Trial Statistical Analysis Plan

c03164258 -01

BI Trial No.:	1289.5
Title:	A multi-centre, double-blind, parallel-group, randomized controlled study to investigate the efficacy, safety and tolerability of orally administered BI 409306 during a 12-week treatment period compared to placebo in patients with Alzheimer's Disease
Investigational Product(s):	BI 409306
Responsible trial statistician(s):	[redacted] Telephone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	13 JUN 2017 SIGNED
Version:	Final

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2 LIST OF ABBREVIATIONS

Term	Definition / description
ABCB1	ATP-binding cassette sub-family B member 1 (gene encoding for P-gp)
ADCS-ADL	Alzheimer's Disease Cooperative Study/Activities of Daily
ADCS-MCI-ADL	ADCS-ADL for mild cognitive impairment
AChE-Is	Acetylcholine Esterase Inhibitors
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale-cognitive subscale
AE	Adverse Event
AESI	Adverse Event of Special Interest
[redacted]	[redacted]
AUC	Area under the Curve
BCRP	Breast cancer resistance protein
[redacted]	[redacted]
b.i.d	bis in die (twice a day)
BPM	Beats per Minute
CDR-SB	Clinical Dementia Rating Scale–Sum of Boxes
BRPM	Blinded report planning meeting
CI	Confidence Interval
CRF	Case Report Form
CT	Concomitant therapy
CCT	Cranial Computer Tomography
CSF	Cerebrospinal fluid
[redacted]	[redacted]
C-SSRS	Columbia Suicide Severity Rating Scale
CTC	Common Terminology Criteria
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome
DAT	Dementia of Alzheimer Type
DMC	Data Monitoring Committee
DMG	Dictionary Maintenance Group
DNA	Deoxyribonucleic Acid
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DRA	Drug Regulatory Affairs
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EM	Extensive metabolizer
EMEA	European Agency for the Evaluation of Medicinal Products
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FTA	Fluorescent treponemal antibody absorbent test
GCP	Good Clinical Practice
[redacted]	[redacted]

HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IM	Intermediate metabolizer
IPV	Important protocol violation
IRB	Institutional Review Board
ISF	Investigator Site File
IRT	Interactive Response Technology
MCPMod	Multiple Comparisons & Modelling
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Multiple Imputation
[redacted]	[redacted]
MMRM	Mixed model repeated measures
MMSE	Mini-Mental-State-Examination
MQRM	Medical Quality Review Meeting
MRI	Magnetic Resonance Imaging
MST	Medical Subteam
NMDA-R	N-methyl-D-aspartate receptor
NTB	Neuropsychological Test Battery
P-gp	P-glycoprotein
O*C	Oracle Clinical
OC	Observed cases
OR	Original result
PD	Pharmacodynamics
[redacted]	[redacted]
PM	Poor metabolizer
POC	Proof of Concept
PPS	Per protocol set
PSTAT	Project Statistician
PK	Pharmacokinetic
PM	Poor metabolizers
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
RDC	Remote Data Capture
REP	Residual Effect Period
RPR	Rapid Plasma Reagin
q.d.	quaque die (once a day)
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SMQ	Standardised MedDRA query
SOC	System organ class

SPC	Summary of Product Characteristics
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis [redacted]
TESS	Treatment emergent signs and symptoms
TMM	Team Member Medicine
TMW	Trial Medical Writer
TOC	Table of contents
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UM	Ultrarapid metabolizer

3 INTRODUCTION

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

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

SAS Version 9.4 will be used for all analyses.

4 CHANGE IN THE PLANNED ANALYSIS OF THE STUDY

The following changes were made:

[redacted]

The data for patients entered prior to Amendment 3 will be handled as follows:

- The data for assessments removed from the study completely or for a specific visit due to the amendment will be summarized descriptively.

5 ENDPOINT

Efficacy, safety and tolerability of different doses of BI 409306 compared to placebo in patients with prodromal AD are the objectives of this trial.

