Clinical Trial Protocol

	Document Number: c13608215-02
BI Trial No.:	1289-0040
BI Investigational Product:	BI 409306
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)
Lay Title:	This study tests in healthy Korean women which effects BI 409306 and a birth-control pill have on each other.
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol(Revised Protocol(based on global amendment1))
Version and Date:	Version: 2.0 Date: 14 Jul 2017

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 409306			
Protocol date: 30 Mar 2017	**Trial number:** 1289-0040		**Revision date:** 14 Jul 2017
Title of trial:	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)		
Principal Investigator:	 Phone: Fax:		
Trial site:			
Clinical phase:	I		
Objectives:	To investigate the effect of multiple dose of ethinylestradiol/levonorgestrel (Microgynon®) on single dose pharmacokinetics of BI 409306 and the effect of single dose of BI 409306 on multiple dose pharmacokinetics of ethinylestradiol/levonorgestrel (Microgynon®)		
Methodology:	Open-label, run-in period, two treatment periods in a fixed-sequence		
No. of subjects:			
total entered:	16		
each treatment:	16		
Diagnosis:	Not applicable		
Main criteria for inclusion:	Healthy Korean premenopausal female subjects, age of 19 to 40 years, body mass index (BMI) of 18.5 to 25.0 kg/m^2, CYP2C19 poor metabolizer (PM) status		
Trial product 1:	BI 409306 film-coated tablets		
strength:	25 mg		
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h on Days 18 and 29		
Trial product 2:	Microgynon® 30		
strength:	0.03 mg ethinylestradiol (EE) and 0.15 mg levonorgestrel (LNG)		
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h on Days 17 and 18 On all other trial days no fasting is required		

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Duration of treatment:	**Run-in period (Day -49/-28 to Day -8)** Microgynon® QD for 21-42 days (until Day -8) (depending on individual stage of menstrual cycle) **Treatment period** Days 1 to 17: Microgynon® QD for 17 days (R2 on Day 17) Day 18: BI 409306 + Microgynon® (T1 and T2) Days 19 to 21: Microgynon® QD for 3 days Day 29: BI 409306 (R1) **Treatments:** **BI 409306 as victim (part 1):** Reference 1 (R1): 1 tablet BI 409306 on Day 29. Test 1 (T1): 1 tablet BI 409306 together with 1 tablet Microgynon® QD on Day 18. **Microgynon® as victim (part 2):** Reference 2 (R2): 1 tablet Microgynon® QD on Day 17 Test 2 (T2) : 1 tablet Microgynon® QD together with 1 tablet BI 409306 on Day 18
Criteria for pharmacokinetics:	Primary endpoints: (part 1) BI 409306 as victim AUC_{0-tz} and C_{max} of BI 409306 in plasma for T1 compared with R1 (part 2) Microgynon® as victim $AUC_{0-24,ss}$ and $C_{max,ss}$ of EE in plasma for T2 compared with R2 $AUC_{0-24,ss}$ and $C_{max,ss}$ of LNG in plasma for T2 compared with R2 Secondary endpoint: (part 1) BI 409306 as victim $AUC_{0-\infty}$ of BI 409306 in plasma for T1 compared with R1

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Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 409306			
Protocol date: 30 Mar 2017	**Trial number:** 1289-0040		**Revision date:** 14 Jul 2017
Criteria for safety:	Adverse events (AEs) including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR])		
Statistical methods:	The effect of Microgynon® on the pharmacokinetics of BI 409306 will be evaluated by estimating the ratios of the geometric means for the primary and secondary PK endpoints (part 1). The effect of BI 409306 on the pharmacokinetics of Microgynon® will be evaluated by estimating the ratios of the geometric means for the primary PK endpoints (part 2). For both parts, the two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified. The statistical model used will be an ANOVA on the logarithmic scale including effects for 'subject' and 'treatment' in part 1 and part 2. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.		

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FLOW CHART

Period	Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{blood} for EE and LNG	PK_{blood} for BI 409306	12-lead ECG	Pregnancy test	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-70 to -29			Screening (SCR)[1]	x[5]			x	x	x	
Run-in[8]	2	-49 to -8			Microgynon® intake[9]							x[9]
		-3 to -1			Ambulatory visit	x			x	x	x	x
Treatment	3	1	-02:00	07:00								x
			00:00	09:00	Drug administration (ambulatory): Microgynon®		x[7]					x
		2	24:00	09:00	Drug administration (ambulatory): Microgynon®							x
		3	48:00	09:00	Drug administration (ambulatory): Microgynon®							x
		4	72:00	09:00	Drug administration (ambulatory): Microgynon®							x
		5	96:00	09:00	Drug administration (ambulatory): Microgynon®							x
		6	120:00	09:00	Drug administration (ambulatory): Microgynon®							x
		7	144:00	09:00	Drug administration (ambulatory): Microgynon®							x
		8	168:00	09:00	Drug administration (ambulatory): Microgynon®							x
		9	192:00	09:00	Drug administration (ambulatory): Microgynon®							x
		10	216:00	09:00	Drug administration (ambulatory): Microgynon®							x
		11	240:00	09:00	Drug administration (ambulatory): Microgynon®							x
		12	264:00	09:00	Drug administration (ambulatory): Microgynon®							x
		13	288:00	09:00	Drug administration (ambulatory): Microgynon®							x
		14	312:00	09:00	Drug administration (ambulatory): Microgynon®							x
		15	336:00	09:00	Drug administration (ambulatory): Microgynon®							x

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FLOW CHART (Cont.)

