Trial Statistical Analysis Plan

c28812145 -01

BI Trial No.:	1346.23
Title:	A multi-centre, double-blind, parallel-group, randomized controlled study to investigate efficacy and safety of orally administered BI 425809 during a 12-week treatment period compared to placebo in patients with cognitive impairment due to Alzheimer's Disease. Including Protocol Amendment 1, 2, 3 and 4 [**c03632269-05]**.
Investigational Product(s):	BI 425809
Responsible trial statistician(s):	Telephone:
Date of statistical analysis plan:	4 OCT 2019 Signed
Version:	Revised

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AChE-Is	Acetylcholine Esterase Inhibitors
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study/Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
BADLs	Basic Activities of Daily Living
CI	Confidence Interval
CIBIC+	Clinician's Interview-Based Impression of Change
CIBIS	Clinical Interview-Based Impression of Severity
COWAT	The Controlled Oral Word Associate Test
CT	Concomitant Therapy
C-SSRS	Columbia Suicide Severity Rating Scale
eCRF	Electronic Case Report Form
EudraCT	European Clinical Trials Database
IADLs	Instrumental Activities of Daily Living
MCPMod	Multiple Comparison & Modelling
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed Model Repeated Measures
MMSE	Mini-Mental-State-Examination
NPI	Neuropsychiatric Scale
OC	Observed Cases
OR	Original Result
PD	Pharmacodynamics
PK	Pharmacokinetic
PG(x)	Pharmacogenomic(s)
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TS	Treated Set
VFT	Verbal Fluency Test

3. INTRODUCTION

As per International Conference on Harmonization (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, randomization.

R Version 3.3.2 with “DoseFinding” package (R15-2001) will be used for analyses based on Multiple Comparison Procedures and Modelling (MCPMod) and SAS Version 9.4 will be used for all other analyses.

4. CHANGE IN THE PLANNED ANALYSIS OF THE STUDY

For detailed description of the analyses, please see Sections 7.4.2

5. ENDPOINTS

The primary objectives of this trial are to establish proof-of-clinical-concept with respect to a non-flat dose-response curve and to define one or more suitable doses for BI 425809 regarding efficacy and safety for further investigation in Phase III trials.

5.1 PRIMARY ENDPOINT

The primary efficacy endpoint is:

The change from baseline in the ADAS-Cog_{11} (Alzheimer's Disease Assessment Scale-Cognitive Subscale: 11-item variant) total score (see Section 9.1 for details) after 12 weeks of

treatment. The sum of the 11 subscale scores would be the ADAS-Cog_{11} total score. For details of the derivation of the ADAS-Cog_{11} total score and its subscales, please refer to Section 6.6.1 and Section 9.1. The ADAS-Cog_{11} is measured at screening (Visit 1), baseline (Visit 2), week 4 (Visit 4) and week 12 (EOT), with a smaller score indicating better cognition.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

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

5.2.2 Secondary endpoints

The secondary efficacy endpoints include:

• Change from baseline in the Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) score after 12 weeks of treatment. The ADCS-ADL is a 23 item scale ranging from 0-78, that is consisted of 6 BADLs items (items 1-6, ranging from 0-22) and 17 IADLs items (items 7-23, ranging from 0-56). A smaller score indicates more severity. ADCS-ADL is measured at screening (Visit 1), baseline (Visit 2) and week 12 (EOT).

• Clinician's Interview-Based Impression of Change (CIBIC+) score after 12 weeks of treatment. CIBIC+ is measured at week 12 (EOT). A smaller score indicates better general condition (except for 0, which means not assessed).

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For regimen and administration details please refer to Sections 3.1 and 4.1 of the CTP.

Table 6.1: 1 Treatment descriptions

Long Name	Short Name
Placebo QD	Placebo QD
BI 425809 2 mg QD	BI 2mg QD
BI 425809 5 mg QD	BI 5mg QD
BI 425809 10 mg QD	BI 10mg QD
BI 425809 25 mg QD	BI 25mg QD

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

Analysing Treatment Period	Start Date	End Date
Screening	Date of informed consent	Date of first treatment administration
Treatment	Date of first treatment administration	Date of last treatment administration + REP + 1 day
Follow-up	Date of last treatment administration + REP +1 day	End of study date

REP is the residual effect period which is defined as 11 days after the last dose of trial treatment.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Important protocol deviations (iPDs) affecting subjects' rights will be identified separately from those affecting analysis sets in the study report. Patients with iPDs that could potentially impact efficacy endpoints will be excluded from the PPS (Refer to Section 6.3).