5.1 PRIMARY ENDPOINT

The primary endpoint is:

The Neuropsychological Test Battery (NTB) response, defined as change from baseline in total z-score after 12 weeks of treatment.

For each patient's raw scores on each of the 9 NTB tests will be converted to the standardized z-score using the baseline means and standard deviations (SDs) for each test. The baseline means and SDs will be calculated using all randomized patients. The resultant z-scores will be averaged to obtain a total z-score, incorporating all 9 NTB tests. Change from baseline will be calculated as the post-baseline composite z-score minus the pre-treatment z-score, such that a positive change indicates an improvement from baseline. The measurements taken at Visit 3 will be considered as baseline values. Further information can be found in section 9.1.

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.

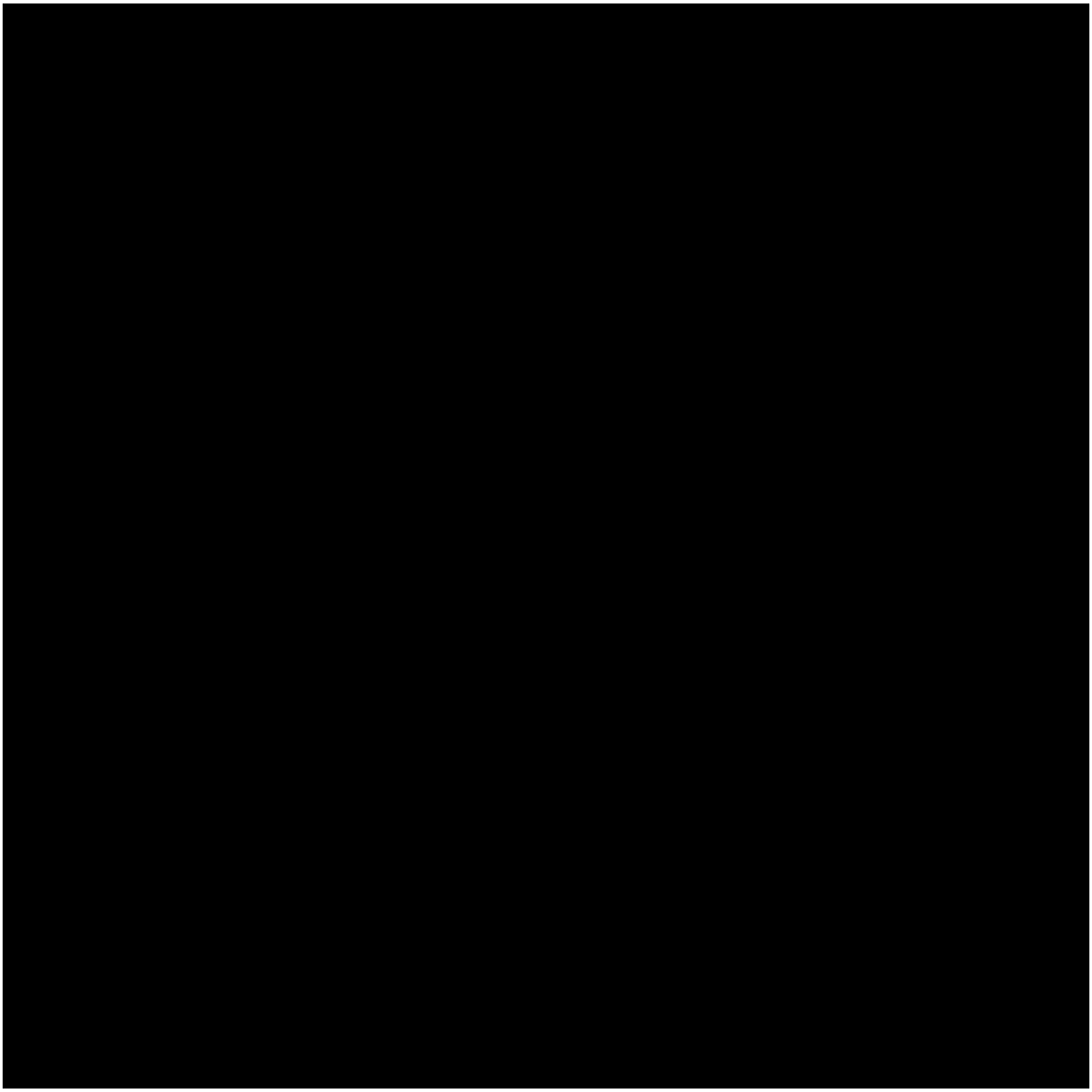
5.2.2 Other Secondary endpoints

Secondary efficacy endpoints are the same as detailed in Section 5.1.1 of the protocol. Namely, they are the following:

Change from baseline in the ADCS-MCI-ADL (Alzheimer's Disease Cooperative Study/Activities of Daily Living for mild cognitive impairment) score after 12 weeks of treatment.

Change from baseline CDR-SB (Clinical Dementia Rating – Sum of Boxes) after 12 weeks of treatment

Change from baseline in ADAS-Cog11 (Alzheimer's Disease Assessment Scale cognitive subscale) total score after 12 weeks of treatment.



6 GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For regimen details refer to Section 3.1 of the CTP.

The treatments and treatment periods are defined as follows:

Table 6.1: 1 Treatment descriptions

TPATT	Long Name	Short Name
A	BI 409306 10 mg QD	10mg QD
B	BI 409306 25 mg QD	25mg QD
C	BI 409306 50 mg QD	50mg QD
D	BI 409306 25 mg BID	25mg BID
E	Placebo	Placebo

Table 6.1: 2 Definition of analyzing treatment period

Label	Interval	Start Date	Start time
Screening	Screening	Date of informed consent	00:00