Period	Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{blood} for EE and LNG	PK_{blood} for BI 409306	12-lead ECG	Pregnancy test	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
Treatment	3	16	360:00	09:00	Drug administration (ambulatory): Microgynon®	x	x[7]					x
			367:00	16:00	Admission to the trial site[10]					x		x
		17	382:00	07:00								
			384:00	09:00	Drug administration: Microgynon®		x[7]					x
			384:30	09:30			x					x
			385:00	10:00			x					x
			385:30	10:30			x					x
			386:00	11:00	240 mL fluid intake (mandatory)		x					x
			388:00	13:00	240 mL fluid intake (mandatory) Lunch[3]		x					x
			392:00	17:00			x					x
			395:00	20:00	Dinner[3]							
			398:00	23:00			x					x
		18	406:00	07:00		x[2]			x[2]		x[2]	x
			408:00	09:00	Drug administration: BI 409306 + Microgynon®		x[7]	x[7]				x
			408:15	09:15				x				x
			408:30	09:30			x	x				x
			408:45	09:45				x				x
			409:00	10:00			x	x				x
			409:30	10:30			x	x				x
			410:00	11:00	240 mL fluid intake (mandatory)		x	x				x
			410:30	11:30				x				x
			411:00	12:00				x				x
			412:00	13:00	240 mL fluid intake (mandatory) Lunch[3]		x	x				x
			414:00	15:00				x				x
			416:00	17:00			x	x				x
			418:00	19:00				x				x
			419:00	20:00	Dinner[3]							
			422:00	23:00			x	x				x
		19	432:00	09:00	Drug administration: Microgynon®		x[7]	x[7]			x	x
			444:00	21:00				x				x
		20	456:00	09:00	Drug administration: Microgynon®			x[7]				x
		21	480:00	09:00	Drug administration: Microgynon®			x[7]			x	x
			480:30	09:30	Discharge from trial site Breakfast[3] (optional)							

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FLOW CHART (Cont.)

Period	Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{blood} for EE and LNG	PK_{blood} for BI 409306	12-lead ECG	Pregnancy test	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
Treatment	3	28	655:00	16:00	Admission to the trial site[10]					x		x
		29	670:00	07:00		x[2]			x[2]		x[2]	x
			672:00	09:00	Drug administration: BI 409306		x[7]	x[7]				x
			672:15	09:15				x				x
			672:30	09:30				x				x
			672:45	09:45				x				x
			673:00	10:00				x				x
			673:30	10:30				x				x
			674:00	11:00	240 mL fluid intake (mandatory)			x				x
			674:30	11:30				x				x
			675:00	12:00				x				x
			676:00	13:00	240 mL fluid intake (mandatory) Lunch[3]			x				x
			678:00	15:00				x				x
			680:00	17:00				x				x
			682:00	19:00				x				x
			683:00	20:00	Dinner[3]							
			686:00	23:00				x				x
		30	696:00	09:00				x			x	x
			708:00	21:00				x				x
		31	720:00	09:00				x				x
		32	744:00	09:00				x			x	x
			744:30	09:30	Discharge from trial site Breakfast[3] (optional)							
EOT	4	33 to 35			End of trial (EOT) examination[4]	x			x	x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status, alcohol history, and pregnancy test), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected for those subjects whose CYP2C19 genotype is not known.
2. The time is approximate; the procedure is to be performed and completed within 2 h prior to drug administration.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. End of trial examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Including urine drug screening and alcohol breath test
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
7. PK sample taken within 10 minutes before dose
8. Days -7 to -1 of the run-in period are Microgynon® free days.

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9. The Microgynon® administration during the run-in period is done by the subjects at home. The subjects are advised to take the Microgynon® tablets with a cup of water at the same time each morning.
   The intake of Microgynon® starts depending on the subjects' actual menstruation cycle and at least -28 days before Day 1 of treatment period. In the run-in period, the subjects will take one tablet of Microgynon® daily until Day -8. On Day -7 to Day -1 no Microgynon® tablets will be given in order to induce withdrawal bleeding.
   During run-in period, phone contacts are scheduled for AE reporting at least every week.
10. Alcohol breath test will be performed prior to each admission.

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ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
ATE	Presence or risk of arterial thromboembolism
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BPM	beats per minute
CA	Competent authority
CHC	Combined hormonal contraceptives
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
COC	combined oral contraceptives
CRF	Case report form
CSF	Cerebrospinal fluid
CTMF	Clinical trial master file
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Genotyping of cytochrome P450
DDI	Drug-drug interactions
DILI	Drug induced liver impairment
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EE	ethinylestradiol

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EOT	End of trial
FDA	Food and Drug Administration
GCP	Good clinical practice
gCV	Geometric coefficient of variation
HR	Heart rate
IB	Investigator's brochure
ICH	Independent ethics committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	liquid chromatography tandem mass spectrometry assays
LNG	levonorgestrel
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{po}	Mean residence time of the analyte in the body after oral administration
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PM	Poor metabolizers
po	oral
PR	Pulse rate
q.d.	*Quaque die*, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
REP	Residual effect period
RDC	Remote Date Control
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SRD	Single-rising dose

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$t_{1/2}$	Terminal half-life of the analyte in plasma
TDMAP	Trial Data Management and Analysis Plan
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
t_z	Time of last measurable concentration of the analyte in plasma
TS	Treated Set
TSAP	Trial statistical analysis plan
VTE	Presence or risk of venous thromboembolism

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1.2 DRUG PROFILE

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1.2.2 Microgynon® (ethinylestradiol + levonorgestrel)

Ethinylestradiol

Ethinylestradiol (EE) is a synthetic estrogen with actions similar to those of estradiol. It is frequently used as the estrogenic component of combined oral contraceptives; a typical daily dose is 20 to 40 µg. Ethinylestradiol is also used as an emergency contraceptive drug combined with levonorgestrel or norgestrel. A combined preparation of ethinylestradiol with the anti-androgen cyproterone is used for the hormonal treatment of acne and hirsutism, particularly when contraception is also required. Ethinylestradiol has also been used for hormone replacement therapy; doses of 10 to 20 µg daily are given (with a progestogen in women with a uterus), but natural estrogens are usually preferred. Ethinylestradiol is also used for the treatment of female hypogonadism and the palliative treatment of prostate cancer and malignant breast cancer.

The adverse effects of estradiol and other estrogens are related, in part, to dose and duration of therapy, and to the sex and age of the recipient. In addition, adverse effects may be modified by administration of progestogen in combined oral contraceptives or hormone replacement therapy. Whether adverse effects of natural and synthetic estrogens differ, and whether the route of administration has an effect, is less clear. The use of estrogens in girls may cause premature closure of the epiphyses resulting in decreased final adult height. Large doses of estrogens used in palliative care have also been associated with nausea, fluid retention, venous and arterial thrombosis, and cholestatic jaundice. In men, large doses of estrogen cause impotence and feminising effects such as gynaecomastia. In women, uterine bleeding may occur after the cessation of estrogen therapy.

