TRIAL STATISTICAL ANALYSIS PLAN c20737022-01

BI Trial No.:	1289-0040
Title:	A study to investigate the pharmacokinetic drug-drug interaction following oral administration of ethinylestradiol/levonorgestrel (Microgynon®) and BI 409306 in healthy Korean premenopausal female subjects (an open-label, two-period, fixed-sequence study) Protocol Amendment 1 1289-0040-protocol-amendment-1 [c13608215-02]
Investigational Product:	BI 409306
Responsible trial statistician:	
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Date of statistical analysis plan:	05 JAN 2018 SIGNED
Version:	Final

1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis data set
AE	Adverse event
BMI	Body mass index
CTP	Clinical trial protocol
CTR	Clinical trial report
DBL	Data base lock
ES	Entered set
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
O * C	Oracle ClinicalTM
PK	Pharmacokinetic
PKS	Pharmacokinetic set
PV	Protocol violation
RAGe	Report Appendix Generator system
REP	Residual effect period
RPM	Report planning meeting
SAE	Serious adverse event
SD	Standard deviation
TS	Treated set
TSAP	Trial statistical analysis plan

3. INTRODUCTION

As per International Conference on Harmonisation (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 trial statistical analysis plan (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 Oracle ClinicalTM (O*C) system.

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin^{TM} software (version 6.3, Certara USA Inc., Princeton, NJ, USA).

The statistical analyses will be performed within the validated working environment CARE, including SASTM (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SASTM-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).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There will be no changes in the planned analysis of the study.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

Primary PK endpoints as defined in Section 5.5.1.1 of the CTP:

The following primary endpoints will be determined for BI 409306

- *AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

The following primary endpoints will be determined for ethinylestradiol and levonorgestrel:

- *$AUC_{0-24,ss}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)*
- *$C_{max,ss}$ (maximum measured concentration of the analyte in plasma)*

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

There are no key secondary endpoints in this trial.

5.2.2 Secondary endpoint(s)

Section 5.5.1.2 of the CTP:

The following secondary endpoints will be evaluated for BI 409306:

- *$AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)*

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on investigational products, assignments of treatment, and selection of doses, please see CTP, Sections 3 and 4. For details of dosage and formulation see Table 6.1: 1 below.

Table 6.1: 1 Labels for treatments for use in the CTR

Treatment	Substance	Formulation	Unit strength	Dosage	Short label
R1 (Reference 1)	BI 409306	Film coated tablet	25 mg	1 tablet on Day 29	BI
T1 (Test 1)	BI 409306	Film coated tablet	25 mg	1 tablet on Day 18	BI+Microgynon®
	Microgynon®	Coated tablet	0.03 mg EE / 0.15 mg LNG	1 tablet on Day 18	
R2 (Reference 2)	Microgynon®	Coated tablet	0.03 mg EE / 0.15 mg LNG	1 tablet on Day 17	Microgynon®
T2 (Test 2)	Microgynon®	Coated tablet	0.03 mg EE / 0.15 mg LNG	1 tablet on Day 18	BI+Microgynon®
	BI 409306	Film coated tablet	25 mg	1 tablet on Day 18	

The following separate study phases will be defined for the analyses of AEs:

- Screening (ranging from day of informed consent until first administration of study drug)
- Microgynon® treatment (ranging from the time of first intake of Microgynon® until the time of first administration of BI 409306 or last intake of Microgynon® + Microgynon® REP (10 days), whatever occurs earlier)
- BI 409306 + Microgynon® treatment (ranging from the first administration of BI 409306 + Microgynon® until end of Microgynon® REP (10 days))
- BI 409306 treatment

- Follow up BI 409306 treatment

The residual effect period (REP) for BI 409306, when measurable drug levels or PD effects are still likely to be present, The REP for Microgynon® is considered to be 10 days.

Displays of AEs will be presented separately for the following treatments during on treatment phase:

- BI 409306, tablet, qd (labelled "BI")
- Microgynon®, tablet, qd (labelled "Microgynon")
- BI 409306, tablet, qd + Microgynon®, tablet, qd (labelled "BI + Microgynon")

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

A) Section 15.3 and Appendix 16.1.9.2.8 (for ClinicalTrials.gov) of the CTR displays:

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

The following total will be provided in addition (Section 15.3 only):

- a total over all on treatment phases involving BI ("Total BI")
- a total over all on treatment phases included in this analysis ("Total on treatment")

B) Section 15.4 and Appendix 16.1.9.2.8 (except for ClinicalTrials.gov) of the CTR displays:

- Screening
- On treatment (labelled with the name of the study treatment (short label))
- Follow-up BI (labelled "FU BI")

In Section 16.1.9.2.8 AE tables, the following totals will be provided in addition:

- a total over all study phases ("Total")

Tables of vital signs and laboratory values will present results by the following separate study phases which will be defined for the analyses of vital signs and laboratory values:

- Screening (ranging from day of informed consent until first administration of study drug)
- Microgynon® treatment (ranging from first intake of Microgynon® until first administration of BI 409306 or last intake of Microgynon® + Microgynon® REP (10 days), whatever occurs earlier)
- BI 409306 + Microgynon® treatment (ranging from first administration of BI 409306 + Microgynon® until administration of BI 409306 +
- Microgynon® treatment (ranging from end of until last intake of Microgynon® + Microgynon® REP (10 days))
- BI 409306 treatment (ranging from first administration of BI 409306 alone until EOT or last intake of BI 409306 + whatever occurs earlier)

- Follow up BI 409306 treatment (ranging from end of last BI 409306 treatment +

For detailed information on the handling of the treatments in the O*C views refer to Technical TSAP analysis data set (ADS) plan.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Data discrepancies and deviations from the CTP will be identified for all subjects in the database (i.e., treated subjects and subjects with serious AE (SAE) which the investigator considered related to the screening procedure). Consistency check listings (for identification of violations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the report planning meeting (RPM) and data base lock meeting (RPM/DBL). At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database.

Each protocol deviation must be assessed to determine whether it is an important protocol violation (PV). For definition of important PVs, and for the process of identification of these, refer to the Boehringer Ingelheim reference document 'Protocol Violation Handling Definitions' (2).

If any important PVs are identified, they are to be summarised into categories and will be captured in the RPM minutes via accompanying Excel spreadsheet (3). The following table contains the categories which are considered to be important PVs in this trial. If the data show other important PVs, this table will be supplemented accordingly by the time of the RPM. If substantial numbers of PVs are reported at the RPM, a decision about summarising the PVs in a tabular format will be made. Otherwise, only a PV listing will be provided.

The following Table 6.2: 1 gives the important PVs for this trial.

Table 6.2: 1 Important Protocol violations

Category / Code		Description
A		**Entrance criteria not met**
	A1	Inclusion criteria violated
	A2	Exclusion criteria violated
B		**Informed consent**
	B1	Informed consent not available
	B2	Informed consent too late
C		**Trial medication and randomization**
	C1	Incorrect trial medication taken
	C2	Non-compliance
	C3	Incorrect intake of trial medication
D		**Concomitant medication**
	D1	Prohibited medication use
E		**Missing data**
	E1	Certain violations of procedures used to measure primary or secondary data
F		**Incorrect timing**
	F1	Certain violations of time schedule used to measure primary or secondary data.
G		**Other trial specific important violations**
	G1	Incorrect intake of meal

6.3 SUBJECT SETS ANALYSED

- **Entered set (ES):**

  This subject set includes all entered subjects, whether treated or not.

- **Treated set (TS):**

  This subject set includes all subjects from the ES who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

  This is the full analysis set population in the sense of ICH-E9 (1). It is used for safety analysis.

  Section 7.3.1 of the CTP:

  Primary and secondary pharmacokinetic parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

  Relevant protocol violations may be

  - *Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to*
  - *Incorrect dose of trial medication taken*
  - *Use of restricted medications.*

  Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

  - *the subject experienced emesis that occurred at or before two times median tmax of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),*
  - *a pre-dose concentration is >5% of the C_{max} value of that subject*
  - *missing samples/concentration data at important phases of PK disposition curve.*

- **Pharmacokinetic set (PKS):**

  The PK parameter analysis set (PKS) includes all subjects in the TS who provide at least one primary or secondary PK parameter that was not excluded according to the description above. Thus, a subject will be included in the PKS, even if she contributes

only one PK parameter value for one period to the statistical assessment. It is used for the PK analysis.

The discussion of all exceptional cases and problems and the decisions on the allocation of subjects to populations will be made at latest at the RPM.

The following table summarizes which subject sets will be used for the different analyses.

Table 6.3: 1 Subject sets analysed

Class of endpoint	ES	TS	PKS
Disposition, exposure	X		
Important PVs	X		
Primary endpoints			X
Secondary endpoints and further parameters of interest in PK analyses			X
Safety endpoints		X	
Demographic/baseline endpoints		X	

6.5 POOLING OF CENTRES

This section is not applicable, because the study was performed in only one centre.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data will be according to the CTP, Section 7.4. Additionally, handling information of missing data is shown as follows:

- Missing data and outliers of PK data are handled according to (4).
- Missing or incomplete AE dates are imputed according to BI standards (see “Handling of missing and incomplete AE dates”) (5).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline values of laboratory data and value of vital sign for safety analysis will be defined as the last values before first drug administration.

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the RPM/DBLM.

7. PLANNED ANALYSIS

In general, a set of descriptive statistics to be displayed for continuous variables in the clinical trial report will be as follows:

Non-pharmacokinetic variables:

For End-Of-Text tables, the set of summary statistics is: N, mean, standard deviation (SD), min, median, and max.

Tabulation of frequencies for categorical or categorised data will include all possible categories and display number of observations (subjects) with the percentage relative to the respective treatment sequence / regimen. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there are actually missing values. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not.

Pharmacokinetic variables:

The analysis of standard PK parameters will be performed according to (4).

Safety analysis (refer to Section 7.8) will be presented in Sections 15.1 to 15.4 of the CTR and in Appendices 16.2 and 16.1.9.2.