Placebo Run-in (PBORI)	Run-in	Date of first administration of run-in medication	Time of first administration of run-in medication 12:00 if missing
BI 409306 10mg QD BI 409306 25mg QD BI 409306 50mg QD BI 409306 25mg BID Placebo	Treatment	Date of first administration of study medication	Time of first administration of study medication 12:00 if missing
Post-treatment	Post-treatment	Date of last intake of study drug + X+1 (see definition of X below)	00:00
Post-study	Post-study	Start date = Last contact date, defined as the maximum of (Trial completion date, last study drug intake + X) +1	00:00

For safety analyses, data up to 7 days after last treatment intake will be considered as on treatment for AEs and for laboratory values. To clarify;

- Screening: starts from the date of informed consent to the date of first administration of run-in medication.
- Placebo run in period: starts from the date of first administration of run-in medication to the date of first administration of randomized study drug.
- On treatment: From the first intake of randomized study drug to last intake of randomized study drug + X days, where X=7 days for safety laboratory and AE.
- Post-treatment: From end of on-treatment period until last contact. Last contact date is defined in Table 6.1: 1. Post treatment period is not applicable for patients with last contact equal to 'last intake + X + 1 days' where X is 7 days as previously specified.
- Post study: From day after last contact defined in Table 6.1: 1. If period starts at end of on-treatment period then post-treatment period is not applicable.

6.2 IMPORTANT PROTOCOL VIOLATIONS

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

The protocol violations are listed in the Table 6.2: 1 below. They will be reviewed at Medical Quality Review Meetings (MQRMs) conducted periodically based on data accumulated during the trial. A list of protocol deviations will be discussed at the blinded report planning meeting (BRPM).

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 DBL.