Ethinylestradiol is rapidly and well absorbed from the gastrointestinal tract with maximum plasma concentrations occurring after 1 h. The presence of an ethinyl group at the 17-position greatly reduces hepatic first-pass metabolism compared with estradiol, enabling the compound to be much more active after oral dosing, but there is some initial conjugation by the gut wall and systemic bioavailability is only about 45% (20-65%). Ethinylestradiol is highly protein bound (98%), but unlike naturally occurring estrogens which are mainly bound to sex-hormone binding globulin, it is principally bound to albumin. The apparent volume of distribution is 2.8 to 8.6 L/kg. It is metabolised in the liver by hydroxylation (mediated by CYP3A4) followed by glucuronidation (UGT1A1) and sulfatation of metabolites that undergo enterohepatic recycling. Metabolites are excreted via urine (40%) and bile (60%). The terminal half-life of ethinylestradiol is 10 to 20 h [R13-3708]. According to the FDA

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DDI guidance, oral contraceptives are weak CYP2C19 inhibitors due to estradiol.[P12-05791]

For a more detailed description of ethinylestradiol, please refer to the SmPC of Microgynon® (R17-0443).

Levonorgestrel

Norgestrel and its active (-)-isomer, levonorgestrel (LNG), are progestogens derived from nortestosterone. They are more potent inhibitors of ovulation than norethisterone and have androgenic activity. Levonorgestrel is more commonly used than norgestrel and is twice as potent. Both are used as hormonal contraceptives. The typical daily levonorgestrel dose is 30 or 37.5 µg when used as an oral progestogen-only contraceptive, 100 to 250 µg when used for the monophasic portion of combined oral contraceptives, and 50 to 125 µg when used in triphasic preparations. Levonorgestrel is also used as a long-acting progestogen-only contraceptive by subcutaneous implantation. An intrauterine device containing levonorgestrel is available for contraception or menorrhagia. For emergency contraception, levonorgestrel may be given alone or in combination with ethinylestradiol.

Progesterone and the progestogens may cause gastrointestinal disturbances, changes in appetite or weight, fluid retention, oedema, acne, chloasma (melasma), allergic skin rashes, urticaria, mental depression, breast changes including discomfort or occasionally gynaecomastia, changes in libido, hair loss, hirsutism, fatigue, drowsiness or insomnia, fever, headache, premenstrual syndrome-like symptoms, and altered menstrual cycles or irregular menstrual bleeding. Anaphylaxis or anaphylactoid reactions may occur rarely (<0.01%).

Levonorgestrel is rapidly and almost completely absorbed after an oral dose and undergoes little first-pass hepatic metabolism. Maximum plasma concentrations occur 1 to 2 hours after oral administration. Levonorgestrel is highly bound to plasma proteins, with 42 to 68% bound to sex hormone binding globulin and 30 to 56% bound to albumin. The proportion bound to sex hormone binding globulin is higher when levonorgestrel is given with an oestrogen.

Levonorgestrel is metabolised in the liver to sulfate and glucuronide conjugates, which are excreted in the urine (40 to 68% of dose) and to a lesser extent in the faeces (16 to 48% of dose). Levonorgestrel distributes into breast milk. The terminal half-life of levonorgestrel is approximately 25 hours [R13-3708]

For a more detailed description of levonorgestrel, please refer to the SmPC of Microgynon® (R17-0443).

Safety

Combined hormonal contraceptives (CHC) including Microgynon® should not be used in the following conditions. Should any of the conditions appear for the first time during CHC use, the product should be stopped immediately.

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- Presence or risk of venous thromboembolism (VTE)
- Presence or risk of arterial thromboembolism (ATE)
- Presence or history of severe hepatic disease or liver tumours
- Current or history of breast cancer
- Hypersensitivity to the active substances or to any of the excipients

The frequency of diagnosis of breast cancer is very slightly increased among combined oral contraceptives (COC) users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown.

The most common adverse events with Microgynon® are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, and breast tenderness. They occur in more than 1% of users.

Less common adverse events are vomiting, diarrhea, fluid retention, migraine, libido decreased, breast hypertrophy, rash, and urticarial.

Serious adverse reactions are VTE and ATE. Special warnings are precautions for use in arterial or venous thromboembolic disorders, strokes, hypertension, and liver tumours.

For a complete listing of adverse reactions including frequency of occurrence please refer to the current version of the summary of product characteristics (SmPC) (R17-0443)

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2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the effect of multiple doses of ethinylestradiol / levonorgestrel (Microgynon®) on single dose pharmacokinetics of BI 409306 and the effect of single dose of BI 409306 on multiple dose pharmacokinetics of ethinylestradiol / levonorgestrel (Microgynon®)

A description of the endpoints to be determined, and the observations along with specific information as how to collect the data for that information, is provided in Section 5.

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Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venipuncture for blood sampling.

The total volume of blood withdrawn during the entire study per subject will not exceed the volume of a normal blood donation (400 mL). No health-related risk to healthy subjects is expected from this blood withdrawal.

Risks related to Microgynon® administration

Microgynon® has been used for over 10 years and is generally well tolerated [R11-0385, R11-0382]. The intake of combined oral contraceptives is associated with an increased risk of serious side effects such as cardiovascular diseases (myocardial infarction, cerebrovascular insult, venous thromboembolism) and tumors of breast and liver. The incidence of venous thromboembolic events is 5-10 per 100.000 women in 1 year, if no hormonal contraceptives are used. The incidence is increased to about 20/100.000 after intake of 2nd generation combined oral contraceptives (containing levonorgestrel, e.g. Microgynon®). In contrast, the intake of 3rd generation combined oral contraceptives (containing gestoden or desogestrel) is associated with a higher risk (up to 40/100.000) of thrombembolic events [R12-0033].

The most frequent side effects (>10%) of Microgynon® are headache, spotting and intermenstrual bleeding. Furthermore the following undesirable effects have been observed: gastric upset, nausea, vomiting, breast tenderness, changes in body weight, changes in libido, and depression. In predisposed women, use of Microgynon® can sometimes cause chloasma which is exacerbated by exposure to sunlight. Women with a predisposition to pigment changes should avoid prolonged exposure to sunlight. Individual cases of poor tolerance of contact lenses have been reported with use of oral contraceptives; therefore, contact lens wearers who develop changes in lens tolerance should be assessed by an ophthalmologist.