Inferential statistical analyses of PK endpoints (refer to Section 7.5.2) will be presented in Section 15.5 of the CTR and in Appendix 16.1.9.3.

Descriptive data analysis of PK endpoints will be performed by BI and will be presented in Section 15.6 of the CTR.

The format of the listings and tables will follow the standards defined in the BI corporate guideline “Reporting of clinical trials and project summaries” [001-MCG-159] (6) with the exception of those generated for PK calculations.

The individual values of all subjects will be listed, sorted by treatment sequence, subject number, visit and actual treatment (if appropriate). The listings will be included in Appendix 16.2 of the CTR.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

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

For analyte 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

For PK parameters, P10, P90, Q1 and Q3 will be calculated.

The data format for descriptive statistics of 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.

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 (%) for each treatment group. Percentages will be rounded to one decimal place and will be based on all subjects in the respective subject set whether they have non-missing values or not. The category 'missing' will be displayed only if there are actually missing values.

Units of variables should be given in the titles or column/row descriptors in square brackets (e.g. [mg]).

Exclusion of PK parameters

The ADS ADPP contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters if they are not flagged for exclusion; that is APEXC is equal to “Included”.

Exclusion of PK concentrations

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

Further details are given in 001-MCS-36-472_RD-01 “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (4) and 001-MCS-36-472_RD-03 “Description of Analytical Transfer Files and PK/PD Data Files” (7).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

Only listing is planned for this section of the report. The data will be summarised in total.

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM/DBLM.

A medication will be considered concomitant to a treatment, if it

- is ongoing at the time of first administration of this treatment, or
- starts within the analysis phase of the respective treatment (see Section 6.1 for a definition of treatments and analysis phases).

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analysed as a specific endpoint. Any deviations from complete intake will be addressed in the RPM and described in the CTR.

7.4 PRIMARY ENDPOINT(S)

The analysis will be performed as defined in the CTP, Sections 7.3.1-2.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

There are no key secondary endpoints in this trial.

7.5.2 (Other) Secondary endpoint(s)

The analysis will be performed as defined in the CTP, Sections 7.3.1-2.

7.7 EXTENT OF EXPOSURE

Only listing is planned for this section of the report.

7.8 SAFETY ANALYSIS

The analysis will be performed as defined in the CTP. All safety analyses will be performed on the TS.

7.8.1 Adverse events

AEs will be coded with the most recent version of MedDRA. The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs.

For analysis multiple AE occurrence data on the case report form (CRF) will be collapsed into one AE provided that all of the following applies:

- All AE attributes are identical (lower level term, intensity, 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 within one hour after end of the first occurrence).

For further details on summarisation of AE data, please refer to (5, 8).

Section 5.2.2.1 of the CTP:

The following are considered as AESIs in this trial:

- *Hepatic injury, as 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 sample, and/or*
  - *marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

The analysis of AEs will be based on the concept of treatment emergent AEs.

Section 5.2.2.2 of the CTP:

The REP for Microgynon is defined as 10 days after the last administration of Microgynon®.

Therefore, all AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment; please see Section 7.3.3 of CTP. *Events which occurred after the REP will be considered as post treatment events.*

For details on the treatment definition, see Section 6.1.

According to ICH E3 (9), AEs classified as 'other significant' needs to be reported and will include those non-serious 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 RPM/database lock (DBL) meeting.

An overall summary of AEs will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class and preferred term (MedDRA levels to be displayed in the tables).

Separate tables will be provided for subjects with other significant AEs according to ICH E3 (9), for subjects with significant non-serious AEs (only if these are defined for the project) and for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug related SAEs and for subjects with AESIs.

The table for the subject with non-serious AEs occurring with incidence in preferred term greater than 5 % will be provided. Additionally, occurred AEs will be listed.

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 (10), descriptive statistics with original values will be provided for baseline, on-treatment values and for changes from baseline. Clinically relevant findings in laboratory data will be reported as AEs and will be analysed as part of AE analysis. Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of subjects within and outside the reference range at baseline and the last measurement on treatment.

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments on the eCRF or at the RPM/DBLM at the latest. It is the investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Standard or project-specific rules for flagging clinically significant values will not be applied in this study.

7.8.3 Vital signs

Only descriptive statistics by planned visit are planned for this section of the report for absolute values and changes from baseline. 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

ECG data will not be listed but clinically relevant abnormal findings will be reported as AEs.

7.8.5 Others

Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such. No separate listing or analysis of physical examination findings will be prepared.

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.
2	*001-MCS-50-413_RD-01*: "Protocol Violation Handling Definitions", current version; IDEA for CON.
3	*001-MCS-50-413_RD-02*: "Important Manual Protocol Violations Spreadsheet", current version; IDEA for CON.
4	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON;
5	*001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version IDEA for CON;
6	*001-MCG-159*: “Reporting of clinical trials and project summaries”, current version;IDEA for CON.
7	*001-MCS-36-472_RD-03*: “Description of Analytical Transfer Files and PK/PD Data Files”, current version; IDEA for CON.
8	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", Version 5; IDEA for CON.
9	*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
10	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**05-JAN-18**		None	