Table 6.2: 1 important protocol violations

Category /Code		Description	Example/Comment	Excluded from PPS	Automatic /Manual
A		**Entrance criteria not met**			
	A1	**Inclusion criteria not met**			
	A1.1	Patient younger than 55 years of age	Inclusion criteria 1 not met as specified in the protocol.	Yes	Automatic
	A1.2	No confirmed diagnosis of prodromal AD on neuropsychological testing	Inclusion criteria 3 not met as specified in the protocol.	Yes	Automatic
	A1.3	No confirmation of abnormal markers of AD pathology	Inclusion criteria 4 not met as specified in the protocol.	Yes	Automatic
	A1.4	Received drugs for treatment of AD within three months of screening	Inclusion criteria 5 not met as specified in the protocol.	Yes	Automatic
	A1.5	Inadequate education and language	Inclusion criteria 6 not met as specified in the protocol.	Yes	Automatic
	A1.6	Inadequate study partner reliability	Inclusion criteria 8 not met as specified in the protocol.	Yes	Automatic
	A2	**Exclusion criteria met**			
	A2.1	Mild cognitive impairment	Exclusion criteria 1 met as specified in the protocol.	Yes	Automatic
	A2.2	Substantial concomitant cerebrovascular disease	Exclusion criteria 2 met as specified in the protocol.	Yes	Automatic
	A2.3	Symptomatic and unstable/uncontrolled conditions	Exclusion criteria 4 met as specified in the protocol.	Yes	Automatic
	A2.4	Any other psychiatric disorder	Exclusion criteria 6 met as specified in the protocol.	Yes	Automatic
	A2.5	Any suicidal behavior in the past 2 years	Exclusion criteria 7 met as specified in the protocol.	No	Automatic
	A2.6	Any suicidal ideation of type 4 or 5 in the C-SSRS in the past 3 months	Exclusion criteria 8 met as specified in the protocol.	No	Automatic
	A2.7	Participation in AD study less than 3 months from screening, treatment for disease modification or non-prescription medications	Exclusion criteria 9 met as specified in the protocol.	Yes	Automatic
	A2.8	Known history of HIV infection	Exclusion criteria 11 met as specified in the protocol.	Yes	Automatic

Table 6.2: 1 (continued) important protocol violations

Category /Code		Description	Example/Comment	Excluded from PPS	Automatic/ Manual
	A2	**Exclusion criteria met**			
	A2.9	Prohibited drugs within 3 months prior to study participation	Exclusion criteria 16 met as specified in the protocol.	Yes	Automatic
	A2.10	Uncompensated hearing loss	Exclusion criteria 20 met as specified in the protocol.	Yes	Automatic
B		**Informed consent not available/not done**			
	B1	Informed consent not available/not done	Informed consent date missing; no signature on ICF	Exclude from All	Automatic /Manual
	B2	Informed consent too late	Check if informed consent date (actual consent date) was prior or on Visit 1. Applicable to all informed consents. 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 IPV	No	Automatic /Manual
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 RDC) 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 (IVRS assignment). If not, and if treated consistently throughout the trial, analyze as treated.	Yes	Automatic

Table 6.2: 1 (continued) important protocol violations

Category /Code		Description	Example/Comment	Excluded from PPS	Automatic /Manual
	C2	**Randomisation 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 IVRS. 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.	Yes	Manual
	C3	**Non-compliance with study medication**			
	C3.1	Non-compliance with study medication	Compliance < 80% or >120 %	Yes if <80%	Automatic /Manual
D		**Concomitant medication**			
	D1	Prohibited medication use before the treatment period of the trial	To be determined on a case by case basis.	Yes	Automatic /Manual
	D2	Prohibited medication use during the conduct of the trial	To be determined on a case by case basis.	Yes	Automatic /Manual
E		**Trial specific protocol violations**			
	E1	Negative pregnancy test result not obtained during the study participation		No	Automatic
	E2	Treatment not discontinued due to HR elevation as described in CTP section 3.3.4.		No	Automatic
	E3	Study partner change during study.		Yes	Automatic
	E4	Assessments administered by unqualified rater		Yes	Manual
	E5	C-SSRS not administered at every visit		No	Automatic