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Menstrual changes associated with the use of oral contraceptives include reduction of menstrual flow and missed menstruation. Intermenstrual bleeding may occur but normally ceases spontaneously. Therefore, treatment with Microgynon® should be continued even if irregular bleeding occurs. If irregular bleeding is persistent, appropriate diagnostic measures to exclude an organic cause are indicated.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure subjects´ safety.

Safety measures

- Close monitoring of adverse events, safety lab, ECG and vital signs
- To reduce the risk of cardiovascular events, subjects with additional risk factors (smoking, adipositas, hypertension) are not to be entered in the trial, per inclusion/exclusion criteria and study restrictions.
- Thrombophilic testing will be performed on each subject to detect a potential thrombophilic disposition (deficiency of antithrombin III, resistance to activated protein C, etc.).
- In addition to the general inclusion examination, the suitability of subjects for taking this oral contraceptive will be assessed by a gynaecologist prior to trial entry.
- Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of alterations in selected liver laboratory parameters to ensure subjects´ safety.

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3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as an open-label, run-in period, two treatment periods in a fixed-sequence.

A total of 16 healthy Korean premenopausal female volunteers with CYP2C19 PM genotype will participate in the trial.

Run-in-period

All subjects will undergo a run-in period (Visit 2) that starts between Day -49 and Day -28. In this period, the subjects will take one tablet of Microgynon® daily (for 21-42 days) until Day -8. In the last 7 days of the run-in period (Day -7 to Day -1) no treatment will be given in order to induce withdrawal bleeding. The next day will be Day 1. Subjects who have already been using oral contraceptives before the study will start the run-in period after the usual tablet-free interval of 7 days. Subjects who have been using hormonal contraceptive vaginal rings before the study will start the run-in-period after the usual hormone-free interval of 7 days.

Treatment period

Visit 3 follows directly after the run-in-period. Subjects will be treated as below.

1 tablet of Microgynon® QD with 240 mL water on Days 1 to 17 (R2 on Day 17)
1 tablet of BI 409306 and 1 tablet of Microgynon® with 240 mL water on Day 18 (T1 and T2)
1 tablet of Microgynon® QD with 240 mL water on Days 19 to 21
1 tablet of BI 409306 with 240 mL water on Day 29 (R1)

Period	Screening	Run-in	Treatment						End of Trial
Visit	1	2	3						4
Day	-70 to -29	-49 to -1	1 to 16	17	18	19 to 21	…	29	33 to 35
BI 409306					X			X	
Microgynon®		X*	X	X	X	X			

* depending on the subjects' actual menstruation cycle. No Microgynon® on the Days -7 to -1.

An overview of all relevant trial activities is provided in the Flow Chart. For visit schedule and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

3.1.1 Administrative structure of the trial

The trial will be conducted at the
under the supervision of the Principal Investigator.

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The trial medication will be provided by the Clinical Trial Supplies Unit (CTSU), BI Pharma GmbH & Co. KG, Biberach, Germany.

On-site monitoring will be performed by BI or a contract research organisation appointed by BI.

The analyses of BI 409306 concentrations in plasma will be performed at the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany.

The analyses of ethinylestradiol and levonorgestrel concentrations in plasma will be performed at the laboratory of

Genotyping of cytochrome P450 (CYP) isoenzyme 2C19 will be performed at the study site.

Safety laboratory tests will be performed by the local laboratory of the trial site.

Electrocardiograms (ECG) are to be evaluated for subject safety at the study site by the investigator or representative.

Data management and statistical evaluation will be done by BI according to BI SOPs.

The trial is sponsored by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The trial will be conducted as an open-label, two-period, fixed-sequence trial.

The design of the study allows each subject to serve as her own control. The comparison between treatments is based on a comparison within subjects rather than between subjects. This means that the inter-subject variability is removed from the comparison between treatments [R94-1529].

Considering possible variations of enzyme activities during the menstrual cycle [R09-5728], a fixed-sequence design was chosen to ensure that pharmacokinetic parameters of the respective investigational drugs would be determined in all subjects at the same time point of the menstrual cycle. To exclude possible interaction with any preceding oral contraceptive regime and to minimize the influence of adaptation to a newly administered oral contraceptive, all participants will undergo a run-in period of at least 28 days (including treatment with Microgynon® for at least 21 days) before the beginning of the first study period. The duration of Microgynon® intake was chosen to ensure steady state condition for Microgynon®.The study design is considered appropriate to assess a possible influence of BI 409306 on the steady state pharmacokinetics of ethinylestradiol and levonorgestrel.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 16 healthy Korean premenopausal female subjects with CYP2C19 poor metabolizer (PM) genotype will enter the study. The CYP2C19 PM genotype is defined by

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the carriage of two non-functional alleles (*2 and *3) of the CYP2C19 gene. Subjects will be recruited from the volunteers' pool of the trial site.

A log of all subjects enrolled into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for study entry

The study will be performed in healthy female subjects.

3.3.2 Inclusion criteria

Subjects will only be included into the trial, if they meet the following criteria:

1. Healthy CYP2C19 PM genotyped (defined 5.3.1) premenopausal female subjects according to the investigator's assessment, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests.
2. Korean ethnicity according to the following criteria
   ; be a current Korean passport or national identification card holder, and have parents and grandparents who were all born in Korea
3. Age of 19 to 40 years (incl.)
4. BMI of 18.5 to 25.0 kg/m^2 (incl.)
5. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation
6. Female subjects who meet any of the following criteria starting from at least 30 days before the first administration of trial medication and until 30 days after trial completion:
   - Use of adequate contraception, e.g. non-hormonal intrauterine device *plus* condom
   - Sexually abstinent
   - A vasectomised sexual partner (vasectomy at least 1 year prior to enrolment)
   - Surgically sterilised (including hysterectomy)

3.3.3 Exclusion criteria

1. Any finding in the medical examination (including BP, PR or ECG) is deviating from normal and judged as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator

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5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, oncologic or hormonal disorders
6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days prior to administration of trial medication that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
12. Participation in another trial (including bioequivalence trial) where an investigational drug has been administered within 3 months prior to planned administration of trial medication
13. Current smoker or ex-smoker who quit smoking less than 30 days prior to screening
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 20 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study.
21. Any relevant finding of the gynaecological examination
22. Thrombotic predisposition according to thrombophilic testing
23. Existing or history of arterial thrombotic or embolic processes, conditions which predispose to them e.g. disorders of the clotting processes, valvular heart disease and atrial fibrillation
24. Existing or history of confirmed venous thromboembolism, family history of venous thromboembolism, and other known risk factors for venous thromboembolism.
25. Relevant varicosis
26. Use of hormone-containing intrauterine device, depot injection or contraceptive implants

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For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

An individual subject is to be removed from the trial if:

1. The subject withdraws consent, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as pregnancy, surgery, adverse events, or diseases)
4. The subject shows 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 needs to be followed up according to the 'DILI checklist' provided in the ISF.