The iPDs are listed in Table 6.2: 1 below. They will be reviewed at Trial Oversight Meeting (TOM) conducted periodically based on data accumulated during the trial. A list of protocol deviations will be discussed at the report planning meeting (RPM).

If the data show other iPDs, this table will be supplemented accordingly at TOMs or RPMs or through team review of the manual PD log. The decision whether a patient will be excluded from the analysis will be made at the final RPM prior to data unblinding.

Table 6.2: 1 Handling of iPDs

Category/ iPD Code		Description	Example/Comment	Excluded from
A		**Entrance criteria not met**		
	A1	**Inclusion criteria not met**		
	A1.1	Patient younger than 55 years of age	Inclusion criteria 7 not met as specified in the protocol.	PPS
	A1.2	Diagnosis of mild to moderate Alzheimer's Disease Dementia not met	Inclusion criteria 1 not met as specified in the protocol.	PPS, FAS
	A1.3	MMSE score beyond range	Inclusion criteria 2 not met as specified in the protocol.	PPS
	A1.4	Previous or current use of ACHE-Is medication requirement not met.	Inclusion criteria 3 not met as specified in the protocol.	PPS
	A1.5	Inadequate education and language	Inclusion criteria 6 not met as specified in the protocol.	PPS
	A1.6	Inadequate study partner reliability	Inclusion criteria 5 not met as specified in the protocol.	PPS
	A2	**Exclusion criteria met**		
	A2.1	Secondary disorder other than Alzheimer's Disease Dementia confirmed	Exclusion criteria 1 met as specified in the protocol.	PPS
	A2.2	Substantial concomitant cerebrovascular disease	Exclusion criteria 2 met as specified in the protocol.	PPS
	A2.3	Patients with conditions that may interfere with the trial testing procedures	Exclusion criteria 3 met as specified in the protocol.	PPS
	A2.4	Medical history of primary or recurrent malignant disease	Exclusion criteria 4 met as specified in the protocol.	PPS
	A2.5	Condition with life expectancy less than 2 years confirmed	Exclusion criteria 5 met as specified in the protocol.	PPS
	A2.6	Any suicidal behavior in the past 2 years	Exclusion criteria 10 met as specified in the protocol.	None

Table 6.2: 1 Handling of iPDs cont

Category/ iPD Code		Description	Example/Comment	Excluded from
A		**Entrance criteria not met**		
	A2	**Exclusion criteria met**		
	A2.7	Any suicidal ideation of type 4 or 5 in the C-SSRS in the past 3 months	Exclusion criteria 11 met as specified in the protocol.	None
	A2.8	Participation in AD study less than 3 months from screening, treatment for disease modification	Exclusion criteria 14 met as specified in the protocol.	PPS
	A2.9	Known history of HIV infection	Exclusion criteria 12 met as specified in the protocol.	PPS
	A2.10	Prohibited drugs prior to visit 1 and/or during the screening period	Exclusion criteria 15 met as specified in the protocol.	PPS
	A2.11	Uncompensated hearing loss	Exclusion criteria 9 met as specified in the protocol.	PPS
B		**Informed consent not available/not done**		
	B1	Informed consent not available/not done	Informed consent date missing; no signature on ICF	All
	B2	Informed consent too late	Inclusion criteria 4. Check if informed consent date (actual consent date) was prior or on Visit 1. Applicable to all informed consents. Check if date of informed consent was after the date of any study-related procedure. If patient signed the wrong version of ICF and then signed the correct version of ICF with the date after screening, it is still deemed as iPD	None

Table 6.2: 1 Handling of iPDs cont

Category/ iPD Code		Description	Example/Comment	Excluded from
C		**Trial medication and randomization**		
	C1	**Incorrect trial medication taken**		
	C1.1	Incorrect trial medication taken during study	Any deviation. Check whether the medication packages dispensed (med. Numbers entered into EDC) has the correct content (to be seen from the med. number list that was the basis for packaging). If content was correct, the deviation will only be noted. Otherwise, the cases will be described individually and possibly excluded. In addition, check whether the dispensed packages match the randomized treatment of the patient (IRT assignment). If not, and if treated consistently throughout the trial, analyze as treated.	PPS
	C2	**Randomization order not followed**		
	C2.1	Error by the vendor who implemented the randomization scheme	E.g., the same randomization number was given to different patients or the assignment of duplicate medication numbers or incorrect medication numbers. Verify by comparing the medication numbers and randomization numbers from IRT. If a patient actually receives the correct medication despite the wrong kit, they will not be excluded from the PPS. Vendor to check before unblinding.	PPS
	C3	**Non-compliance with study medication**		
	C3.1	Non-compliance with study medication	Compliance < 80% or >120 %	PPS if <80%
D		**Concomitant medication**		
	D1	Prohibited medication use before the treatment period of the trial	To be determined on a case by case basis.	PPS
	D2	Prohibited medication use during the conduct of the trial	To be determined on a case by case basis.	PPS

KEY: PPS – Per Protocol Set

6.3 SUBJECT SETS ANALYSED

SCR - Screened set: All patients screened for the trial, with informed consent given and signed and who completed at least one screening procedure at Visit 1.

RS- Randomized set: This patient set includes all patients who signed the informed consent form and were also randomized, regardless whether the patient was treated with trial medication or not.

TS-Treated set: All patients who were randomized and treated with at least one dose of study medication.

FAS- Full analysis set: The full analysis set (FAS) will consist of all randomized patients who were treated with at least one dose of study drug and had a baseline and at least one corresponding post baseline on treatment measurement for any efficacy endpoints. In particular, for the secondary endpoint CIBIC+, CIBIS is considered its' corresponding baseline measurement.

PPS- Per protocol set: All patients in the FAS without important protocol deviations that impact efficacy assessments. PPS analyses will be conducted if more than 10% of patients in FAS have an iPD.

The SCR, RS and TS will be used to populate patient disposition and the TS will be used for demographics, baseline characteristics, treatment exposure, and safety analyses (including adverse events, laboratory measurements, vital signs, and ECG). Safety analyses will assign patients to the treatment group based on the treatment received.

Table 6.3: 1 Subject sets analyzed

	Subject set				
Analysis	SCR	RS	TS	FAS	PPS
Primary endpoint				OC	OC[3]
Secondary endpoints				OC	
Safety variables			OR		
Disposition	OR[1]	OR[1]	OR[1]		
Demographics		OR[2]	OR		
Baseline cognitive assessments			OC		
Disclosure tables	OR		OR		

1) Disposition table requires multiple patient sets to populate
2) Additional table for clinical trial disclosure requirements
3) PPS analyses only conducted if more than 10% of patients in FAS have an iPD

Note: For definitions of OC (Observed Case), OR (Original Results) refer to Section 6.6.

Note that the number of patients with available data for different endpoints may differ. For details, see Section 6.6 below.

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

Original result (OR) analysis

Original result analysis implies the analysis of data exactly as observed. OR analysis will be performed on variables that are not meaningful to apply any imputation rule on them for replacing the missing values.

6.6.1 Missing efficacy data

If a time point is entirely missing, it is handled via the MMRM model, and no other imputation rule will be applied. If some items' scores of a questionnaire are missing, the imputation of the total scores will be based on the rules below.

Details on ADAS-Cog_{11} items and the derived composite endpoint items are described in Sections 9.1 and 9.2.

ADAS-Cog_{11}

If a subscale score of ADAS-Cog_{11} is missing for a subject due to cognitive reasons, the worst possible score for that subscale will be given to the corresponding subject, if it is missing due to non-cognitive reasons, the corresponding subscale score will be treated as missing.

If a patient has 3 or fewer missing ADAS-Cog_{11} subscale scores, the following algorithm will be used to impute the ADAS-Cog_{11} total score:

Total score = [(sum of scores from completed items) / (maximum possible sum of scores for completed items)]*(maximum total score [=70] for ADAS-Cog_{11})

If there are more than 3 missing ADAS-Cog_{11} items, ADAS-Cog_{11} score will be considered missing at that time point.

The imputed number will be rounded to the nearest integer. If the nearest integer is greater than the maximum possible score, the imputed score will be equal to the maximum possible score.