Table 6.2: 1 (continued) important protocol violations

Category /Code		Description	Example/Comment	Excluded from PPS	Automatic/ Manual
F		**Incorrect timing of endpoint measurements**			
	F1	**Incorrect timing - assessments**			
	F1.1	Assessment order not followed	NTB not administered in order specified in CTP	Yes	Automatic
	F1.2	Rater switch on primary endpoint	NTB not administered by same rater	Yes	Manual
	F2	**Incorrect timing – times of measurements**			
	F2.1	Assessment of NTB outside of window between visits	NTB assessment time >2 hour from Visit 3 NTB assessment time.	Yes	Automatic

KEY: PPS – Per Protocol Set

6.3 PATIENT SETS ANALYSED

SCR - Screened set: All patients screened for the trial, with informed consent given 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 drug.

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 post baseline on treatment primary endpoint NTB assessment (or secondary endpoint assessment). The FAS will be used for the primary analyses (and secondary analyses).

PPS- Per protocol set: All patients in the FAS without important protocol deviations that impact efficacy assessments. No analyses for the CTR are planned using the PPS set.

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.

If a patient erroneously receives the wrong dose of study drug, the patient's efficacy data will be analyzed in the randomized treatment group and the patient's safety data will be analyzed in the actual treatment group.

The efficacy analyses will follow the intention-to-treat (ITT) principle in assigning patients to treatment groups. I.e., efficacy analyses will be analyzed as randomized using the FAS.

If a patient receives a different study drug than randomized, this will be noted as an IPV.

Table 6.3: 1 Patient sets analyzed

	Patient set			
Class of endpoint	SCR	RS	TS	FAS
Primary				OC
Secondary				OC
Further				OC
Safety endpoints			OR	
Disposition	OR[1]	OR[1]	OR[1]	
Demographic		OR[2]	OR	
Baseline endpoints		OC		
Disclosure tables	OR		OR	

1) Disposition table requires multiple patient sets to populate
2) Additional table for clinical trial disclosure requirements

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

Note that the number of patients with available data for an endpoint may differ. For details, see Section 6.6.

[redacted]

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 endpoints that are not meaningful to apply any imputation rule on them for replacing the missing values.

6.6.1 Missing efficacy data

NTB

Details on scoring with missing items are described in section 9.1.

ADAS-Cog11

If a patient has 3 or fewer missing ADAS-Cog/11 items, the following algorithm will be used to compute the ADAS-Cog/11 total score:

Total score = [(total score from completed items) / (maximum total score for completed items)]*(maximum total score[=70] for all items in the scale)

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

ADCS-ADL-MCI

For ADCS-ADL-MCI, if <30% of the items are missing, the total score will be imputed. The sum of the nonmissing items will be prorated to the sum of total items. The imputed number will be rounded up to the nearest integer. If the nearest integer is greater than the maximum possible score, the imputed score will be equal to the maximum score. If >30% of the items are missing, the total score at that visit will be considered missing. For e.g Total score = [(total score from completed items) / (maximum total score for completed items)]*(maximum total score[=69] for all items in the scale)

Supplementary material for [8].

CDR-SB

If only 1 box (of 6) of the CDR is missing, the sum of the boxes will be imputed by prorating the sum from the other 5 boxes. If the score from more than 1 box is not available, the CDR-SB at that visit will be considered missing. For e.g Total score = [(total score from completed items) / (maximum total score for completed items)]*(maximum total score[=18] for all items in the scale) Supplementary material for [16].

Observed cases (OC) analysis

For all efficacy endpoints using MMRM analyses, it is planned to analyze only the available data that were observed 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.

The following imputation methods will be used if the rate of missing data is greater than 5%.

The method below will be used for the endpoints using ANCOVA analyses.

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 last on-treatment value within the time window will be carried forward, while the visit value can be the value that was observed closest to the planned visit date or the first value observed in the time window. See Table 6.7: 2 for further details.

Baseline Observation Carried Forward (BOCF)

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 (see "Handling of missing and incomplete AE dates") (2).

6.6.4 Missing plasma concentrations and pharmacokinetic parameters

Missing data and outliers of PK data are handled according to (1).

6.7 BASELINE, TIME WINDOWS, AND CALCULATED VISITS

For efficacy, the baseline is defined as the pre-treatment observation at Visit 3. All other baseline variables will be observed from Visit 1.

For laboratory safety measurements, the last values prior to study 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.

Table 6.7: 1 Time windows for all pre/on-treatment safety visits

Visit number	Visit label	Planned days	Interval (actual days on treatment)
1	Screening	-28	(-∞, PBORI-1]
2	Placebo Run-in period	-14	[PBORI ,TREATMENT-1]
3	Baseline	1	[NA, 1]
4a	Week 1	8	[2, 11]
4b	Week 2	15	[12, 18]
4c	Week 3	22	[19, 25]
5	Week 4	29	[26, 43]
6	Week 8	57	[44, 73]
EOT	Week 12	85	[74, 99]
FU	Follow-up	113	[100, Study drug stop date + 7 days]

These time windows are defined based on the planned number of days after the date of first administration of study drug. Reasons to base the time windows on the actual treatment start date rather than the randomization date are:

- If first intake of study drug shows a large delay by e.g. more than one week after the date of randomization, a measurement taken four weeks after randomization rather reflects the drug effect after three weeks than after four weeks and thus may underestimate the treatment effect at this visit.
- With large delays of the introduction of study drug after the randomization, the time window for the first on-treatment visit could include times the patient was not yet on study drug.

Table 6.7: 2 Time windows for on-treatment efficacy measurement scheduled for each on treatment visit

			Time window (actual days on treatment)	
Visit Number	Visit label	Planned days	Start	End[A]
3	Baseline	1	NA	1[B]
5	Week 4	29	2	57
EOT	Week 12	85	58	Study drug stop date + 7 days

A In case of premature discontinuation of the study drug an EOT Visit has to be performed. If such an EOT Visit falls into the time window of a previous visit, measurements will be assigned to this previous visit and the visit value will be determined as described below. In this case the time window for the visit that includes EOT Visit will end 7 days after the study drug stop date, including Day 7.

B Only values taken prior to the start of treatment with randomized study drug can be considered baseline values. Time windows will be used for assignment of measurements to scheduled visits.

-

Repeated and unscheduled efficacy and safety measurements will be assigned to the nominal visits and listed in the subject data listing (SDL) according to the time windows described above.

If there are several safety laboratory values in one time window on treatment, the worst of these will be selected for the by-visit analyses.

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 closest to the protocol planned visit day. 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.

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

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

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.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

A summary of concomitant diseases will be provided by treatment group, System Organ Class (SOC) and Preferred Term (PT).

7.3 TREATMENT COMPLIANCE

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

Overall compliance will be calculated as mentioned in CTP section 4.3

7.4 PRIMARY ENDPOINT

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

Figures and tables will be displayed for the MMRM analysis results over time.

7.4.1 Primary efficacy analysis

The primary analysis and hypothesis testing are described in section 7.3.1 of the CTP.

7.5 SECONDARY ENDPOINTS

Figures and tables will be displayed for the MMRM and ANCOVA analyses results over time.

7.5.1 Key secondary endpoint

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

7.5.2 Other Secondary endpoints

The same primary analysis model will be performed for the secondary endpoint CDR-SB.

The secondary endpoints ADAS-Cog11 and ADCS-ADL-MCI will use the following model:

ANCOVA:

Analysis of covariance will be used for the change from baseline secondary endpoint score after 12 weeks of treatment; terms include baseline value for secondary endpoint measure and treatment.

[redacted]

[redacted]

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. Cumulative exposure will be displayed by >=weeks displayed in the CTP flowchart.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

Analysis will be performed as defined in Section 7.3.3 of the CTP.

7.8.1 Adverse events

7.8.1.1 Assignment of AEs to treatment

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 multiple AE occurrence data on the CRF will be collapsed into an 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, 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)

For further details on summarization of AE data, please refer to (2, 3)

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 last drug intake + residual effect period will be assigned to the randomized treatment. All adverse events occurring before first drug intake will be assigned to ‘screening’ and all adverse events occurring after the residual effect period will be assigned to ‘post-treatment’ (for listings only). For details on the treatment definition, see section 6.1.

7.8.1.2 Analysis of other significant AEs

According to ICH E3 (11), 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.

7.8.1.3 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 (mention MedDRA levels to be displayed in the tables). Separate tables will be provided for patients with other significant adverse events according to ICH E3 (4), for patients with significant non-serious adverse events (only if these are defined for the project) and for patients with serious adverse events, for patients with AEs leading to discontinuation, and for patients with drug-related AEs.

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

7.8.1.4 AE summaries for disclosure

The following AE data is needed for disclosure on clinicaltrials.gov and EudraCT. This data will be included in section 16.1.9.2:

- Number of patients with non-serious AEs > of 5 %
- Total number of deaths (all causes – entire study period)
- Total number of deaths resulting from drug-related adverse events
- Total number of serious adverse events
- Total number of serious adverse events related to treatment
- Total number of fatal adverse events
- Total number of fatal adverse events related to treatment

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (5).

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

Laboratory measurements taken up to 7 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.

7.8.4 ECG

12-lead ECG measurements will be assessed as described in the CTP Flow Chart. ECG-findings before first intake of study 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 and analyzed as planned in section 7.8.1.

7.8.5 Others

7.8.5.1 C-SSRS

The individual items and categories of suicidal ideation and behaviour from the C-SSRS will be summarized through descriptive statistics according to section 9.2 and [9].

8 REFERENCES

1 *001 MCS 36-472: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.*

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

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

4 *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*

5 *001-MCG-157: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.*

6 *Harrison J, Minassian SL, Jenkins L, Black RS, Koller M, Grundman M, . A neuropsychological test battery for use in Alzheimer disease clinical trials. Arch Neurol 2007;64(9):1323-1329.*

7 Salloway S, Sperling R, Fox NC, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 2014;370:322-33.

8 Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 2014;370:311-21.

9 *001-MCG-117: "*Implementation at BI of the FDA guidance on prospective assessment of suicidal ideation and behavior*", current version; IDEA for CON*

9 ADDITIONAL SECTIONS

9.1 CALCULATION OF NTB TOTAL SCORE

Below is a description for the NTB along with detail on deriving the scores for the total scores and several subscales. The derivations are based on [6] and the supplementary information from [7].

Table 9.1: 1 NTB description and scoring

The NTB is a cognitive assessment made up of the following 9 component tests:

1. Wechsler Memory Scale Visual Paired Associates–Immediate (WMVis-I), range 0 to 18;

2. Wechsler Memory Scale Verbal Paired Associates–Immediate (WMVer-I), range 0 to 24;

3. Rey Auditory Verbal Learning Test–Immediate (RAVL-I), range 0 to 105;

4. Wechsler Memory Scale–Digit Span (WMDS), range 0 to 24;

5. Controlled Word Association Test (COWAT);

6. Category Fluency Test (CFT);

7. Wechsler Memory Scale Visual Paired Associates–Delayed (WMVis-D), range 0 to 6;

8. Wechsler Memory Scale Verbal Paired Associates–Delayed (WMVer-D), range 0 to 8;

9. Rey Auditory Verbal Learning Test–Delayed (RAVL-D), range 0 to 30.

The first 3 tests assess immediate memory (WMVis-I, WMVer-I, RAVL-I), the second 3 assess executive function (WMDS, COWAT, CFT), and the last 3 assess delayed memory (WMVis-D,
WMVer-D, RAVL-D). Higher scores indicate better cognition on all tests.

First, a total score for each component test except the RAVL-D is calculated by summing all the scores. For the RAVL-D, the total score is calculated as:

total part 7 + total part 8 correct + (15 - total part 8 incorrect).