A subject can also be removed from the trial if eligibility criteria are being violated or if the subject fails to comply with the protocol (for instance, by non-adherence to dietary rules, or non-attendance at study assessments).

If a subject is removed from or withdraws from the trial prior to first administration of trial medication in run-in period, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after first administration of trial medication in run-in period, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. These discontinuations will be discussed in the CTR.

If it is known that a subject becomes pregnant during the trial, administration of the trial medication has to be stopped immediately, and the subject has to be removed from the trial. The subject is to be followed until she has given birth or until the end of pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the clinical trial report. For reporting of pregnancy and all related events refer to Section 5.2.2.2.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for any of the following reasons:

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50%

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of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported that is considered to be unacceptable.

2. The expected enrolment goals overall are not met
3. Violation of GCP, or the CTP, or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

3.3.5 Replacement of subjects

In case some subjects do not complete the trial, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced. A replacement subject will be assigned a unique study subject number.

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4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of BI investigational product and comparator product.

Trial Product 1

Substance:	BI 409306
Pharmaceutical formulation:	film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	25 mg
Posology:	1-0-0
Route of administration:	p.o.
Duration of use:	Days 18 and 29

Trial Product 2

Name:	Microgynon® 30
Substance:	ethinylestradiol (EE) and levonorgestrel (LNG)
Pharmaceutical formulation:	coated tablet (sugar-coated)
Source:	Bayer plc, Bayer House
Unit strength:	0.03 mg EE and 0.15 mg LNG
Posology:	1-0-0
Route of administration:	p.o.
Duration of use:	Maximum 42 days in run-in period, 21 days in treatment period

4.1.2 Method of assigning subjects to treatment groups

This is an open-label, two-period, fixed-sequence trial.

The allocation of subjects to study subject numbers will be performed after screening. Once a subject number has been assigned, it cannot be reassigned to any other subject.

4.1.3 Selection of doses in the trial

The ethinylestradiol/levonorgestrel (Microgynon®) doses of 0.03 / 0.15 mg QD are standard clinical doses and were selected to achieve a the relevant plasma exposure for evaluation of a possible drug-drug interaction (see section 1.2).

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4.1.4 Drug assignment and administration of doses for each subject

All subjects will receive the two treatments in a fixed sequence order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

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

Run-in period:

The Microgynon® tablets for the run-in period (duration depends on the actual menstrual cycle of the subject) will be dispensed to the eligible subjects. The administration during the run-in period is done by the subjects and documented in a diary. The subjects are advised to

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take the Microgynon® tablets with a cup of water at the same in the morning. No Microgynon® tablets are to be taken in the last 7 days of the run-in period.

Treatment period:

The medication will be administered as an oral dose together with about 240 mL of water to a subject in the standing position under supervision of the investigating physician or an authorised designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. Administration in the morning of Days 17, 18 and 29 will be performed following an overnight fast starting no later than 10 h before scheduled dosing. For medication at all other time points no fasting is required.

Subjects will be kept under close medical surveillance for at least 12 h post dose on Days 17, 18 and 29.

During the first 2 h after drug administration on these days, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture, except for trial activities). For restrictions with regard to diet see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

No blinding was performed because the treatments are distinguishable from each another. This Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

Emergency envelopes will not be provided, since all subjects receive the same dose of different formulations in an open label design.

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The clinical trial supply containers for BI 409306 will be labelled with:

- BI trial number
- Batch number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units
- Route and mode of administration
- Term ‘For Clinical Trial Use’ (domestic language)
- Sponsor name and address
- Storage conditions
- Use-by date

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The blisters are labelled with reduced requirements.

The telephone number of the sponsor and name, address and telephone number of the trial site are given in the subject information form. Examples of the labels will be available in the ISF.

No re-supply is planned.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended (labelled) storage conditions. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) is to be immediately contacted.

4.1.8 Drug accountability

The investigator / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the study protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol

Only authorised personnel as documented in the form ‘Trial Staff List’ may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication must be returned to the sponsor. Receipt, usage and return must be documented on the respective forms in ISF. Account must be given for any discrepancies.

The investigator / pharmacist / investigational drug storage manager must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the returned to the sponsor of unused products.

These records will include dates, quantities, batch / serial numbers and expiry (‘use-by’) dates. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of return to the sponsor, the investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the investigator’s possession.

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4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

There are no specific rescue drugs foreseen for the treatment of AEs. No special emergency procedures are to be followed. No additional treatment is planned. However, in case of adverse events in need of treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed.

If a concomitant medication is required for treatment of adverse events the interaction potential with the trial drugs must be checked prior to administration. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart. No food is allowed for at least 4 h after drug intake.

On Days 17, 18 and 29 the following applies:
From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 12 h post-dose, total fluid intake is restricted to 2000 mL.

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Smoking is not allowed.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed from 24 h before administration of trial medication until 24 h after the last PK sample of each study period is collected.

Excessive physical activity (such as competitive sport) should be avoided starting 7 days before the first administration of trial medication until the end of trial examination.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study.

Adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for adequate measures).

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. This does not apply for dosing of Microgynon® in the run-in phase. The measured plasma concentrations will provide additional confirmation of compliance.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

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5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

Safety and tolerability of the investigational drug will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

These parameters will be evaluated in a descriptive way only, and are therefore considered to be 'further parameters of interest'. A confirmatory analysis is not planned (see Section 7.3).

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

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Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,

  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AEs considered 'Always Serious'

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be 'serious' even though they may not have met the criteria of an SAE as given above.

The latest list of 'Always Serious AEs' can be found in the RDC system, a remote data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.