ADCS-ADL

For ADCS-ADL, if <30% of the items are missing, the total score will be imputed. The sum of the non-missing items will be prorated to the sum of total items. The imputed number will be rounded to the nearest integer. If the nearest integer is greater than the maximum possible score, the imputed score will be equal to the maximum possible score. If >30% of the items are missing, the total score at that visit will be considered missing. For example, total score = [(sum of scores from completed items) / (sum of maximum possible scores for completed items)]*(maximum total score [=78] for ADCS-ADL). Please refer to supplementary material (R14-0512) for details.

Observed cases (OC) analysis

For the analyses of all efficacy endpoints using MMRM analyses, it is planned to analyze only the available data that were observed or imputed per the imputation rules specified above while patients were on treatment, i.e., excluding the missing data. In other words, OC analysis will be performed and missing data in this analysis will not be replaced.

Last observation carried forward (LOCF) analysis

The last observation on-treatment need not necessarily be a value selected as a visit value if multiple measurements were performed within a time window for a visit. In this case the first

on-treatment value or the value that was observed closest to the planned visit date within the last on-treatment time window will be carried forward.

Baseline observation carried forward (BOCF) analysis

As part of the LOCF technique, baseline values will be carried forward if no post-baseline value is available.

6.6.2 Missing safety data and other data

In general, missing data will not be imputed and only observed values will be analyzed. Data of patients who withdrew after the screening examination or were not treated will be only listed.

6.6.3 Missing AE dates and times

Missing or incomplete AE dates are imputed according to BI standards

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline values are defined as the last pre-treatment observation at or prior to Visit 2. For laboratory safety measurements, the last value prior to the first drug administration will be considered as baseline values.

The midpoint between two on-treatment visits defines the end of a time window, with the midpoint being included in the time window of the preceding visit.

The time windows are defined based on the planned number of days as compare to the date of first administration of study drug, with the later date being day 1.

Table 6.7: 1 Time windows for efficacy measurements scheduled for each visit

		Time window (actual days on treatment)	
Visit number	Planned days	Start	End
1	-14	NA	Treatment - 1
2	1	1	1
4	29	2	57
EOT	85	58	Date of last administration of trial treatment + 8 days

Repeated and unscheduled efficacy measurements will be assigned to the nominal visits according to the time windows described above.

For efficacy measurements, only one observation per time window will be selected for analysis at an on-treatment visit – the value will be selected which is the first one in the corresponding time window. If there are two observations which have the same difference in days to the planned day or if there are two observations on the same day, the first value will be used. If an observation is available on the last day of treatment, this observation will be preferably selected over any later observation that is still within the time window.

For safety measurements, collected visits numbers will be used.

For repeated and unscheduled safety measurements for the same visit on treatment, the worst of these will be selected for analysis. In case there is no standard reference direction for the safety parameter, the average of all values for the same visit will be used for analysis.

Note: for LOCF imputation, the last observed on-treatment value will be carried forward, whether or not it was selected in the previous time window. For more details on LOCF refer to Section 6.6.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline

The individual values of all subjects will be listed, sorted by dose group, subject number and visit. AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix of the CTR.

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

Disposition of the patient population participating in the trial will be analyzed by treatment and presented by the categories in the standard CRF groups and presented in the clinical trial report as a frequency-distribution.

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). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

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

The age categories for the demographic table are <65 and >=65.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant medication use will be summarized by Anatomical-Therapeutic-Chemical classification 3 (ATC 3) and preferred name. AD related and non-AD related summaries will be presented for concomitant medications taken previously, taken during randomized treatment and those taken at baseline. A separate table presenting Non-Drug therapy will also be provided.

A summary of concomitant diseases will be provided by treatment group, System Organ Class (SOC) and Preferred Term (PT). The most current MedDRA version and WHO B3 format on Sep. 2019 versions will be used.

7.3 TREATMENT COMPLIANCE

Treatment compliance is calculated at week 4, 8, and 12/EOT based on protocol Section 4.3.

The cumulative treatment compliance during the entire treatment period is derived using the following formulas:

For completers: if a subject's observed treatment compliance rates are 85% at Week 4, 90% at Week 8 and 100% at EOT, then the cumulative treatment compliance rate = (0.85*4 + 0.90*4 + 1*4)/12 * 100% = 91.67%.

For early discontinued subject: if a subject's observed treatment compliance rates are 85% at Week 4, 100% at Week 8, 50% at EOT, then the cumulative treatment compliance rate = (0.85*4 + 1*4 + 0.5*((EOT date – drug start date + 1)/7 – 8))/((EOT date – drug start date + 1)/7) * 100% = 89.7% if EOT date – drug start date + 1 = 60 days.

Only descriptive statistics are planned for this section of the report. Summary statistics of compliance in the treated set will be given for the number of subjects as well as the corresponding percentage with compliance in the categories <80%, 80% - 120%, >120%, missing.

7.4 PRIMARY ENDPOINT

The primary analysis is at 12 weeks and will be performed on the full analysis set (FAS).

7.4.1 Primary analysis of the primary endpoint

The hypothesis testing and primary analysis are described in Sections 7.2 and 7.3.1 of the CTP, respectively.

The Multiple Comparison Procedures and Modeling (MCPMod) 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 Sections 7.3.1 and 7.7. The procedures for the trial analysis stage are specified below.

The change from baseline in ADAS-Cog_{11} at week 12 for each dose group as well as the corresponding variance-covariance matrix are estimated by an mixed effects model repeated measure including the fixed, categorical covariates of treatment, visit, baseline MMSE strata indicator (>=20, <20) and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline ADAS-Cog_{11} value and baseline-by-visit interaction. Patient is considered as random effect. The unstructured covariance matrix is used to estimate the within subject variability. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Analyses will be implemented using SAS 9.4 PROC MIXED. If the MMRM fails to converge, the compound symmetry covariance matrix may be considered.

The adjusted mean estimates of the doses and their estimated variance-covariance matrix from MMRM are used in the trial analysis stage. Then the 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 shown in Table 7.4.1: 1 below. They will be updated using the expected model means from candidate set and the estimated variance-covariance matrix from the data.

Table 7.4.1: 1 Optimal contrast coefficients

	Contrast coefficients for dose				
Model	Placebo	2mg	5mg	10mg	25mg
Linear	0.419	0.320	0.170	-0.080	-0.829
Linear Logistic	0.772	0.147	-0.094	-0.284	-0.541
Emax	0.641	0.303	-0.009	-0.297	-0.639
Sigmoid Emax	0.450	0.430	0.169	-0.394	-0.655
Logistic	0.372	0.352	0.269	-0.203	-0.790
Beta Model	0.656	-0.133	-0.392	-0.507	0.375

Proof of concept is established if at least one dose-response model is statistically significant, rejecting the null hypothesis of a flat dose-response curve, indicating a benefit of BI 425809 over placebo.

Once the significance of a dose-response signal is established, the dose-response profile and the target dose can be estimated using the model averaging method. The selected dose-response model(s) will be re-fitted to the data without any parameter assumptions to generate sets of new estimates of the model parameters from the data. The final dose-response model

will be obtained via weighted model averaging of the significant models based on Akaike Information Criterion (AIC) (the smaller the AIC value the better the model fit). Estimates for the target dose will be the smallest dose producing a delta greater than or equal to the target value of 2 points in the mean change from baseline in ADAS-Cog_{11} total score after 12 weeks of treatment, based on the final dose-response model, as well as considering safety information and other relevant information.

Figures and tables will be displayed for the MCPMod modelling.

Test statistics and p-values will also be displayed for different dose-response models.

7.4.2 Secondary Analysis

The secondary analysis of the primary endpoint will be done by fitting the same MMRM model that is used in the MCPMod analysis in Section 7.4.1.

The primary treatment comparisons will be between the placebo and the different doses of BI 425809 with respect to the mean change from baseline in the ADAS-Cog_{11} total score after 12 weeks of treatment. Adjusted mean change from baseline as well as the treatment contrasts will be presented together with the 95% confidence intervals. The primary treatment comparisons will be the contrast between treatments at week 12.

Comparisons between placebo and different BI 425809 doses are exploratory in nature and based on the numerical comparison of the respective treatment means.

Figures that display the adjusted means from the MMRM approach on change from baseline in the ADAS-Cog_{11} total score for each dose level on each visit will also be presented.

7.4.3 Sensitivity analyses and subgroup analysis of the primary endpoint

The following sensitivity analyses will be done for the primary endpoint on FAS:

ANCOVA:

Analysis of covariance based on observed cases (OC) and LOCF will be used as sensitivity analyses for the primary endpoint, the model includes baseline value for the primary endpoint measure, MMSE stratification (>=20, <20) at baseline and treatment.

7.5 SECONDARY ENDPOINTS

The analyses for the secondary endpoints are described in Section 7.3.2 of the CTP.

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 analyses of secondary endpoints are based on FAS. ANCOVA based on (OC) and BOCF will be used for the primary and sensitivity analyses of the secondary endpoints, respectively. The model will include the same corresponding variables as the ANCOVA model for the sensitivity analysis of the primary endpoint, i.e., baseline value for the corresponding secondary endpoints measures, MMSE stratification factor (>=20, <20) at baseline and treatment. For CIBIC+, CIBIS will be included as the baseline adjustment term. Comparisons between treatment groups will be considered exploratory in nature and based on the numerical comparison of the respective treatment means.

7.7 EXTENT OF EXPOSURE

Extent of exposure will be calculated as the difference between last intake of study drug and the first administration of the study drug plus one day. Descriptive statistics will be provided for number of days of exposure for each treatment arm. In addition, cumulative exposure of number and percentage (N, %) of subjects will also be displayed as “1 to < 2 weeks”, “2 to <3 weeks”, “3 to <4 weeks”, “4 to <8 weeks”, “8 to <12 weeks”, “>=12 weeks” or “missing”.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

AEs will be coded based on the most current version of MedDRA®.

Analysis will be performed as defined in Section 7.3.4 of the CTP.

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.

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

- All AE attributes are identical (LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship and outcome)
- 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)

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between the date of the first drug intake till the date of the last drug intake + residual effect period will be assigned to the on-treatment period. All adverse events occurring before first drug intake will be assigned to ‘screening’ and all adverse events occurring after the residual effect period but within 28 days afterwards will be assigned to ‘follow-up’ (for listings only). For details on the treatment definition, see Section 6.1.

Adverse events of special interest (AESIs)

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST and / or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample; and / or
- marked peak aminotransferase (ALT and / or AST) elevations ≥ 10 fold ULN.

Refer to CTP Section 5.3.6.1 for details.

Analysis of other significant AEs

According to ICH E3 (12), 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 (MQRM).

AE summaries

An overall summary of adverse events will be presented. The frequency of patients with adverse events will be summarized by treatment, primary system organ class and preferred term according to MedDRA. Separate tables will be provided for patients with:

- AEs occurring with incidence in preferred term greater than 2%
- AEs occurring with incidence in preferred term greater than 5%
- AEs leading to discontinuation
- AEs leading to death
- AESIs
- Drug-related AEs
- Serious adverse events
- Series related AEs
- Other significant adverse events according to ICH E3 (12)
- Post-treatment AEs

The system organ classes will be sorted by default alphabetically, preferred terms will be sorted by frequency (within system organ class).

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards

Baseline for safety laboratory parameters will be the last available measurement before the start of randomized study drug.

Laboratory measurements taken up to the residual effect period of 11 days after the last administration of randomized study drug will be considered as on-treatment.

Only patients with at least one available on-treatment value will be included in the analysis of an individual laboratory parameter. All individual data will be presented in listings.

Study visits will be presented by the Visit labels in Table 6.7.1.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report. In case of multiple measurements including unscheduled visits, the value for the vital sign measurement will be the average of all the measurements for the corresponding visit.

7.8.4 ECG

12-lead ECG measurements will be assessed as described in the CTP Flow Chart. ECG-findings before first intake of trial drug will be considered as baseline condition. Any clinically significant new findings in the ECG measurement after the first ECG will be considered as AEs.

7.8.5 Others

7.8.5.2 C-SSRS

The individual items and categories of suicidal ideation and behavior from the C-SSRS will be summarized through descriptive statistics according to Section 9.4

8. REFERENCES

1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
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10 HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**5-AUG-19**		All	This is the version 1.0 Core TSAP
1.9	**4-OCT-19**		Table 6.7.1	This is the version 1.9 Core TSAP