Then, a z-score for each component test is calculated as follows. For each subject j, at assessment time point t (with $t = 0$ denoting baseline), let y_{ijt} denote subject j's score at time t for the ith component test ($i = 1, \ldots, 9$). Then the corresponding z-score, denoted z_{ijt}, is defined as:

$$z_{ijt} = (y_{ijt} - \bar{y}_{i0}) / s_{i0}$$

Where y_{i0} and s_{i0} denote the average and the standard deviation of the baseline scores on the ith component test across all study subjects in the FAS.

Finally, the NTB total score z_{jt} for the jth subject at time t is calculated by averaging the 9 component test z-scores:

$$z_{ijt} = (z_{1jt} + \cdots + z_{9jt})/9$$

The NTB total z-score will be calculated only if scores for at least 6 of the 9 component tests are not missing [6].

In addition, the following subscales are defined:

- NTB Immediate Memory z-score - average of the 3 immediate memory component test zscores;
- NTB Delayed Memory z-score - average of the 3 delayed memory component test z-scores;
- NTB All Memory z-score - average of all 6 memory component test z-scores;
- NTB Executive Function z-score - average of the 3 executive function component test zscores.
-

The Immediate Memory, Delayed Memory, and Executive Function z-scores will be calculated only if at least 2 of the 3 components tests are not missing. The All Memory z-score will be calculated only if at least 4 of the 6 components tests are not missing.

The NTB total z-score (as well as NTB Immediate Memory, NTB Delayed Memory, NTB All Memory, and NTB Executive Function z-scores) will be analyzed using the same MMRM as described for the primary analyses. These analyses will be conducted for the FAS.

9.2 C-SSRS FDA CATEGORIES

Eleven FDA categories and equivalent C-SSRS categories as the standard for classifying suicidal ideation and behavior

Table 9.2.1 CSSRS and FDA categories

FDA Categories	Equivalent C-SSRS categories
Suicidal ideation: 1. Passive 2. Active: Nonspecific (no method, intent, or plan) 3. Active: Method, but no intent or plan 4. Active: Method and intent, but no plan 5. Active: Method, intent, and plan Suicidal behavior: 6. Preparatory actions toward imminent suicidal behaviors 7. Aborted attempt 8. Interrupted attempt 9. Suicide attempt 10. Completed suicide 11. Self-injurious behavior, no suicidal intent	Suicidal ideation: 1. Wish to be dead 2. Non-specific active suicidal thoughts 3. Active suicidal ideation with any methods (not plan) without intent to act 4. Active suicidal ideation with some intent to act, without specific plan 5. Active suicidal ideation with specific plan and intent Suicidal behavior: 6. Preparatory acts or behaviour 7. Aborted attempt 8. Interrupted attempt 9. Non-fatal suicide attempt 10. Completed suicide 11. Self-injurious behavior without suicidal intent

9.3 SAS CODE

The below table summarizes the SAS code for the main analyses

Table 9.3.1 SAS Code for main analyses

Analysis	Code	Comments
Dose response	Test the following model: $\mu(d_i) = \beta_0 + \beta_1 d_i + \beta_2 d_i^2$ PROC GLM DATA=one; MODEL chgept = trt trt*trt; RUN; Treat BID dose as an in between dose = (QD + 2*QD)/2	Dose is treated as a continuous variable. $\mu(d_i)$ denotes the mean response of dose level i.
MMRM	PROC MIXED DATA=dat cl method=reml ORDER=formatted; CLASS trt visit patient ; MODEL chgept = trt baseline visit trt*visit baseline / ddfm=KR solution; REPEATED visit / type=un subject=patient r rcorr ; LSMEANS trt*visit / pdiff=all cl; RUN ;	
ANCOVA	PROC MIXED data=one METHOD=reml ORDER=formatted; CLASS trt ; MODEL chgept = baseline trt ; LSMEANS trt / CL DIFF OM ; RUN;	

10 HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	**13-Jun-17**	[redacted]	None	This is the final TSAP without any modification