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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

  These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF.
  In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity of AEs

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Causal relationship of AEs

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).

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- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

5.2.2.2 Adverse event collection and reporting

AEs collection

Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A careful written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, and intensity of the event as well as any treatment or action required for the event and its outcome.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards through the residual effect period (REP), until an individual subject's end of trial:
    - All AEs (serious and non-serious) and all AESIs.
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In

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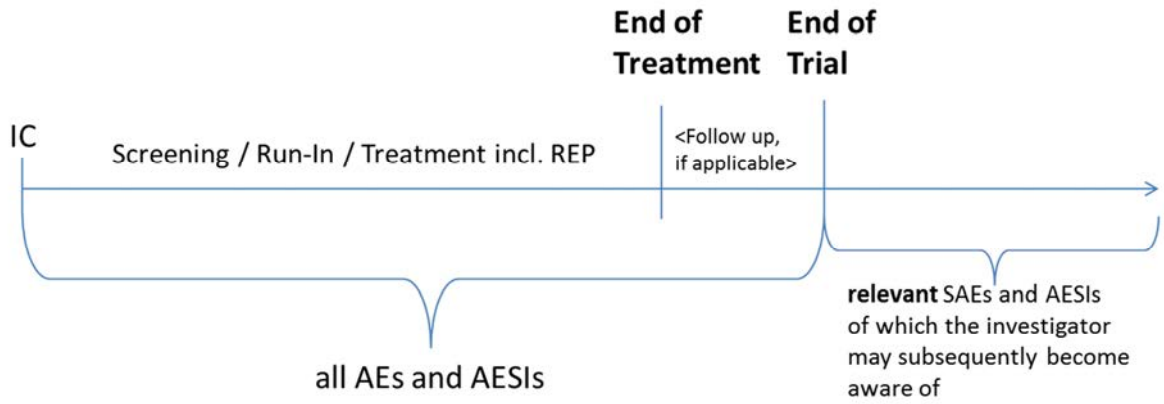
these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.

- After the individual subject's end of trial:
  - The investigator does not need to actively monitor the subject for AEs but should only report relevant SAEs and relevant AESIs of which may become aware of.



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. Events which occurred after the REP will be considered as post treatment events.

The follow-up period describes the period of time from the last administration of trial medication including the REP until the end of trial examination (last per protocol contact).

AE reporting to sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours of awareness) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form. The same timeline applies if follow-up information becomes available.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required

For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form (if applicable). The investigator should determine the causal relationship to the trial medication

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The following should also be recorded as an (S)AE in the CRF and on the SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual subject's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a subject has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 h. Overnight fasting is not required at the discretion of the investigator or designate for retests.

The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

Manual differential white blood cell count or urine sediment examinations will only be performed if there is a clinically relevant abnormality in the automatic blood cell count or in the urinalysis, respectively.

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Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name	Set A[1]	Set B[2]	Set C[3]
Hematology	Hematocrit	x	x	x
	Hemoglobin	x	x	x
	Red blood cell count (RBC)	x	x	x
	Reticulocyte count	x	-	-
	White blood cell count (WBC)	x	x	x
	Platelet count	x	x	x
Automatic WBC differential (relative)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes	x	x	x
Manual differential WBC (if automatic differential WBC is clinically relevant abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes	x	x	x
Coagulation	Activated partial thromboplastin time (aPTT)	x	-	x
	Prothrombin time (Quick's test and INR)	x	-	x
	Thrombophilic tests[4]	x	-	-
Enzymes	Aspartate transaminase (AST/GOT)	x	x	x
	Alanine transaminase (ALT/GPT)	x	x	x
	Alkaline phosphatase (ALP)	x	x	x
	Gamma-glutamyl transferase (GGT)	x	x	x
	Creatine kinase (CK)	x	x	x
	CK-MB, only if CK is elevated	x	x	x
	Lactate dehydrogenase (LDH)	x	x	x
	Amylase	x	-	-
	Lipase	x	-	-
Hormones	Thyroid stimulating hormone (TSH)	x	-	-
Substrates	Serum Glucose	x	x	x
	Creatinine	x	x	x
	Total bilirubin	x	x	x
	Direct bilirubin	x	x	x
	Total protein	x	-	-
	Uric acid	x	-	-
	Total cholesterol	x	-	-
	Triglycerides	x	-	-
	hs-CRP (high sensitivity C-Reactive Protein)	x	x	x

1 Parameters of Set A will be determined at the screening examination
2 Parameters of Set B will be determined during treatment periods at the time points given in the Flow Chart
3 Parameters of Set C will be determined at the end of trial examination
4 Thrombosis panel (Lupus anticoagulant / Anti-cardiolipin antibody (ACA) (IgM, IgG) / Protein C / Protein S / antithrombin III /anti-beta2 Glycoprotein I antibody (IgM, IgG) / Plasminogen)

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Table 5.2.3: 1 Routine laboratory tests (cont.).

Functional lab group	Test name	Set A[1]	Set B[2]	Set C[3]
Electrolytes	Sodium	x	x	x
	Potassium	x	x	x
	Calcium	x	-	-
Urinalysis[4] (Stix)		x	x	x
	Urine nitrite			
	Urine protein (albumin)			
	Urine glucose			
	Urine ketone			
	Urobilinogen			
	Urine bilirubin			
	Urine erythrocytes (RBC)			
	Urine leukocytes (WBC)			
	Urine pH			

1 Parameters of Set A will be determined at the screening examination
2 Parameters of Set B will be determined during treatment periods at the time points given in the Flow Chart
3 Parameters of Set C will be determined at the end of trial examination
4 Urine sediment: Microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine. Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name	Set A[1]	Set B[2]	Set C[3]
Drug screening (urine)	Includes: Amphetamine/MDA Barbiturates Benzodiazepine Cannabis, Cocaine Methadone Methamphetamines/MDMA/XTC Opiates , Phencyclidine Tricyclic antidepressants	x	-	-
Infectious serology (blood)	Includes: Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV 1+2-antibody	x	-	-
Pregnancy test (urine)	Beta human chorionic gonadotropin (beta-HCG)	x	x	x

1 Parameters of Set A will be determined at the screening examination
2 Parameters of Set B will be determined during treatment periods at the time points given in the Flow Chart
3 Parameters of Set C will be determined at the end of trial examination

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To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed at screening and prior to each admission, and may be repeated at any time during the study at the discretion of an investigator or designate. The results will not be included in the CTR.

