 6.2: 1. Important PVs will be reviewed at Medical Quality Review Meetings (MQRMs) conducted periodically during the trial. A list of protocol deviations will be discussed at the Blinded Report Planning Meetings (BRPMs).

If the data show other important PVs, this table will be supplemented accordingly at MQRMs or BRPMs or through team review of the manual PV log. The decision whether a patient will be excluded from the analysis will be made at the final BRPM prior to Database Lock (DBL).

Table 6.2: 1 Important protocol violations

Category / Code		Description	Comment	Excluded from
A	**Entrance criteria not met**			
A1	**Target indication not met**			
	A1.01	Clinical evidence of NASH	Inclusion criterion checked	PPS
A2	**Inclusion criteria not met**			

Table 6.2: 1 Important protocol violations (continued)

Category / Code		Description	Comment	Excluded from
	A2.01	ALT >1.5 ULN at screening and ALT >1.25 ULN in a local lab within 1 week to 3 months prior screening	Inclusion criterion checked	PPS
	A2.02	Age ≥ 18 and ≤75 years at screening	Inclusion criterion checked	None
	A2.03	BMI ≥25kg/m^2 and <45kg/m^2 at screening	Inclusion criterion checked	None
	A2.04	Stable body weight	Inclusion criterion checked	None
	A2.05	Stable concomitant medication (Antidiabetic, anti-obesity, Vitamine E)	Inclusion criterion checked	PPS
	A2.06	Stable concomitant medication (All other)	Inclusion criterion checked	None
	A2.07	For females: use of double barrier contraception	Inclusion criterion checked	None
A3	**Exclusion criteria met**			
	A3.01	Current or history of significant alcohol consumption	Exclusion criterion checked	PPS
	A3.02	Prior participation in an interventional NASH trial	Exclusion criterion checked	PPS
	A3.03	Prior or planned bariatric surgery	Exclusion criterion checked	PPS
	A3.04	Drugs associated with liver injury, hepatic steatosis or steatohepatitis prior screening	Exclusion criterion checked	PPS
	A3.05	History of liver cirrhosis or other forms of liver disease	Exclusion criterion checked	PPS
	A3.06	active infection	Exclusion criterion checked	None
	A3.07	Solid liver lesions other than haemangiomas	Exclusion criterion checked	PPS
	A3.08	eGFR <60ml/min/1.73m^2 at screening (or Renal insufficiency or renal impairment (assessed by eGFR))	Exclusion criterion checked	None
	A3.09	ALT >5.0 ULN at screening	Exclusion criterion checked	PPS
	A3.10	Platelet count < 150.000/µL	Exclusion criterion checked	PPS
	A3.11	Bilirubin level > 1.25xULN	Exclusion criterion checked	PPS
	A3.12	Uncontrolled diabetes	Exclusion criterion checked	PPS
	A3.13	Diagnosis of a serious or unstable disease	Exclusion criterion checked	PPS
	A3.14	Prior or planned major surgery	Exclusion criterion checked	PPS
	A3.15	Active, suspected or history of Malignancy	Exclusion criterion checked	None
	A3.16	Use of restricted medication	Exclusion criterion checked	PPS
	A3.17	Previous randomisation in this trial	Exclusion criterion checked	PPS
	A3.18	Currently enrolled in another investigational study	Exclusion criterion checked	PPS
	A3.19	Chronic drug abuse or any condition unsuitable for trial participation	Exclusion criterion checked	PPS
	A3.20	Pregnant, nursing or who plan to become pregnant women	Exclusion criterion checked	None
	A3.21	baseline QT issue or WPW syndrome	Exclusion criterion checked	None
	A3.22	Use of MAO-B inhibitors at screening or planned during study*	Exclusion criterion checked	PPS
	A3.23	Safety concerns by investigator opinion	Exclusion criterion checked	None
B	**Informed consent**			
	B1	Informed consent not available	Date or signatory missing	All

Table 6.2: 1 Important protocol violations (continued)

Category / Code		Description	Comment	Excluded from
	B2	Informed consent too late	Date of informed consent not obtained prior to any study related procedure	None
	B5	Informed consent obtained with error		None
C	**Trial medication and randomisation**			
C1	**Incorrect trial medication**			
	C1.01	No study medication taken	Patient randomised but no study medication taken	TS, FAS, PPS,
	C1.02	Incorrect trial medication taken	Wrong medication taken for more than 20% of the overall treatment duration or for more than 20% of the last visit interval before the primary endpoint assessment (different medication than the patient was randomised to taken i.e. drug kit recorded in eCRF from different treatment group than drug kit assigned by IVRS [automated check PV])	PPS
C3	**Non-compliance**			
	C3.01	Non-compliance with study drug intake	Overall study treatment compliance outside 80% and 120% (exclusive) or study treatment compliance below 80% in the last visit interval before primary endpoint assessment.	PPS
C4	**Medication code broken**			
	C4.01	Medication code broken at site without just cause	Medication code was broken for no valid reason. Final decision at the DBL meeting based on medical judgement	None Final decision at the DBL meeting.
D1	**Concomitant medication**			
	D1.01	Non stable concomitant medication during treatment (Amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens (excluding oral contraception), anabolic steroids, valproic acid, Pioglitazone and GLP1-Agonists as well as the initiation of insulin)	Review of eCRF for concomitant medication use. Final decision at the DBL meeting based on medical judgement.	PPS Final decision at the DBL meeting

Table 6.2: 1 Important protocol violations (continued)

Category / Code		Description	Comment	Excluded from
D2	**Prohibited medication use**			
	D2.01	Use of prohibited medication during treatment period	Review of eCRF for prohibited medication. Final decision at the DBL meeting based on medical judgement.	PPS Final decision at the DBL meeting.
E	**Missing data****			
	E1.01	No baseline biomarker value (for all of AOC3 activity, ALT, AST, AP, γ-GT, CK-18 caspase and CK-18 total)	No valid baseline biomarker value	FAS, PPS
	E1.02	No on-treatment biomarker value (for all of AOC3 activity, ALT, AST, AP, γ-GT, CK-18 caspase and CK-18 total)	No valid on-treatment biomarker value	FAS, PPS
G	**Trial specific**			
	G1.01	Too short treatment duration	at least 8 weeks on treatment	PPS
	G1.02	Pregnant female during trial		None

* Exclusion criteria was deleted in CTP Version 3 (16 March 2018).
**Further missing data beyond the explicitly described in E will not be considered as IPV.

The IPV category B5, D1 and D2 will be a manual IPV and need to be identified at a site level on the manual PV log. All remaining IPVs are programmed automatically.

6.3 PATIENT SETS ANALYSED

The following patient analysis sets are defined for this trial:

- Screened Set (SCR): includes all patients who signed informed consent.
- Randomised Set (RS): includes all patients who were screened for the trial and were randomised to trial treatment, regardless of whether any trial treatment was administered.
- Treated Set (TS): includes all patients who signed informed consent and were treated with at least one dose of the trial medication. The TS is used for safety analyses as well as demographics and baseline characteristics.
- Full Analysis Set (FAS): includes all patients in treated set who had non-missing baseline and at least one non-missing post-baseline and on-treatment measurement on any primary, secondary or further biomarker endpoint. Patients in FAS are analysed according to the intent-to-treat principle.
- Per Protocol Set (PPS): includes all patients from the FAS without IPVs leading to exclusion.
-

- ECG Set (ECGS): This patient set includes all patients in the TS who do not have artificial cardiac pacemakers and have at least one on-treatment value for at least one ECG endpoint, which is not excluded due to ECG relevant protocol violations. Relevant protocol violations may be e.g. the use of pro-arrhythmic medications. Exclusion of single ECG values due to relevant PVs is to be decided no later than in the BRPM before data base lock and will be documented in the CTR.
- ECG Pharmacokinetic Concentration Set (ECGPCS): This patient set includes all patients from the ECGS who provide at least one pair of a valid drug plasma concentration and a corresponding (i.e. time-matched) ECG endpoint on-treatment to be used in the exposure-response analysis. Since placebo patients will be included in the exposure response analyses with plasma concentrations set to 0, a plasma concentration BLQ is considered a valid drug plasma concentration for placebo patients. The decision about concentration value validity needs to be assessed within the Clinical Pharmacology group. The decision whether a time deviation between PK blood sampling and ECG recording is acceptable (and thus whether the pair of values will be used) is to be made no later than at the BRPM before data base lock.

Table 6.3: 1 Patient sets analysed

	Patient set					
Class of endpoint	SCR	TS	FAS	PPS	ECGS	ECGPCS
Primary and secondary endpoints				x		
Safety endpoints		x				
ECG endpoints					x	x**
Demographic/baseline endpoints		x				
Important protocol violations	x					
Disposition	x					

; ** only for exposure response analysis

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

Based on the different reasons of patients' data missing for different endpoints, various methods will be used to assess the impact of missing data on the efficacy endpoints of this trial, depending upon the type of the endpoint:

6.6.1 Definition of criteria for censoring

The new introduction or change of concomitant therapies can influence certain study endpoints of interest. To allow the assessment of the impact of such changes, specific efficacy endpoint values after changes of concomitant medication will be set to missing. I.e. there may be the case that there is a an IPV with regard to D1 or D2 which only leads to exclusion of certain measurements within a certain time frame, but not to exclusion of the patient from the analysis set. This will be decided and documented before DBL.

6.6.2 Endpoint specific handling of missing data

Primary endpoint:
Handling of missing AOC3 activity values is covered by using multiple imputation described in more detail in Section 7.3.1 of the CTP. Sensitivity analyses with other methods how to handle missing values are described in Section 7.4.2.

Secondary biomarker endpoints:
Missing values of the secondary biomarker endpoints are directly handled within the applied MMRM model based on the likelihood method under the "missing at random" assumption.

Safety endpoints and other variables:
As already described in the CTP Section 7.5 it is not planned to impute missing values. The only exceptions where imputation might be necessary for safety evaluation are AE dates.

Missing or incomplete AE dates are imputed according to BI standards (see 001-MCG-156_RD-01 (3)).

ECG variables:
If single cardiac cycles of an ECG (out of the three) are missing, the arithmetic mean for this single ECG will be computed with the reduced (1 or 2) number of cardiac cycles.

For the classification of the on-treatment QTc/QT intervals into 'no new onset' / 'new onset' categories, a missing value is obtained only in case that

i. all on-treatment values are missing and
ii. the baseline value is less than or equal to 500 msec, or missing.

If condition (i) is fulfilled but the baseline value is greater than 500 msec, this case will be categorized as 'no new onset'. If baseline is missing and the maximum on-treatment QTc interval is greater than 450 msec (or 500 msec for QT interval, respectively), this is classified as a 'new onset' in the respective category. If baseline is missing and the maximum QTc interval is less than or equal to 450 msec (or 500 msec for QT interval, respectively), this will be categorized as 'no new onset'. If baseline is missing, a QTc/QT interval > 500 msec at any time on treatment will be a notable finding.

For patients on active drug, missing plasma concentration values with 'BLQ' in the comment field will be replaced by ½ LLOQ.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Unless a different definition is provided below, baseline values are the last measurements taken prior to the first administration of trial treatment. If this value is not available, the measurement at the screening visit is used.

Centralized 12-lead ECG
There will be a centralised evaluation of all 12-lead ECG recordings at the time points specified in the Table 6.7: 1 below for the first of the three replicate ECGs at a single assessment time, except for baseline where triplicates are used. The baseline value of an ECG variable is then defined as the mean of the triple ECG measurements prior to drug administration:

Table 6.7: 1 Time schedule of 12-lead ECG recordings

Visit	**Planned Day**	**Planned time relative to drug administration [hh:mm]**	**Study phase**
1	Within -28 to-7 days before drug administration		Baseline
2	1	1.5	On-treatment
3	15	1.5	
4	29	1.5	
5	43	1.5	
6	57	1.5	
EOT/ ED	85	1.5	
FU	EOT+28	-	

For the exposure response analyses, pair of ECG variables and corresponding plasma concentrations will be built using the same planned time points, e.g. HR change from baseline and plasma sample taken at planned time 0:30 will build one pair. Whether a time deviation between PK sample and corresponding ECG extraction is too big and the pair has to be excluded or matched to another time point will be decided no later than at the BRPM/DBLM.

For quantitative analysis except exposure response analysis, data will be presented according to visit window described below.

Table 6.7: 2 Visit window for centralized ECG endpoints

		Interval Definition		
Visit	**Planned day**	**From day**	**To day**	**Visit description**
1	-28 to -7	-28	-1	Baseline
2	1	1	1	Day 1
3	15	2	22	Day 15 (week 2)
4	29	23	36	Day 29 (week 4)
5	43	37	50	Day 43 (week 6)
6	57	51	71	Day 57 (week 8)
EOT	85	72	Date of drug intake in EOT visit+1	Day 85 (week 12)
FU	113	Date of drug intake in EOT visit+2	Last assessment date	Day 113 (FU)

Primary endpoint:

Table 6.7: 3 Visit window for AOC3

		Interval Definition		
Visit	**Planned day**	**From day**	**To day**	**Visit description**
2	1	1	1	Baseline*
	1	1	7	Day 1*
3	15	8	22	Day 15 (week 2)
4	29	23	36	Day 29 (week 4)
5	43	37	50	Day 43 (week 6)
6	57	51	71	Day 57 (week 8)
EOT	85	72	Date of drug intake in EOT visit+1	Day 85 (week 12)
FU	113	Date of drug intake in EOT visit+2	Last assessment date	Day 113 (FU)

*before drug admin its baseline, afterwards its Day 1

In addition to the visit window, a time window for planned time should be used for AOC3 as defined in the table below.

Table 6.7: 4 Time window for AOC3

	Planned time		**Interval definition (in minutes after treatment administration in that visit)**	
Planned Day	**hour**	**minute**	**from**	**to**
1, 29	-0.5	-30	-150	0
	0.5	30	1	45
	1	60	46	90
	2	120	91	150
	3	180	151	270
	6	360	271	420
	8	480	421	540
15, 43, 57	-0.5	-30	-150	0
85	-0.5	-30	-150	0
	0.5	30	1	45
	1	60	46	90
	2	120	91	150
	3	180	151	270
	6	360	271	420
	8	480	421	960
	24	1440	961	1620
113*	672	40320	Sample taken on follow up visit	

* For follow-up visit time from treatment administration in EOT visit is considered.

Secondary biomarker endpoints:

Table 6.7: 5 Visit window for secondary and further biomarker endpoints*

		Interval Definition		
Visit	**Planned day**	**From day**	**To day**	**Visit description**
1	-28 to -7	NA	0	Screening
2	1	1	1	Baseline**
3	15	8	22	Day 15 (week 2)
4	29	23	36	Day 29 (week 4)
5	43	37	50	Day 43 (week 6)
6	57	51	71	Day 57 (week 8)
EOT	85	72	Date of drug intake in EOT visit +1	Day 85 (week 12)
FU	113	Date of drug intake in EOT visit +2	Last assessment date	Day 113 (FU)

*Measurements that are within some definition gaps will be assigned to the later window but will not be valid for the analysis of the window
**last value before drug admin is baseline, all previous measurements are called screening, when the measurement before first drug administration was done more than 8 weeks before first drug admin, this value will not be used as baseline.

For parameters which are not measured at each visit, still the defined windowing from Table 6.7:5 for the respective visit applies.

Safety endpoints including vital signs and lab parameters

Table 6.7: 6 Visit window for safety endpoints

		Interval Definition		
Visit	**Planned day**	**from**	**to**	**Visit description**
1	-28- -7	NA	0	Screening
2	1	1	1	Baseline*
3	15	2	22	Day 15 (week 2)
4	29	23	36	Day 29 (week 4)
5	43	37	50	Day 43 (week 6)
6	57	51	71	Day 57 (week 8)
EOT	85	72	Date of drug intake in EOT visit +14	Day 85 (week 12)
FU	113	Date of drug intake in EOT visit +15	Last assessment date	Day 113 (FU)

*last value before drug admin is baseline, all previous measurements are called screening, when the baseline measurement was done more than 8 weeks before first drug admin, this value will not be used anymore.

Screening visits will only be shown in listings. If there is no measurement at the baseline visit, the screening measurement which is closest to the drug administration will be taken.

Repeated and unscheduled efficacy measurements will be listed in SDL according to visit window described below. Only one observation per time window will be selected for analysis at an on-treatment visit.

For efficacy measurements, the value will be selected which is closest to the protocol planned visit day.

For safety analysis except vital signs, worst value will be selected for analysis in case of multiple values within one visit window (see guidance for Handling, Display and Analysis of Laboratory Data (6)). For vital signs measurements, the value will be selected which is closest to the protocol planned visit day.

7. PLANNED ANALYSIS

In general the display format of the analysis results follows BI guideline and standards as much as possible.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

Biomarker and safety lab values will show in addition Q1 (25th percentile) and Q3 (75th percentile).

For plasma concentrations as well as for all PK parameters, the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile
Q1	25th percentile
Q3	75th percentile
P90	90th percentile

The data format for descriptive statistics of plasma concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

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).

The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. The category missing will be displayed only if there are actually missing values.

The individual values of all patients will be listed, sorted by treatment group, centre (investigator site), patient number and visit, with ascending doses starting with placebo. The source data listings (SDL) will be contained in Appendix 16.2 of the CTR.

The tables and graphs will be contained in CTR in-text and Section 15.1-7 or in Appendix 16.1.9.13.

Analysis of biomarkers will be presented in 15.7 of the CTR and in Appendix 16.1.9.13.6

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. The evaluation of demographics and baseline characteristics will be based on the TS. The data will be summarized separately for each treatment and in total. Additionally the demographics and baseline biomarker parameters will be summarized for the defined subgroups in Section 6.4.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant therapies (CTs) are coded according to WHO DD. CTs 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-three category will be counted more than once; a footnote will clarify this possible double counting in tables. Summaries will be presented for new concomitant therapies added during randomised treatment phase and those taken at baseline. Therapies will be considered new if the added therapy is coded to a preferred name, where the patient did not report any medication that was coded to the same preferred name at baseline, except if the medication was stopped for more than one week.

Concomitant diseases are coded similarly as AEs based on the most current MedDRA® version. A summary of concomitant diseases will be provided by treatment group, system organ class (SOC), and preferred term (PT) and sorted alphabetically.

The coding version number will be displayed as a footnote in the respective output.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. The number and percentage of patients with overall compliance will be reported. Overall compliance will be calculated as a weighted average of reported compliance. The sum of all reported compliance

over the observed visits 2 to EOT visit will be multiplied by their duration and then divided by 100.

Example: 70% compliance between visit 2-3 (2 weeks)
90% compliance between visit 3-4 (2 weeks)
95% compliance between visit 4-5 (2 weeks)
100% compliance between visit 5-6 (2 weeks)
75% compliance between visit 6-EOT (4 weeks)
➔ Overall compliance = (70*2+90*2+95*2+100*2+75*4)/12= 84%

This patient would be overall compliant, but he didn't reach 80% compliance within the last 4 weeks of treatment, so he will be excluded from PPS.

7.4 PRIMARY ENDPOINT

7.4.1 Primary analysis

The primary analysis of the primary endpoint will be performed as described in the CTP Section 7.3.1.
Relevant time points are:
predose (-0:30h relative to drug administration) at visit 2,3,4,5,6 and 24h at EOT. In case of missing 24h value at EOT, predose value planned -0.5h relative to drug administration can be used.

To account for heterogeneity between active and placebo treatment the power of mean variance estimates (POM) according to the paper (R17-1924) will be used.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

Not applicable.

7.5.2 Secondary endpoints

Primary analysis

The number (%) patients with adverse reactions will be evaluated descriptively based on the TS. For more details see Section 7.8.1.

The primary analysis of the secondary biomarker endpoints defined in Section 5.2.2 is a MCPMod analysis with a previous applied MMRM model.

First a Mixed effects Model for Repeated Measurements (MMRM) over time is applied to the log transformed data (natural logarithms). The model will include the fixed effects 'base', 'treatment', 'time', 'base*time' interaction, and 'treatment*time' interaction. The covariance model for the repeated effect 'time' will be unstructured (i.e. TYPE=UN *or* UNR). For each dose group and each time point, the contrast of the means for 'treatment-placebo' will be estimated by the difference in the corresponding adjusted means (Least Squares Means); two-sided 90% CIs based on the t-distribution will also be computed. Baseline and all on-treatment time points will be used within the analysis. In case of convergence problem step 1-4 from Section 9.1.3 can be applied. The time profiles of the mean differences to placebo of the relative ALT (AST, AP, γ-GT, CK-18 caspase and CK-18 total respectively) change from baseline and the corresponding 90% CIs will be presented in a figure (back transformed on original scale using delta-delta method to calculate approximate SE and CIs). The dose-response relationship of the week 12 estimates from MMRM will then be analysed using MCPMod.
The Multiple Comparison Procedures and Modelling (MCP-Mod) approach (R10-1424, R15-4293) is implemented in two main steps: (1) trial design stage; (2) trial analysis stage. The procedures for the trial design stage, including the selection of candidate models covering a suitable range of dose-response shapes and sample size and power calculations, are provided in the CTP Section 7.3.2 and 7.7. The procedures for the trial analysis stage are specified below.

The treatment difference estimates over placebo for each active dose group, as well as their estimated variance-covariance matrix estimate from the MMRM are used in the trial analysis stage. Multiple comparison procedure will be implemented using optimal contrast tests which control the family-wise type I error rate at one-sided $\alpha = 0.05$. The optimal contrasts

corresponding to the candidate models are calculated as in the trial design stage and are shown in Table 7.5.2: 1. They will be updated using the expected model means from candidate set and the estimated variance-covariance matrix from the data.

Table 7.5.2: 1 Contrast coefficients

	Contrast coefficients for dose				
Model	Dose 0 mg	Dose 1 mg	Dose 3 mg	Dose 6 mg	Dose 10 mg
Linear	0.492	0.369	0.123	-0.246	-0.739
Linear in log	0.797	0.141	-0.143	-0.328	-0.466
Quadratic	0.598	0.377	0.003	-0.388	-0.591
Exponential	0.387	0.336	0.204	-0.099	-0.828
Emax	0.831	0.094	-0.210	-0.329	-0.385
Sigmoid Emax	0.462	0.453	0.135	-0.453	-0.597
Logistic	0.468	0.418	0.168	-0.422	-0.632
Beta model	0.449	0.280	-0.452	-0.627	0.350

If at least one dose-response model is statistically significant, rejecting the null hypothesis of a flat dose-response curve is indicating a benefit of BI 1467335 over placebo.

When the null hypothesis is rechecked, the best-fitting model from the above set of eight models can be refitted to the data without any parameter assumptions to generate new estimates of the model parameters from the data. The target dose will be obtained via model averaging across the significant models based on Akaike Information Criterion (AIC) (the smaller the AIC value the better the model fit).

7.7 EXTENT OF EXPOSURE

Basis for the assessment of the treatment exposure will be the amount of trial medication intake and the duration of exposure counted in days. Standard statistical parameters will be displayed by treatment.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse events

Unless otherwise specified, the analyses of AEs 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. The reporting and analyses of AEs will follow the BI guideline (4).

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (LLT, intensity according to CTCAE Version 4.03, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest).
- 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)

For further details on summarization of AE data, please refer to guidelines (3, 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 until trial termination date will be assigned to the treatment they were randomised to. All adverse events occurring before first drug intake will be assigned to 'screening'. For details on the treatment definition, see Section 6.1.

According to ICH E3 (5), AEs classified as 'other significant' needs to be reported and 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 Medical Quality Review Meeting.

An overall summary of adverse events for BI 1467335 will be presented. For further details on which summaries will be provided see Section 6.1.

The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for patients with other significant adverse events according to ICH E3 (5), for patients with adverse events of special interest and for patients with serious adverse events.

The system organ classes will be sorted alphabetically; preferred terms will be sorted alphabetically as well (within system organ class).

7.8.2 Laboratory data

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

For continuous safety laboratory parameters standardised and normalised values will be derived as well as the differences to baseline. The process of standardisation and normalisation as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data (6).

Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range at baseline and with 12 weeks of treatment and with the follow up visit 4 weeks after last drug administration. Descriptive statistics will be provided by treatment group for baseline, on-

treatment values and for changes from baseline. Frequency tables will summarise the number of patients with potentially clinically significant abnormalities as defined for the new XLAB macro.

Clinically relevant findings in laboratory data will be reported as AEs and will be analysed as part of AE analysis.

The Estimated Glomerular filtration rate as assessed by the CKD-EPI formula:

$$\text{eGFR (ml/min/1.73 m}^2\text{)} = 141 * \min(S_{Cr}/\kappa, 1)^{\alpha} * \max(S_{Cr}/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018 \text{ [if female]} * 1.159 \text{ [if black]}$$

where S_{Cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{Cr}/κ or 1, and max indicates the maximum of S_{Cr}/κ or 1. The process of standardisation and normalisation as described in the guidance document (6) does not apply. Additionally the shift tables for eGFR will use the following categories (similar to the staging of renal impairment): eGFR ≥ 90; 60-<90; 30-<60; and<30.

7.8.3 Vital signs

Descriptive statistics of absolute values, changes from baseline and compared to placebo of the exploratory vital signs endpoints defined in Section 5.3.2 over time will be provided.

Clinically relevant findings in vital signs data will be reported as AEs and will be analysed as part of AE analysis.

7.8.4 ECG

All evaluation of ECG data except of exposure response analysis will be based on the ECGS. The exposure-response analysis will then be done on the ECGPCS.

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. Occurrences of notable findings will be flagged.

For all patients with any notable finding in quantitative ECG recordings, a separate listing will be created as end-of-text display (based on the same display template as in Appendix 16.2), and the corresponding time profiles will be shown.

Comments regarding the ECGs will be listed.

Analyses categorical Endpoints

For the categorical endpoints, frequency tables will be provided.

The findings (ECG abnormalities) resulting from morphological analyses of the ECGs will also analysed as categorical endpoints.

Analyses of quantitative endpoints

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the absolute values as well as the changes from baseline over time for QTcF, HR, QT, PR and QRS. Time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by treatment.

For QTcF and HR changes from baseline the relationship to the corresponding plasma concentration is evaluated using an exposure response model.

For the following analyses, all time points with available ECG endpoints and corresponding plasma concentrations will be included. For patients on active drug, in case of BLQ values they will be replaced by ½ LLOQ for analysis.

The changes from baseline in QTcF (ΔQTcF) can be investigated as response variable. The placebo patients in the analysis will be included, with zero plasma concentrations.

As a first step, it is investigated if there is a potential delayed or accelerated (e.g. due to metabolites) effect of the drug on QTcF. A general visual impression will be provided by overlaying time profiles of plasma concentrations and QTcF changes from baseline (ΔQTcF).All figures will be generated for each patient (presented in Appendix 16.1.13.1.9.1 of the CTR), as well as for means per active treatment (presented in Section 15.3 of the CTR).

The relationship between BI 1467335 plasma concentrations and QTcF changes from baseline will be investigated in an exploratory manner using a random coefficient model to estimate the difference in means between BI 1467335 and placebo of QTcF change from baseline and its 90% confidence interval at the geometric mean of C_{max} for each dose. Additionally, the estimated overall slope with its 90% confidence interval will be provided. The used random coefficient model is based on a white paper from Garnett et. al. (R18-0143) with ΔQTcF as response variable, centered baseline QTc and plasma concentration as continuous covariates, treatment and day as fixed categorical effects, and a random intercept and slope for each patient. For more details refer to Section 9.1.2.

For visualization, a scatterplot of the BI 1467335 plasma concentration against the following individual QTcF values will be provided: For each patient on active treatment and each time point, subtract the mean value of all individual observed ΔQTcF values from the placebo group for this time point from the individual observed ΔQTcF value for this patient and time point. This results in estimates for “individual ΔΔQTcF” values, which should only be used for plotting purposes. The corresponding regression line and its pointwise confidence bands as well as and the geometric mean of C_{max} for each dose will additionally be displayed in the plot.

To check model assumptions, the conditional residuals will be plotted and presented in Appendix 16.1.13.1.9.1 of the CTR. In case of non-linearity or if there is evidence for a

delayed effect, further models will be explored in order to better characterise the PK-ECG relationship (e.g. effect compartment models, non-linear models, etc.).

All of the above described graphical and statistical analyses will be also performed for HR in place of QTcF.

Appropriateness of heart rate correction methods of QT interval

To evaluate the appropriateness of the heart rate correction methods, the slope of the relationship of QTcF interval versus RR interval (values log-transformed using the natural logarithm) will be estimated by applying the random coefficient model described in Section 9.1.1 using all time points. A scatterplot of QTcF vs RR including the overall regression line will be included in the Statistical Appendix of the CTR. The resulting (fixed effect) slope together with two-sided 95% confidence intervals will be included in the footnote for this plot.

8. REFERENCES

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8.	*R05-0788*: Hoffman D, Kringle R, Lockwood G, Turpault S, Yow E, Mathieu G. Nonlinear mixed effects modelling for estimation of steady state attainment. Pharm Stat. 2005.
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10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**03-APR-2017**		None	This is the initial TSAP with necessary information for trial conduct
FINAL	**10-AUG-2017**		All	This is the final TSAP version. All missing information from initial TSAP version was added.