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at the trial site. Laboratory data will be transmitted electronically from the trial site to BI.

5.2.4 Electrocardiogram

For safety monitoring 12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph Mac 5500, GE Medical Systems, Milwauekee, USA or Philips Pagewriter trim III).

The ECGs will be recorded for 10 second duration after the subjects have rested for at least 5 min in a supine position. Electrode placement will be performed according to the method of Einthoven/Goldberger modified by Mason/Likar (hips and shoulders instead of ankles and wrists). At time points, indicated in the Flow Chart, single ECGs will be recorded.

All locally printed ECGs will be evaluated by the investigator or a designee. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure monitor at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

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5.3 OTHER

5.3.1.2 Analytical determinations

Genotyping will be performed at the trial site (
. Genomic DNA will be extracted from blood samples according to standard molecular genetics methods and analyzed by TaqMan-PCR or other standard genotyping technologies.

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be recorded in the CRFs.

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5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoints

The following primary endpoints will be determined for BI 409306

- $AUC_{0\text{-}tz}$ (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:

- $AUC_{0\text{-}24,ss}$ (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)

5.5.1.2 Secondary endpoints

The following secondary endpoints will be evaluated for BI 409306:

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

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Further pharmacokinetic parameters might be calculated as appropriate.

5.5.2 Methods of sample collection

5.5.2.2 Plasma sampling for pharmacokinetic analysis of ethinylestradiol and levonorgestrel

For quantification of ethinylestradiol and levonorgestrel, approximately 6 mL of blood will be taken from an antecubital or forearm vein into an EDTA (ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

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The EDTA-anticoagulated blood samples will be centrifuged for about 15 min at about 2100 g and at 4 to 8 °C. If samples cannot be centrifuged immediately store them in an ice bath (up to 60 min) until centrifugation. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 1.5 mL plasma whereas the second aliquot should contain the remaining plasma. Within a maximum time of 1 hour after sampling at room temperature, the samples should be stored in a freezer. Until shipment on dry ice to the analytical laboratory, plasma samples will be stored frozen in an upright position at about –20°C or below. The second aliquot will be shipped after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory the plasma samples will be stored at about –20°C or below until analysis

At a minimum, the sample tube labels should list the following information: BI trial number, subject number, visit, and planned sampling time. Further information such as matrix and analyte may also be provided.

After completion of the trial the plasma samples may be used for further methodological investigations, e.g. for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of analyte plasma concentration

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Analysis of ethinylestradiol and levonorgestrel in plasma study samples will be performed using validated liquid chromatography tandem mass spectrometry assays (LC-MS/MS) in the laboratory:

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6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and end of trial examination are given in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Days 17, 18 and 29 are to be performed and completed within a 2 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 60 min.

For PK sampling, pre-dose PK samples (nominal time, 0 hours) on Days 17, 18 and 29 have to be performed within 10 minutes before each morning administration.

Acceptable deviations will be ± 5 minutes for collection of samples within 1 hour after drug administration in the morning, ± 10 minutes for collection of samples within up to 12 hours after drug administration in the morning, and ± 30 minutes for collection of samples within up to 24 hours after drug administration in the morning and ± 60 minutes samples collected after 24 hours after drug administration in the morning. Blood sampling for plasma trough concentration is to be performed within 10 minutes before each morning administration.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned individual plasma concentration sampling times refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameter.

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period

After having been informed about the trial, all subjects will give their written informed consent in accordance with GCP and local legislation prior to enrolment in the study.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, physical examination gynaecological examination including Pap smear, refer to Sections 5.2.3 to 5.2.5.

Pharmacogenomic genotyping will be performed in those subjects whose genotypes are not known (for details see Section 5.3).

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After passing the screening examination the subjects will be allocated to a subject number and will be given a 2-month package of Microgynon® tablets for the run-in-period. The intake of these tablets starts depending on the subjects' actual menstruation cycle and at least 28 days before Day 1 of the treatment period (see Section 3.1). In the last 7 days of the run-in period, no Microgynon® tablets will be taken to induce a withdrawal bleeding.

6.2.2 Treatment periods

Each subject is expected to participate in the treatment periods (Days 1 to 32).

On Days 16 and 28 study participants will be admitted to the trial site and kept under close medical surveillance for at least 12 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other study days, the study will be performed in an ambulatory fashion.

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.5.2.

The safety measurements performed during the treatment period are specified in Section 5.2. of this protocol and in the Flow Chart. For details on time points for all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 End of trial period

For AE assessment, laboratory tests, recording of ECG and vital signs and physical examination during the end of trial period, see Sections 5.2.2 to 5.2.5.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the end of trial visit.

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. Adverse events persisting after trial completion must be monitored until they have normalised or have been sufficiently characterised. The end of the trial as a whole is defined by the 'last regular visit completed by last subject' or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to investigate whether and to what extend BI 409306 affects multiple dose pharmacokinetics of Microgynon® and whether and to what extend Microgynon® affetcs single dose pharmacokinetics of BI 409306. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of an appropriate linear model.

The secondary objective is the evaluation and comparison of several pharmacokinetic parameters between the treatments. The secondary objectives will be assessed by descriptive statistics.

The assessment of safety and tolerability will be an additional objective of this trial, and will be evaluated by descriptive statistics.

7.1.2 Endpoints

Relative bioavailability is to be determined on the basis of the primary and secondary pharmacokinetic endpoints (see Section 5.5.1).
Safety and tolerability will be determined on the basis of the parameters specified in Section 5.2.1.

7.1.3 Model

The statistical model used for the analysis of primary and secondary endpoints will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation:'subjects' and 'treatment'. The effect 'subjects' will be considered as a random effect, whereas the treatment effects will be considered as a fixed effect. The model is described by the following equation:

$y_{km} = \mu + s_m + \tau_k + e_{km}$, where

y_{km} = logarithm of response (endpoint, see Section 7.1.3) measured on subject m receiving treatment k,

μ = the overall mean,

s_m = the effect associated with the m^{th} subject, m = 1, 2, ..., n

τ_k = the k^{th} treatment effect, k = 1, 2,

e_{km} = the random error associated with the m^{th} subject who received treatment k.

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7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of combined treatment of BI 409306 and Microgynon® compared to multiple treatment of Microgynon® and to single treatment of BI 409306 will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary PK endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified, that is, no hypothesis will be tested.
Confidence intervals will be computed, but have to be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

The primary and secondary pharmacokinetic endpoints listed in Section 5.5.1 will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

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 t_{max} 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.

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The PK parameter analysis set (PKS) includes all subjects in the Treated Set (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 he/she contributes only one PK parameter value for one period to the statistical assessment.

Subjects who are not included in the PKS (refer to Section 7.3.1.) will be reported with their individual plasma concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. Only concentrations within the validated concentration range and actual sampling times will be used for the calculation of PK parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

Plasma concentrations will be plotted graphically versus time for all subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the arithmetic mean, geometric mean and the planned blood sampling times will be used.

If a predose concentration value is greater than 5% of C_{max}, the subject's pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidances. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a predose concentration is above BLQ, but less than or equal to 5% of the subject's C_{max} value, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

Point estimates of bioavailability, the intra-subject ratios of the geometric means (test/reference) for the primary and secondary endpoints (see 5.5.1.1, 5.5.1.2), and their two-sided 90% confidence intervals (CIs) will be provided.

To this end, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model (cf. Section 7.1.3). For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means), and a two-sided 90% confidence interval based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

7.3.2 Secondary analyses

As sensitivity analysis, the ANOVA performed as primary analysis will be repeated with subject as fixed effect instead of random effect. The results will be presented in the same manner as for primary analyses.

The following descriptive statistics will be calculated for primary and secondary PK parameters and for further endpoints: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be

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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 3 significant digits in the clinical trial report.

7.3.3 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety evaluation. Safety analyses will be descriptive in nature and will be based on BI standards.

The analyses will be done by 'treatment at onset'.

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs).

Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until end of the residual effect period (see 5.2.2.2) will be assigned to the treatment period. Events after the residual effect period but prior to end of trial examination will be summarized as 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, intensity and causal relationship of AEs will be tabulated by treatment, primary system organ class and preferred term. SAEs and other significant AEs (according to ICH E3), and AESIs will be listed separately (see Section 5.2.2.1).

Laboratory data will be compared to their reference ranges. Values outside the reference range will be flagged. Additionally, differences from baseline (Day 1 of period 1) will be evaluated.

For vital signs, the differences from baseline will be evaluated.

Relevant ECG findings will be reported as AEs.

7.3.4 Interim analyses

No interim analysis is planned.

7.3.5 Pharmacokinetic analyses

For the analysis of pharmacokinetic parameters please refer to Section 7.3.1.

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7.4 HANDLING OF MISSING DATA

7.4.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.4.2 Plasma drug concentration - time profiles

Handling of missing PK data will be performed according to the relevant Corporate Procedure of the Sponsor (001-MCS-36-472).

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), or BLQ (below the lower limit of quantification), will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).

7.4.3 Pharmacokinetic parameters

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (001-MCS-36-472).

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.5 RANDOMISATION

Randomization is not applicable in this open-label and single group clinical study. All subjects will receive the same treatment. (see Section 4.1.2 for details of allocation of subject numbers to subjects).

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 16 subjects into the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial.

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All calculations were performed as described by Kupper and Hafner [R12-0972] using R Version 3.2.2.

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8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in a separate agreement between the investigator or the trial site and the sponsor. As a general rule, no trial results should be published prior to finalisation of the CTR.

Insurance Coverage: The certificate of insurance cover is made available to the Investigator and the subjects, and is stored in the ISF.

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject information form are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his or her medical records may be examined by authorised monitors (Clinical Monitor Local/Clinical Research Associate) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, by IRBs/IECs, or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

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The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the CTMF.

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

All data reported in the CRFs must be consistent with the source data or the discrepancies must be explained.

The investigator may need to request previous medical records or transfer records, depending on the trial.

8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate/on site monitor and auditor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

Trial site:
The trial site must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY

Individual subject medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Subject confidentiality will be ensured by using subject identification code numbers.

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Treatment data may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

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10. APPENDICES

Not applicable.

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		14 Jul 2017
EudraCT number		
BI Trial number		1289-0040
BI Investigational Product(s)		BI 409306
Title of protocol		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)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		1. Flow Chart 2. Section 1.2.1 3. Section 3.3.4.1 4. Section 4.1.4 5. Section 5.2.3 6. Section 5.5.3.1 7. Section 5.5.2.2 8. Section 7.3.1
Description of change		1. Remove ‘Assignment of medication numbers’ on Day 1 Change ‘684:00’ and ’21:00’ ➔ ‘686:00’ and ‘23:00’ 2. Change ‘visual blurred’ ➔ ‘vision blurred’ 3. Remove ‘The only exception to this rule is when the subject had an AESI and/or SAE

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Number of global amendment		1
		that the investigator considers related to the screening procedure.' Change 'first administration of trial medication' ➔ 'first administration of trial medication in run-in period' 4. Change 'No Microgynon® tablets are to be taken in the last 6 days of the run-in period.' ➔ 'No Microgynon® tablets are to be taken in the last 7 days of the run-in period.' 5. Change 'Plasma glucose' ➔ 'Serum glucose' Add punctuation and 'Anti-cardiolipin antibody' in thrombosis panel 6. Delete the name of analysts 7. Change 'The second aliquot will be shipped after the bioanalyst has acknowledged safe arrival of the first and second aliquots.' ➔ 'The second aliquot will be shipped after the bioanalyst has acknowledged safe arrival of the first aliquot.' 8. Change 'plasma and urine' → 'plasma'
Rationale for change		1. Correction 2. Correction 3. To avoid confliction with section 5.2.2.2 4. Correction 5. To clarify the safety lab test 6. Correction 7. To avoid further amendment 8. Correction

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-revision-01

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)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Statistician		19 Jul 2017 04:43 CEST
Approval-Clinical Pharmacokinetics		19 Jul 2017 09:37 CEST
Approval-Therapeutic Area		19 Jul 2017 14:14 CEST
Author-Clinical Monitor		20 Jul 2017 04:45 CEST
Approval-Team Member Medicine		21 Jul 2017 20:59 CEST
Verification-Paper Signature Completion		24 Jul 2017 04:26 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed