Clinical Trial Protocol

	Document Number: **c41232811-04**
EU Trial No.	2022-502861-78-00
BI Trial No.	1402-0019
BI Investigational Medicinal Product	BI 1358894
Title	An open-label, fixed-sequence cross-over, two-period, phase I trial to evaluate the effect of multiple doses of BI 1358894 on the pharmacokinetics of a combination of ethinylestradiol and drospirenone in healthy female subjects
Lay Title	A study in healthy women to test whether BI 1358894 influences the amount of a contraceptive in the blood
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: +[redacted]
[redacted]**Investigator**	[redacted] Phone: +[redacted]
Current Version, Date	Version 4.0, 19 Oct 2023
Original Protocol Date	06 Mar 2023

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	06 Mar 2023
Revision date	19 Oct 2023
BI trial number	1402-0019
Title of trial	An open-label, fixed-sequence cross-over, two-period, phase I trial to evaluate the effect of multiple doses of BI 1358894 on pharmacokinetics of a combination of ethinylestradiol and drospirenone in healthy female subjects
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	[redacted] o further inform on prescription possibilities of BI 1358894 together with oral contraceptives, this investigation of potential drug-drug interaction aims to assure safe and effective use of oral contraceptives if combined with BI 1358894
Trial objective	To investigate the effect of multiple oral doses of BI 1358894 on pharmacokinetics of ethinylestradiol (EE) and drospirenone (DRSP) (Yasmin®)
Trial endpoints	*Primary endpoints:* • $AUC_{\tau,ss}$, and $C_{max,ss}$ of EE and DRSP in plasma *Secondary endpoint:* • $C_{min,ss}$ of EE and DRSP in plasma
Trial design	Open-label, two-period, fixed-sequence with a run-in period
Number of subjects **total entered** **on each treatment**	 32 32
Diagnosis	Not applicable
Main inclusion criteria	Healthy female subjects, premenopausal, age of 18 to 35 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)

Test product 1	BI 1358894, film-coated tablets, dose strength [redacted] and [redacted]
dose	[redacted]
mode of administration	Oral with 240 mL of water after a continental breakfast
Test product 2	Yasmin®, film-coated tablets
dose	30 microgram ethinylestradiol + 3 milligram drospirenone q.d.
mode of admin.	Oral with 240 mL of water after a continental breakfast
Duration of treatment	*Run-in period:* • 1 tablet of Yasmin® q.d. for 21-49 days *Reference treatment (Period 1):* • 1 tablet of Yasmin® q.d on study days 1 – 21 *Test treatment (Period 2):* • 1 tablet of Yasmin® q.d. +1 [redacted] on study days 1 – 21
Statistical methods	The effect of multiple doses of BI 1358894 on COC Yasmin® (EE+ DRSP) will be estimated by the ratios of the geometric means (test/reference) for the primary endpoints $AUC_{\tau,ss}$, $C_{max,ss}$ and secondary endpoint $C_{min,ss}$ (of EE and DRSP separately). Additionally, two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range will not be specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for "subjects" and "treatment". CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK plasma, BI 1358894	PK plasma, COC	Exploratory PD serum[11]	12-lead ECG	Vital signs (BP, PR)	Suicidality Assesessment[10]	Questioning for AEs and concomitant therapy[5]
SCR	1	-91 to -35			Screening (SCR)[1]	A[6]				x	x	x	
Run-in[7]	2	-56 to -8			Self-administration of COC	x[8]							x
		-7 to -1			Follow up call (COC free interval)								x
Period 1	3	1	0:00	08:00	Dosing COC[12]	B[8]		x[9]	x[9]				x
		2	24:00	08:00	Dosing COC[12]								x
		3	48:00	08:00	Dosing COC[12]								x
		4	72:00	08:00	Dosing COC[12]								x
		5	96:00	08:00	Dosing COC[12]								x
		6	120:00	08:00	Dosing COC[12]								x
		7	144:00	08:00	Dosing COC[12]								x
		8	168:00	08:00	Dosing COC[12]								x
		9	192:00	08:00	Dosing COC[12]								x
		10	216:00	08:00	Dosing COC[12]	x[8]							x
		11	240:00	08:00	Dosing COC[12]								x
		12	264:00	08:00	Dosing COC[12]								x
		13	288:00	08:00	Dosing COC[12]								x
		14	312:00	08:00	Dosing COC[12]								x
		15	336:00	08:00	Dosing COC[12]								x
		16	360:00	08:00	Dosing COC[12]								x
		17	384:00	08:00	Dosing COC[12]								x
		18	408:00	08:00	Dosing COC[12]								x
		19	432:00	08:00	Dosing COC[12]								x
		20	456:00	08:00	Dosing COC[12]								x
			466:00	18:00	Admission to trial site	x[8]					x		x
		21	479:30	07:30	Start of continental breakfast								x
			480:00	08:00	Dosing COC[12]			x[9]	x[9]				x
			480:30	08:30				x					x
			481:00	09:00				x					x
			481:30	09:30				x					x
			482:00	10:00	240 mL fluid intake			x					x
			482:30	10:30				x					x
			483:00	11:00				x					x
			483:30	11:30				x					x
			484:00	12:00	240 mL fluid intake, Lunch[3]			x					x

Period	Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK plasma, BI 1358894	PK plasma, COC	Exploratory PD serum[11]	12-lead ECG	Vital signs (BP, PR)	Suicidality Assessment[10]	Questioning for AEs and concomitant therapy[5]
			485:00	13:00				x					x
			486:00	14:00				x					x
			488:00	16:00	Snack (voluntary)[3]			x					x
			490:00	18:00				x					x
			492:00	20:00	Dinner[3]			x					x
		22	504:00	08:00	Breakfast[3], discharge from trial site			x		x	x		x
		23-28			Follow-up call (COC free interval)								x
Period 2	4	1	0:00	08:00	Dosing COC + BI 1358894 [12]	B[8]	x[9]	x[9]				x[2]	x
		2	24:00	08:00	Dosing COC + BI 1358894 [12]								x
		3	48:00	08:00	Dosing COC + BI 1358894 [12]								x
		4	72:00	08:00	Dosing COC + BI 1358894 [12]								x
		5	96:00	08:00	Dosing COC + BI 1358894 [12]								x
		6	120:00	08:00	Dosing COC + BI 1358894 [12]								x
		7	144:00	08:00	Dosing COC + BI 1358894 [12]							x[2]	x
		8	168:00	08:00	Dosing COC + BI 1358894 [12]								x
		9	192:00	08:00	Dosing COC + BI 1358894 [12]								x
		10	216:00	08:00	Dosing COC + BI 1358894 [12]	x[8]							x
		11	240:00	08:00	Dosing COC + BI 1358894 [12]								x
		12	264:00	08:00	Dosing COC + BI 1358894 [12]								x
		13	288:00	08:00	Dosing COC + BI 1358894 [12]								x
		14	312:00	08:00	Dosing COC + BI 1358894 [12]							x[2]	x
		15	336:00	08:00	Dosing COC + BI 1358894 [12]								x
		16	360:00	08:00	Dosing COC + BI 1358894 [12]								x
		17	384:00	08:00	Dosing COC + BI 1358894 [12]								x
		18	408:00	08:00	Dosing COC + BI 1358894 [12]		x[9]						x
		19	432:00	08:00	Dosing COC + BI 1358894 [12]		x[9]						x
		20	456:00	08:00	Dosing COC + BI 1358894 [12]		x[9]						x
			466:00	18:00	Admission to trial site	x[8]					x	x[2]	x
		21	479:30	07:30	Start of continental breakfast								x
			480:00	08:00	Dosing COC + BI 1358894 [12]		x[9]	x[9]	x[9]				x
			480:30	08:30				x					x
			481:00	09:00				x					x
			481:30	09:30				x					x
			482:00	10:00	240 mL fluid intake			x					x
			482:30	10:30				x					x
			483:00	11:00				x					x
			483:30	11:30				x					x
			484:00	12:00	240 mL fluid intake, Lunch[3]			x					x
			485:00	13:00				x					x

Period	Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK plasma, BI 1358894	PK plasma, COC	Exploratory PD serum[11]	12-lead ECG	Vital signs (BP, PR)	Suicidality Assessment[10]	Questioning for AEs and concomitant therapy[5]
			486:00	14:00				x					x
			488:00	16:00	Snack (voluntary)[3]			x					x
			490:00	18:00				x					x
			492:00	20:00	Dinner[3]			x					x
		22	504:00	08:00	Breakfast[3], discharge from trial site			x		x	x	x	x
		23-28			Follow-up call (COC free interval)							x	x
EoS	5	42 to 52			End of study (EoS) examination[4]	C[6]				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 and cotinine test), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. In addition, a gynaecological examination will be performed prior to trial entry.
2. Pre-dose
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of study (synonym for end of trial), the EoS examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
6. Including hematology, biochemistry, coagulation, urinalysis, drug screen (only at screening), cotinine test (only at screening) and serum pregnancy test.
7. The intake of Yasmin® starts depending on the subjects' actual menstruation cycle and at least -28 days before Day 1 of first treatment period. In the run-in period, the subjects will take one tablet of COC daily until Day -8. On Day - 7 to Day -1 no COC tablets will be given in order to induce withdrawal bleeding. Self-administration in the morning with no requirement of fasting. Self-administration to be documented in the diary. A negative urine pregnancy test should be performed at the site 1 to 7 days before start of the run-in. Details are outlined in Section 4.1.4
8. Urine pregnancy test. Additional urine drug screening on day 20 of each period.
9. Blood collection takes place within 10 minutes before dosing.
10. Suicidality assessment using the Columbia-Suicidal Severity Rating Scale (C-SSRS): 'Screening/Baseline' version at Visit 1, and 'since last visit' version at other visits.
11. Measurement of exploratory pharmacodynamic parameters: estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH), and progesterone. The samples will be taken in duplicate.
12. Dosing at the trial site after a continental breakfast (for details see Section 4.1.4).

TABLE OF CONTENTS

[redacted]

ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
AUC	Area under curve
AUC_{0-24h}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
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
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BPD	Borderline personality disorder
CA	Competent authority
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state
C_{min}	Minimum measured concentration of the analyte in plasma
$C_{min,ss}$	Minimum measured concentration of the analyte in plasma at steady state
COC	Combined oral contraceptive
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
C-SSRS	Colombia-Suicidal Severity Rating Scale
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DRSP	Drospirenone
ECG	Electrocardiogram
eCRF	Electronic case report form
EE	Ethinylestradiol
eDC	Electronic data capture

EDTA	Ethylenediaminetetraacetic acid
EoS	End of Study (synonym for End of Trial)
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GLP	Good Laboratory Practice
gMean	Geometric mean
IB	Investigator's brochure
ICH	International Council for Harmonisation
iCF	Intended commercial formulation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LH	Luteinizing hormone
MDA	Methylenedioxyamphetamine
MDD	Major depressive disorder
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
NOAEL	No observed adverse effect level
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
PTSD	Post-traumatic stress disorder
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
ss	(at) steady state

SUSAR	Suspected unexpected serious adverse reaction
T	Test product or treatment
[redacted]	[redacted]
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
$t_{max,ss}$	Time from (last) dosing to the maximum measured concentration of the analyte in plasma at steady state
TS	Treated set
TSAP	Trial statistical analysis plan
UGT	UDP-Glucuronosyltransferase
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration

1. INTRODUCTION

[redacted] is being developed for major depressive disorder (MDD), borderline personality disorder (BPD), and post-traumatic stress disorder (PTSD).

1.1 MEDICAL BACKGROUND

MDD is a debilitating disease characterized by low mood and often by low self-esteem, low energy, and a loss of interest. It can strongly impact a person's life and health, including significantly increased risk of suicidality, and is difficult to treat, even with systematic antidepressant strategies. In the National Institute of Mental Health funded STAR*D trial of >4000 patients with nonpsychotic depression, about 30% of the patients did not reach remission after 4 different medications [P06-11895] and continued to experience residual symptoms [R16-5475] that significantly impacted the patients' quality of life [R06-2872].

BPD is a chronic mental disorder with an estimated prevalence of around 2% in the general community [R16-5476] and severely impaired quality of life [R16-5474]. The main symptom clusters of BPD include impulsive-behavioural dyscontrol, cognitive-perceptual symptoms, disturbed interpersonal relations, and affective instability. Patients with BPD have high rates of deliberate self-harm and a rate of completed suicide that is 50 times higher than in the general population [R16-5477]. Even the presence of a single diagnostic feature of BPD is predictive for poor functioning and psychiatric illness burden [R16-5483]. Treatment guidelines recommend psychotherapy as the mainstay of treatment, but pharmacotherapy is commonly used as an adjunctive, symptom-targeted component of treatment. However, no drug is approved for the treatment of BPD.

PTSD is a disabling mental disorder that can develop after first- or second-hand exposure to a traumatic event. Lifetime prevalence in the US was estimated at 6.8%, with 1-year prevalence at 3.6%, but more than twice as high in women (5.2%) than men (1.8%) [R08-4516]. Classic symptoms involve intrusive flashbacks and nightmares of the trauma [R15-4424]. The firstline treatment in adults is psychotherapy, such as cognitive behavioural therapy. Only sertraline and paroxetine (both antidepressants of the serotonin reuptake inhibitor class) have been licensed for the treatment of PTSD in the US, EU, Japan and several other regions globally [R21-1276].

1.2 DRUG PROFILE

1.2.1 BI1358894

Non-clinical Studies

[redacted]

The toxicology profile of BI 1358894 has been evaluated so far in a comprehensive set of *in vitro* and *in vivo* studies in accordance with ICH guidance. Pivotal studies were performed in compliance with Good Laboratory Practice (GLP). [redacted]

[redacted]

Clinical pharmacology
At the time of last IB update (July 2023), 312 healthy volunteers and 73 patients with MDD had participated in 12 completed Phase I clinical trials with BI 1358894. In Phase II, there have been 2 completed trials, which included 45 patients with MDD and 390 patients with BPD[c10354149].

[redacted]

For a more detailed description of the BI 1358894 profile, please refer to the current Investigator's Brochure (IB) [c10354149].

1.2.2 Yasmin® (ethinylestradiol + drospirenone)

1.2.2.1 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 has also been used for hormone replacement therapy. 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 EE 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].

For a more detailed description of ethinylestradiol, please refer to the SmPC of Yasmin® [R23-0484].

1.2.2.2 Drospirenone

Drospirenone (DRSP) is a synthetic progestin used in oral contraceptives for the prevention of pregnancy. It is commonly found in combination with EE in combined oral contraceptives (COC). Aside from its contraceptive effects, DRSP is used with estrogens to control acne and premenstrual dysphoric disorder. DRSP and EE in combination inhibit the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH), resulting in ovulation suppression. Other changes include changes in the cervical mucus consistency, hindering sperm movement and preventing embryo implantation. DRSP is an analog of the diuretic spironolactone, which means that DRSP has ant mineralocorticoid activity. Therefore, DRSP should not be used in patients with renal or hepatic impairment or adrenal insufficiency. 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%).

After an oral dose DRSP is rapidly absorbed, with a bioavailability of about 76% due to first-pass effect. It is about 97% bound to plasma proteins, likely to albumin. The maximum concentration occurs within 1 to 2 hours. It is heavily metabolized with a terminal half-life of about 30 to 40 hours. DRSP undergoes oxidative metabolism via the hepatic cytochrome enzyme CYP3A4. The metabolites are excreted in urine and faeces. [R23-0688].

For a more detailed description of drospirenone, please refer to the SmPC of Yasmin® [R23-0484].

1.2.2.3 Safety

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

- Presence or risk of venous thromboembolism (VTE)
- Presence or risk of arterial thromboembolism (ATE)
- Presence or history of severe hepatic disease or liver tumors
- 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 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 Yasmin® are nausea, headache, migraine, depressed mood, menstrual cycle alteration, breast tenderness, vaginal discharge and candidiasis vulvovaginal altered mood, breast pain, and breast tenderness.

Less common adverse events are changes in the libido, hypertension, hypotension, vomiting, diarrhoea, acne, eczema, pruritus, alopecia, breast hypertrophy, vaginal infections, fluid retention and weight changes.

Rare adverse events are hypersensitive reactions, asthma, hearing loss, venous and arterial thromboembolism, erythema nodosum, erythema multiforme and discharge of the mammary glands.

Drospirenone, as many other progestogens, has been linked to increased risk of venous thromboembolism [R23-0501] A statement from FDA concluded that the increase in the risk of thromboembolism resulting from the use of drospirenone remains unclear; in its statement, the FDA mentioned that increased risk of venous thromboembolism with oral contraceptives such as drospirenone exists but remains lower than the risk of this condition during pregnancy and during the postpartum period [R23-0680].

For a complete listing of adverse reactions including frequency of occurrence please refer to the current version of the summary of product characteristics (SmPC) [R23-0484].

1.2.3 Residual Effect Period

[redacted]

The REP of ethinylestradiol is 5 days based on a minimum observation period of at least 5-fold estimated t½ (i.e. 5 x 20 h, or 4.2 days, rounded to 5 days). The REP of drospirenone is 6 days based on a minimum observation period of at least 5-fold estimated t½ (i.e. 5 x 40 h, or 8.3 days, rounded up to 9 days).

[redacted]

1.3 RATIONALE FOR PERFORMING THE TRIAL

[redacted]

The combination of BI 1358894 and oral contraceptives containing EE and DRSP may be widely used in a clinical setting. [redacted] the aim of this study is to investigate any possible drug-drug interaction to assure the safe and effective use of COCs with BI 1358894.

There is evidence that EE containing oral contraceptives have only a very small effect on CYP3A4 activity as determined by midazolam metabolism [P05-12887, R03-1002, R03-1128]. The pharmacokinetics of telapravir, a hepatitic C virus protease inhibitor and substrate of CYP3A4, were not changed by coadministration of ethinylestradiol /norethindrone [R12-0031]. [redacted]

[redacted]

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 1358894.

1.4.2 Risks

Subjects are exposed to risks of trial procedures and risks related to the exposure to the trial medication.

[redacted] The trial staff will supervise the correct taking of the COC. Thus, a failure rate of less than 1% can be assumed. Pregnancy testing will also be implemented at different times of the study.

An overview of trial-related risks is given in Table 1.4.2: 1

Table 1.4.2: 1 Overview of trial-related risks for this trial

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: BI 1358894		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Possible or known risks of clinical relevance	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: BI 1358894		
[redacted]	[redacted]	[redacted]
Investigational Medicinal Product: Yasmin®		
Increased risk of venous and arterial thromboembolism	The incidence of venous thromboembolic events is 2 per 10000 women in one year, if no hormonal contraceptives are used. The incidence is increased to 9 - 12 per 10000 women after intake of COC containing drospirenone [R23-0484]. The risk of venous thromboembolism increases in the presence of pre-existing risk factors such as obesity, immobilization, family history of thromboembolism, hypercoagulability states and increased age. Epidemiologic studies showed that the use of COC increases the risk of arterial thromboembolism (myocardial infarct) and cerebrovascular events (transient ischaemic attack, stroke). The risk increases when there are pre-existing conditions such as older age, smoking, arterial hypertension, obesity, family history, migraine, prothesis valves, atrial fibrillation, dyslipidaemia, lupus) [R23-0484]	- Close monitoring of adverse events, safety lab, ECG and vital signs - Subjects with additional risk factors will not be allowed in participation in the trial - Subjects with a recent history of malignancy within 5 years (except appropriately treated basal cell carcinoma of the skin) will be excluded from participation - In case of occurrence of a serious side effect, trial treatment to be discontinued, and diagnostics and treatment have to be initiated according to local standard of care - 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

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Possible or known risks of clinical relevance	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: Yasmin®		
Increased risk of tumors	Some epidemiologic data suggest the presence of increased incidence of cervix carcinoma. The data is not clear in this respect (SmPC of Yasmin). A metanalysis of 54 epidemiologic studies showed a light increase risk (RR = 1.24) in breast cancer in women who take COC. The risk goes back to baseline within 10 years of stopping the COC [R23-0484]. In rare cases it was observed the presence of malignant liver neoplasms in women taking COCs [R23-0484].	- Close monitoring of signs and symptoms that suggest the presence of malignancy - Subjects with a recent history of malignancy within 5 years (except appropriately treated basal cell carcinoma of the skin) will be excluded from participation. Subjects with any history of breast cancer will be excluded from the trial.
Risk of hyperkalaemia	Due to the aldosterone agonism of drospirenone possible increase in the kalium concentration can occur. This is particularly important in patients with mild to moderate renal insufficiency [R23-0484].	- Only subjects with normal kidney function will be allowed in the trial
The most frequent side effects of Yasmin® are: - Headache - Migraine - Nausea - Spotting and intermenstrual bleeding - Irregularities of menstrual cycle - Breast tenderness - Depressive mood - Vulvovaginal candidiasis	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. Based on SmPC of Yasmin® [R23-0484]	- Symptomatic treatment of headache and breast tenderness if required - Treatment of vulvovaginal candidiasis if required - Treatment with Yasmin® should be continued even if irregular bleeding occurs as it normally ceases spontaneously - If irregular bleeding is persistent, appropriate diagnostic measures to exclude an organic cause are indicated - Women with history of migraine or major depressive disorder will be excluded

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Possible or known risks of clinical relevance	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: Yasmin®		
The following undesirable effects have been observed: - Changes in libido - Hypertension - Hypotension - Vomiting - Diarrhea - Acne, Eczema, pruritus, alopecia - Breast hypertrophy - Vaginal infection - Fluid retention - Weight changes	Based on SmPC of Yasmin® [R23-0484]	- Increased awareness of symptoms - Symptomatic treatment if required - If required, further diagnostics and treatment have to be initiated according to local standard of care
Drug-drug interaction between Yasmin® and other drugs	CYP3A4 inhibitors or inducers may impact the exposure of oral contraceptives. Whereas an increase of exposure may increase the number and intensity of side effects, a decrease would result in reduced efficacy.	Subjects will not be allowed to use other drugs which may interfere with Yasmin® in accordance to the SmPC within 30 days before start of run-in period (including moderate and strong CYP3A4 inhibitors, CYP3A4 inducers, grapefruit juice, St. John's wort (Hypericum perforatum), etc.)

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Trial procedures		
Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paresthesia, reduced sensibility, and/or pain	General risk by venipuncture for blood sampling, acceptable in the framework of trial participation.	Medical expertise of the trial site
General risk of psychoactive drugs		
Impaired thinking, judgment, and/or motor skills	Because psychoactive drugs may impair thinking, judgment, and/or motor skills, patients should be cautioned about operating machinery, including automobiles, until they are reasonably certain that the study medication does not adversely affect their ability to engage in such activities. It is recommended that patients should exercise caution when driving or operating machinery	Participants should be cautioned about operating machinery, including automobiles, until they are reasonably certain that the study medication does not adversely affect their ability to engage in such activities.

The total volume of blood withdrawn per subject during the entire trial will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

1.4.3 Discussion

[redacted]

In the context of the available clinical and preclinical information of BI 1358894, the above mentioned risk mitigation activities to minimise the risk of pregnancy during the trial and the anticipated benefit of BI 1358894 in patients, the risk of participation of a population of healthy individuals is considered acceptable.

Yasmin® has been used extensively for many years and is generally well tolerated. The intake of combined oral contraceptives is associated with an increased risk of serious side effects such as cardiovascular diseases (myocardial infarction, cerebrovascular events, venous

thromboembolism) and tumours. With a duration of treatment of only 3 months and the mitigation strategies planned the risks are considered acceptable.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objective

The main objective of this trial is to investigate the effect of multiple oral doses of BI 1358894 on pharmacokinetics of ethinylestradiol (EE) and drospirenone (DRSP) (Yasmin®).

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for ethinylestradiol and drospirenone:

- $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over the uniform dosing interval τ),

- $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over the uniform dosing interval τ)

2.1.3 Secondary endpoint

- $C_{min,ss}$ (minimum measured concentration of the analyte in plasma at steady state over the uniform dosing interval τ)

2.2.2.3 Safety and tolerability

Safety and tolerability of BI 1358894 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)
- Suicidality assessment (C-SSRS)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as a non-randomised, open-label, two-period, fixed sequence trial with run-in period in healthy female subjects in order to compare the test treatment (T) to the reference treatment (R).

Reference (R): one tablet of Yasmin® q.d. after a continental breakfast on Days 1-21 in Period 1.

Test (T): one tablet of Yasmin® q.d. ± one tablet of BI 1358894 25 mg q.d. + two tablets of BI 1358894 50 mg q.d. after a continental breakfast on Days 1-21 in Period 2.

The Reference Treatment will always be followed by the Test Treatment in a fixed sequence. There will be no wash-out period between the treatments.

All subjects will undergo a run-in period that starts between Day -56 and Day -28. In this period, the subjects will take one tablet of Yasmin® daily until Day -8.

In the last 7 days of each treatment period (i.e., Day 22 to Day 28) and the run-in period (i.e. Day -7 to Day -1) no treatment will be given in order to induce bleeding.

For details, refer to Section 4.1.

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 Section 6.1 and 6.2, respectively.

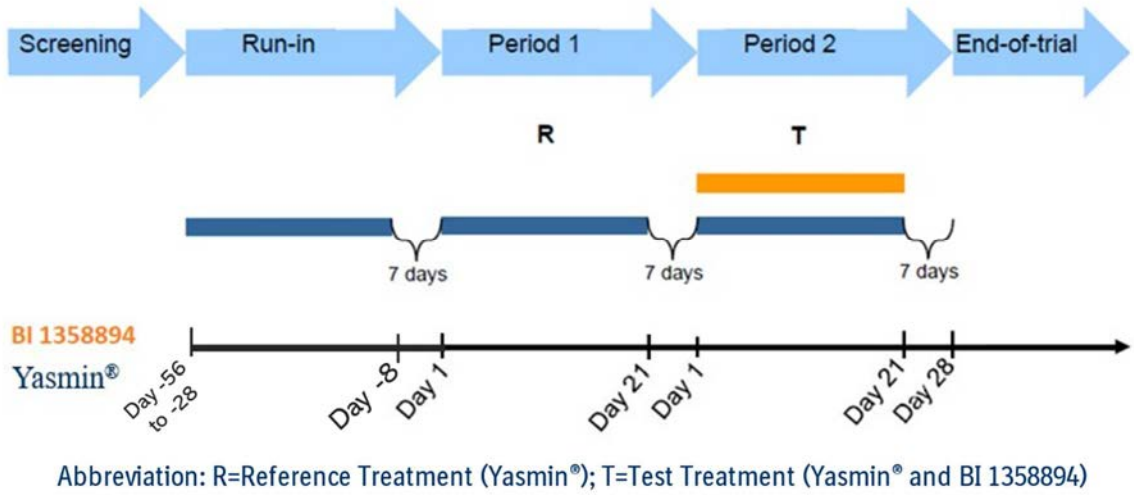


Figure 3.1: 1 Trial design

3.2 DISCUSSION OF TRIAL DESIGN

For this DDI-trial, a fixed-sequence design was chosen to ensure that pharmacokinetic parameters of the respective investigational drugs would be determined in all subjects at approximately the same time point of the menstrual cycle. In this regard BI 1358894 is

considered the offender drug and the COC the victim drug. The design of the trial allows each subject to serve as her own control, the comparison between treatments is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between treatments [R94-1529].

[redacted] The fixed-sequence design is not expected to lead to systematic errors in the estimation of the treatment effects since non-specific time-effects are unlikely to happen due to the short trial duration.

The open-label treatment is not expected to bias results since the primary endpoints are derived from measurement of plasma concentrations of the analyte.

[redacted]
The PD biomarkers will be measured on day 21 of both periods for exploratory reasons.

For the victim drug (EE + DRSP) the dosing duration (21 days dosing followed by 7 days of no treatment) is long enough to reliably achieve steady-state drug exposure in both treatment periods.

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 Yasmin® for at least 21 days) before the beginning of the first study period.

3.3 SELECTION OF TRIAL POPULATION

It is planned that approximately 32 healthy female subjects will enter the trial and start period 1. They will be recruited from the volunteers pool of the trial site.

A log of all subjects enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF, irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy female subjects.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

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

1. Healthy premenopausal female subjects according to the assessment of the investigator, as based on a complete medical history including a physical and gynaecological examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 35 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
5. Female subject who meet any of the following criteria for a highly effective contraception from at least 30 days before the first administration of trial medication until 30 days after trial completion:

   - Use of an oral hormonal contraception method in combination with a barrier contraception method and willing to stop the hormonal method and to continue using the barrier method plus Yasmin® for the duration of the trial
   - Use of non-hormonal intrauterine device (IUD)
   - Sexually abstinent
   - Female subject who underwent tubal ligation
   - A vasectomised sexual partner who received medical assessment of the surgical success (documented absence of sperm) and provided that partner is the sole sexual partner of the trial participant

3.3.3 Exclusion criteria

Subjects will not be allowed to participate, if any of the following general criteria apply:

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator (e.g. pronounced varicosis, thrombophlebitis, and evidence of peripheral circulatory disturbances)
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 50 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 assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or 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. Relevant chronic or acute infections
10. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs within 30 days prior to treatment allocation that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
13. Intake of an investigational drug in another clinical trial within 60 days prior to treatment allocation, or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker (former smokers must have stopped smoking at least 6 months before screening) or positive cotinine test at screening
15. Alcohol abuse (consumption of more than 12 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to treatment allocation or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to treatment allocation or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked prolongation of QT/QTcF interval (such as QTcF intervals that are repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
23. Lactation or pregnancy within the last 6 months, or plans to become pregnant during the trial or within 30 days after trial completion
24. Positive pregnancy test

In addition, the following trial-specific exclusion criteria apply:

25. Use of drugs which may interfere with Yasmin® in accordance to the SmPC within 30 days prior to treatment allocation (including moderate and strong CYP3A4 inhibitors, CYP3A4 inducers, St. John's wort, etc.)
26. Use of other hormone-containing methods of contraception except Yasmin® per trial protocol, e.g. hormone-containing intrauterine device, depot injection or contraceptive implants. Subjects taking oral contraceptives other than Yasmin® will be allowed to participate as long as they agree to stop their current oral contraceptive and accept taking Yasmin® for the duration of the trial.
27. History of confirmed venous thromboembolism, family history of venous thromboembolism, and other known risk factors for venous thromboembolism
28. History of malignancy within 5 years (except appropriately treated basal cell carcinoma of the skin). Any history of breast cancer will lead to exclusion.
29. History or evidence of arterial thrombotic or embolic processes, conditions which predispose to them (such as disorders of the clotting processes, valvular heart disease, atrial fibrillation, autoimmune diseases, dyslipidaemia, etc.)
30. History of migraine in the past 5 years
31. History of relevant liver diseases (e.g. disturbances of liver function, jaundice or persistent itching during a previous pregnancy, Dubin-Johnson syndrome, Rotor syndrome, or previous or existing liver tumours)
32. History of bipolar mood disorder, bulimia or anorexia
33. History of suicidal ideation of type 2 to 5 on the C-SSRS in the past 12 months (i.e. active suicidal thought, active suicidal thought with method, active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent) or any suicide attempt in the past 24 months (i.e. actual attempt, interrupted attempt) prior to screening
34. History of major depressive disorder
35. Clinically relevant finding in the gynaecological anamnesis, gynaecological examination which in the opinion of the gynaecologist oppose the prescription of Yasmin®
36. Clinically relevant result of the cervical smear

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may withdraw or may be removed from trial treatment or may withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; please see Section 3.3.4.1 and 3.3.4.2 below.

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR).

If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR.

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.3), the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as she is not willing or able to adhere to the trial requirements in the future. For details regarding missed visits see Section 6.1.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, adverse events (AEs), or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and 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
6. Suicidal ideation (type 2-5) or any suicidal behaviour based on C-SSRS questionnaires during the trial
7. The subject experiences a drug-related adverse event of severe intensity or a serious adverse event
8. In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.
9. If it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section 5.2.6.2.3.
10. If new efficacy or safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the

trial treatment for all subjects or take any other appropriate action to guarantee the safety of the trial subjects.

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons (if reasons 4 and/or 5 are met, the trial should be discontinued immediately):

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational products
3. Deviation from GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial
4. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)
5. More than 50% 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. [redacted]

The investigator / trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except if item 3 applies).

3.3.5 Replacement of subjects

It is planned that 32 subjects enter the trial and start period 1. Additional subjects may start the run-in period to assure that at least 32 subjects will start period 1. In case more than 6 subjects (and it is anticipated that at least 2 more will drop out) do not complete the trial after starting period 1 (including subjects non- evaluable for PK), subjects may be replaced if considered necessary to reach the objective of the trial. Subjects who withdraw or are withdrawn from the trial after starting period 1 due to a drug-related adverse event will not be replaced. The Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced (i.e. will be recruited in addition to achieve sufficient precision of the estimated effects). The total number of

replacements (after starting period 1) may not exceed 1/3 of the total number of evaluable subjects anticipated to complete the trial. A replacement subject will be assigned a unique trial subject number (or Subject Identification Number).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product 1 are given below:

Substance:	BI 1358894
Pharmaceutical formulation:	[redacted]
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	[redacted]
Posology:	[redacted]
Mode of administration:	[redacted]
Duration of use:	21 days q.d. (once daily) in Period 2

The characteristics of the test product 2 are given below:

Name:	Yasmin®
Substance:	ethinylestradiol (EE) and drospirenone (DRSP)
Pharmaceutical formulation:	Film-coated tablet
Source:	[redacted]
Unit strength:	30 ug EE + 3 mg DRSP
Posology:	1-0-0
Mode of administration:	Oral
Duration of use:	21 days q.d. followed by 7 days of no treatment in of Periods 1 and 2. In the run-in period, up to 49 days q.d. followed by 7 days of no treatment. For details, refer to Section 3.1 and 4.1.4.

4.1.2 Selection of doses in the trial

The dose of 30 µg EE and 3 mg DRSP selected for this trial is the standard clinical dose and is sufficient to achieve the relevant plasma exposure for evaluation of a possible drug-drug interaction.

The dose of [redacted] of BI 1358894 is the highest dose currently tested in Phase II clinical trials.

4.1.3 Method of assigning subjects to treatment groups

There is only one treatment sequence investigated in this trial, and each subject will be allocated to the same treatment sequence (R-T). The subjects will be allocated to a trial

subject number (or Subject Identification Number) on a first-come, first-served basis prior to run-in after a re-check of the relevant inclusion and exclusion criteria.

Once a subject number has been assigned, it cannot be reassigned to any other subject.

All subjects may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required. Treatment of all subjects on the same calendar day is acceptable.

4.1.4 Drug assignment and administration of doses for each subject

This trial is a non-randomised trial with two periods. All subjects will receive the two treatments in a fixed order. The treatments to be evaluated are summarised in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total daily dose
R (Reference)	Yasmin®	Tablet	30 ug EE /3 mg DRSP	1 tablet q.d. (Period 1, Days 1-21)	30 ug EE /3 mg DRSP
T (Test)	Yasmin®	Tablet	30 ug EE /3 mg DRSP	1 tablet q.d. (Period 2, Days 1-21)	30 ug EE /3 mg DRSP
	BI 1358894	[redacted]	[redacted]	[redacted]	[redacted]

Run-in period (Visit 2):

Yasmin® tablets for the run-in period (duration depends on the actual menstrual cycle of the subject) will be dispensed in its original package to the eligible subjects. A pregnancy test should be performed 1 to 7 days before start of the run-in. The administration during the run-in period will be done by the subjects and documented in a diary. The subjects will be instructed to take Yasmin® tablets with a cup of water at the same in the morning. Fasting will not be required prior to intake. No Yasmin® tablets will be taken in the last 7 days of the run-in period. The next day will be defined as Day 1 of Period 1.

Treatment Periods 1 and 2 (Visits 3 and 4):

Administration of trial medication in both treatment periods will be performed after subjects have fasted overnight; fasting is to start no later than 8 h before the scheduled dosing. The subjects will be asked to start consuming a continental breakfast 30 minutes before administration of trial medication. The subjects must completely consume the meal prior to drug intake. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial

medication, and – if applicable – its preparation, if correct dosage cannot be ensured otherwise. The composition of the continental breakfast is detailed in Table 4.1.4: 2. For restrictions with regard to diet, see Section 4.2.2.2.

Table 4.1.4: 2 Composition of the light (standard continental) breakfast

Ingredients	kcal
1 bread roll	164
15 g butter	113
1 slice of Gouda cheese (approximately 40g)	146
20 g of curd cheese (approximately)	33
1 cup of decaffeinated coffee or tea (without sugar)	2
Sum[1]	458

[1] The total caloric content was supplied approximately as following: 88 kcal as protein, 133 kcal as carbohydrate, and 237 kcal as fat.

During the in-house stays subjects will be kept under close medical surveillance until 24 h after drug administration. During the first 4 h after drug administration on day 21 of both periods, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

There will be no wash-out phase between the run-in period and both treatment periods. No Yasmin® tablets are to be taken in the last 7 days of each of Period 1 and Period 2 in order to induce bleeding.

4.1.5 Blinding and procedures for unblinding

This non-randomised open-label Phase I trial will be handled in an open fashion throughout. The treatment assignment will be available to all involved parties.

4.1.6 Packaging, labelling, and re-supply

BI 1358894

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

The label will be prepared according to Regulation (EU) No 536/2014, Annex 6, Section D.8. omitting certain particulars with the following justifications:

The investigator name was omitted from the label because it is included on the Trial Identification Card (TIC), which will be issued to each trial participant.

The "keep out of reach of children" statement was omitted from the label because the product will remain at the clinical site.

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The EU Trial number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

No re-supply is planned.

Yasmin®

Yasmin® tablets are manufactured by [redacted] and have a market authorisation. Yasmin® will be obtained by the clinical trial site from a public pharmacy. The drug will be dispensed out of the original, unmodified packages.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area in accordance with the recommended (labelled) storage conditions. If 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 Clinical Research Associate (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered from the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site
- 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

Only authorised personnel documented in the form 'Trial Delegation List' may dispense investigational drugs to trial subjects. Investigational drugs are not allowed to be used outside of this protocol.

The investigator or designee must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products. These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee 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.

All unused medication will be disposed of locally by the trial site upon written authorisation of the Clinical Trial Leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require 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 results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. All concomitant or rescue therapies will be recorded (including time of intake on trial days) on the appropriate pages of the CRF. Occasional use of paracetamol or ibuprofen to treat pain could be allowed after consultation with the investigator.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after drug intake.

On day 21 of each treatment period additional 240 mL of water at 2 h and 4 h post-dose will be provided (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication until after the last PK sample of the second trial period is collected.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed during in-house confinement in both treatment periods.

Smoking is not allowed.

Excessive physical activity (such as competitive sport) is not allowed from 7 days before the first administration of trial medication until the end of trial examination.

4.2.2.3 Contraception requirements

Since all participants in this trial will be female subjects of child-bearing potential, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for the definition of adequate measures).

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in periods 1 and 2 in the trial centre under supervision of the investigating physician or a designee. The measured plasma concentrations of trial medication 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).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (alcohol history not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including determination of body weight.

In addition, a gynaecological examination will be performed by a board-certified gynaecologist in order to assess if there are any reasons opposing the prescription of Yasmin® to the subject. The gynaecological examination will include a gynaecological anamnesis (including description of perimenstrual symptoms) and inspection and palpation of the breasts and genital organs. Furthermore, a cytological cervical smear and a transvaginal ultrasound examination (uterus, ovaries, Douglas pouch) will be performed. Additional examinations may be performed in case of suspicion.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor ([redacted] IntelliVue MP 70 patient monitor, [redacted], [redacted]) 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.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 8 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

The parameters to be assessed 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 an abnormality in the automatic blood cell count or in the urinalysis, respectively.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	Reticulocytes, absol.	X	X	X
	Reticulocytes/Erythrocyte	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
	Erythrocyte Sedimentation Rate 1 h	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.			
Coagulation	Activated Partial Thromboplastin Time	X	--	--
	Prothrombin time	X	--	--
	Prothrombin time – INR (International Normalization Ratio)	X	--	--
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X	X
	ALT [Alanine aminotransferase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Creatine Kinase [CK]	X	--	--
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	--	--
Hormones	Thyroid Stimulating Hormone	X	--	--
	Estradiol	X	--	--
	LH (Luteinizing hormone)	X	--	--
	FSH (follicle stimulating hormone)	X	--	--
	Progesterone	X	--	--

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	X
	GFR/ CKD-EPI	X	--	--
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	X
	C-Reactive Protein (Quant)	X	X	X
	Uric Acid	X	--	--
	Cholesterol, total	X	--	--
	Cholesterol, HDL	X	--	--
	Cholesterol, LDL	X	--	--
	Triglyceride	X	--	--
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	--	X
	Urine Protein (qual)	X	--	X
	Urine Glucose (qual)	X	--	X
	Urine Ketone (qual)	X	--	X
	Urobilinogen (qual)	X	--	X
	Urine Bilirubin (qual)	X	--	X
	Urine HGB (qual)	X	--	X
	Urine leukocyte esterase (qual)	X	--	X
	Urine pH	X	--	X
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)			

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined on Day 1 of each period (for time points refer to Flow Chart)
C: parameters to be determined at Visit 5 (end of trial examination)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy tests and drug screening, it is planned to perform these tests during screening only. Pregnancy testing will be performed at screening, prior to run-in, prior to each treatment period, and as part of the end of trial examination. Drug screening will be performed at screening and on day 20 of each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine THC Cocaine Methadone Methamphetamines/MDMA/Ecstasy Morphine (MOP) Phencyclidine Tricyclic antidepressants
Cotinine test (urine)	Cotinine (metabolite of nicotine) in urine
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)
Pregnancy test (blood/urine)[1]	Beta human chorionic gonadotropin (beta-HCG)
Cervical smear	Papanicolaou test

[1] Pregnancy test in serum at screening and EoS and in urine at the beginning of run-in, at the beginning of each period and on days 10 and 20 of each period.

To encourage compliance with alcoholic restrictions, a breath alcohol test ([redacted] Alcotest®, [redacted]) will be performed prior to admission to trial site on day 20 and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted], with the exception of drug screening, cotinine test and urine pregnancy tests. These tests will be performed at the trial site using SURESTEP Urine Drug Test, Cotinine SureStep Test by [redacted] TestPack™ Plus hCG Urine Test with OBC, respectively, or comparable test systems.

Laboratory data will be transmitted electronically from the laboratory to the trial site.

It is the responsibility of the Investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the Investigator are to be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4).

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System, [redacted] at the times provided in the Flow Chart.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other trial procedures scheduled for the same time to avoid compromising ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System ([redacted]. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (if identified at the screening visit) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

5.2.5.1 Suicidality assessment

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behaviour and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behaviour and ideation [R08-1147].

The C-SSRS interview may be administered by a physician or a study nurse with C-SSRS training. It has a typical duration of five minutes, and causes only a low burden on subjects. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behaviour, and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed.

The C-SSRS has been widely used in large multinational CTs. The C-SSRS will be administered at the screening visit (using the ‘screening / baseline’ version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to the screening or baseline visit. The life time history of suicidal ideation and behaviour will also be recorded. See Section 10.1 for the original English C-SSRS. For this trial, the paper version of the respective German translation will be used. After the screening visit, the ‘since last visit’ version is used for the suicidality assessment at the time points indicated in the Flow Chart.

Positive reports are generated for any of the following findings:

Suicidal ideation

- Suicidal ideation with intention to act (type 4)

- Suicidal ideation with specific plan and intent (type 5)

Suicidal behavior

- Completed suicide
- Suicide attempt
- Interrupted attempt
- Aborted attempt
- Preparatory actions toward imminent suicidal behaviors.

Negative reports of suicidal ideation are defined as reports when there are no indications of the above, i.e. suicidal ideation of type 1-3.

The investigator is to review positive and negative reports for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist.

If there is a confirmed positive report of suicidal behaviour or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the subject during the clinic visit, and/or is to consult a psychiatrist. If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.

For details regarding AE reporting see section 5.2.6.2.4

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 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 considered related or not.

The following should also be recorded as an AE in the CRF and BI 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 to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- Results in death
- Is life-threatening, which 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
- Is 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. 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

5.2.6.1.3 AEs considered 'Always Serious'

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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 defined above.

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. A copy of the latest list of 'Always Serious AEs' will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

Cancers of new histology must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in Section 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (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. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.
The following are considered as AESIs:

- Potential severe DILI

A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

- An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
- Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN

These lab findings constitute a hepatic injury alert and the subjects 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 that 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.

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

Medical judgment should be used to determine whether there is a reasonable possibility of a causal relationship between the AE and the given trial treatment, 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)
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced)

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
- There is an 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 trial drug treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE 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. 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 carefully 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, intensity of the event, and 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 until an individual subject's end of trial (the End of Study (EoS) visit):
    - 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 these cases, the subjects' data must be collected at trial site but will not be entered in the CRF 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 new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the 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 to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific reporting process will be provided in the ISF. The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

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

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

5.2.6.2.4 AE reporting from suicidality assessment

All positive reports from C-SSRS suicidality assessment (see Section 5.2.5.1), i.e. reports of suicidal ideation type 4 or 5 and all reports of suicidal behaviour must be reported as separate SAEs by the investigator.
Negative reports (i.e. suicidal ideation type 1, 2 or 3) can be reported as AEs, at the discretion of the investigator. All negative reports should be reviewed by the Investigator for clinical relevance and determination if an AE report is warranted

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis of ethinylestradiol and drospirenone

For quantification of ethinylestradiol and drospirenone concentrations in plasma, for each analyte, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium 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.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 x g to 4000 x g and 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.8 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 1 h, with interim storage of blood samples and aliquots in ice water or on ice. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, barcode, subject number, visit, and planned sampling time.

After analysis, the plasma samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. 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 trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

5.3.2.2 Blood sampling for pharmacokinetic analysis of BI 1358894

For quantification of BI 1358894 concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K2-EDTA (dipotassium 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.

[redacted]

At a minimum, the sample tube labels should list BI trial number, barcode, subject number, visit, and planned sampling time.
After analysis, the plasma samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. 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 trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

[redacted]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

Not applicable.

5.4 ASSESSMENT OF BIOMARKERS

5.4.1 Drug-Drug Interaction Biomarkers

Not applicable.

5.4.2 Exploratory pharmacodynamic biomarkers

The following hormone concentrations will be determined: luteinizing hormone, follicle-stimulating hormone, estradiol and progesterone.

5.4.2.1 Methods of sample collection

For quantification of luteinizing hormone, follicle-stimulating hormone, estradiol and progesterone concentrations in serum, 4.9 mL of blood will be drawn from an antecubital or forearm vein into a Serum-Monovette® 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.
The blood samples will be allowed to clot for 30 minutes at room temperature and then centrifuged for approximately 10 min at 2500 x g at room temperature. Until transfer the same day the samples will be stored ambient. If the samples cannot be sent on the same day they should be stored at 2 – 8 °C until shipment.

[redacted]

5.4.3 Pharmacogenomic biomarkers

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 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 5.3 are generally used assessments of drug exposure. The pharmacodynamic biomarkers measurements outlined in Section 5.4 are of exploratory nature only.

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 the end of trial examination are provided in the Flow Chart.

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

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min.

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 blood 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 the determination of pharmacokinetic parameters.

During the run-in period, administration of Yasmin® tablets must be done by the subjects at home. The subjects are advised to take Yasmin® tablets with a cup of water at the same time each day, approximately between 06.00 and 10.00 am local time.

Ambulatory dosing in periods 1 and 2 should be performed between 06.00 and 10.00 am local time.

If a subject misses an ambulatory visit in weeks 1 or 2 of any period all efforts should be made for the subject to attend the visit as soon as possible. In such case dosing of Yasmin® can occur at any time of the day or can even be taken together with the next planned dose. [redacted]. If a subject misses 2 visits they must be separated by at least 7 days. Subjects who miss a visit in weeks 1 or 2 will be reminded of the importance of using additional contraception methods. All visits in week 3 must be attended. 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 provide written informed consent in accordance with GCP and local legislation prior to enrolment in the trial.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.5.

In addition, a gynaecological examination will be performed in order to assess the suitability of subjects for taking the oral contraceptive prior to trial entry.

After eligibility has been confirmed subjects will come to the site to perform an urine pregnancy test and they will be given 1-2 packages of Yasmin® tablets for the run-in-period. The start and end of the run-in will be decided by the investigator depending on the subjects actual menstrual cycle duration (see Section 3.1). In the last 7 days of the run-in period, subjects will be instructed to stop taking Yasmin® in order to induce a withdrawal bleeding.

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (Days 1 to 28 in each period). There will be no wash-out period between the treatments.

On Day 1 of the first study period the subjects will be asked to return unused tablets of Yasmin®, including packages and blisters. On Day 20 of each treatment period, trial participants will be admitted to the trial site and kept under close medical surveillance for at least 24 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 trial days in treatment periods (Days 1 to 20), subjects will be treated ambulatorily. In the last 7 days of each treatment period (i.e., Days 22 to Day 28) no treatment will be given in order to induce withdrawal bleeding.

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed continuously from obtaining subject's written informed consent until the end of trial examination.

For details on times of all other trial procedures, refer to the Flow Chart.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Section 5.2.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoS Visit.

If needed in the opinion of the investigator, additional visits may be scheduled after the EoS Visit for continued safety monitoring.

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's EoS Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The main objective of this trial is to investigate the relative bioavailability of COC Yasmin® (30 ug EE + 3 mg DRSP) under [redacted] dose exposure of BI 1358894 (Test, T) compared with COC Yasmin® (30 ug EE + 3 mg DRSP) alone (Reference, R) on the basis of the primary pharmacokinetic endpoints, as listed in Section 2.1.2. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

A further objective is to evaluate and compare further pharmacokinetic parameters between the treatments. These pharmacokinetic parameters will be assessed by descriptive statistics. The assessment of safety and tolerability is a further objective of this trial, and will be evaluated by descriptive statistics.

7.1 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses for this trial.

The relative bioavailability of COC (30 ug EE + 3 mg DRSP) under [redacted] with BI 1358894 (Test, T) compared with COC alone (Reference, R) will be estimated by the ratios of the geometric means (test/reference) of the primary endpoints, and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

[redacted]

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection

'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.

Descriptions of additional analysis sets may be provided in the TSAP.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be suggested in the iPD specification file. IPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for EE and DRSP (components of COC Yasmin®) will be calculated according to the relevant BI internal procedures.

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation 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.

Important protocol deviations 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),
- The subject experiences emesis at any time during the labelled dosing interval.
- Missing samples/concentration data at important phases of PK disposition curve

Plasma concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic 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).

7.2.2 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale and will be applied to each analyte (EE, DRSP) separately. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: subjects and treatment. The effects 'subjects' and 'treatment' will be considered as fixed. The model is described by the following equation:

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

y_{km} = logarithm of response measured on subject m in receiving treatment k,

μ = the overall mean,

γ_m = the effect associated with the m^{th} subject, m = 1, 2, ..., 32,

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.

where $e_{km} \sim N(0, \sigma_W^2)$ i.i.d. and e_{km} is an independent random variable.

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

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). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

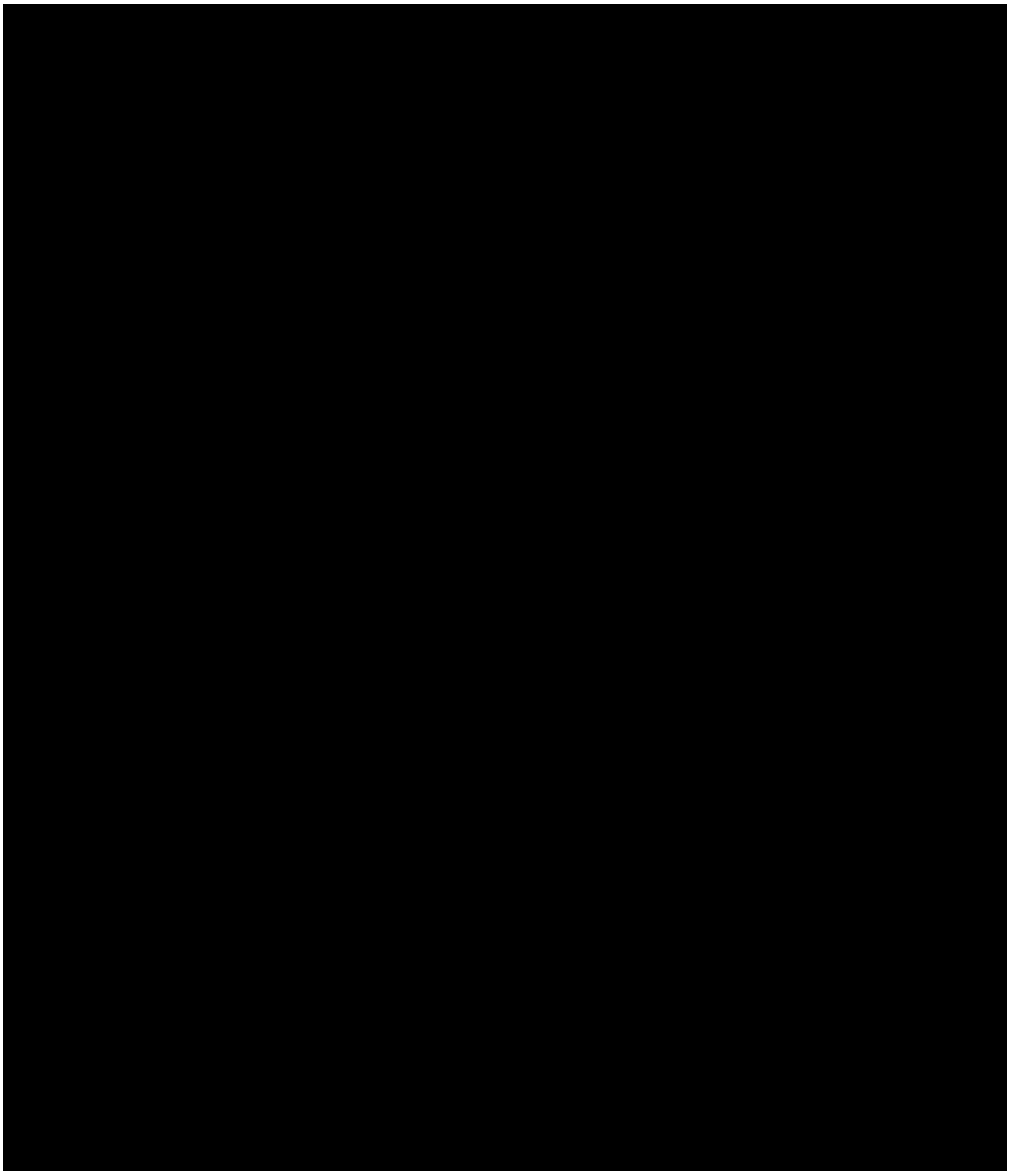
Further exploratory analyses

The same statistical model as stated above will be repeated for the primary endpoints but the effect 'subjects' will be considered as random, whereas the effect 'treatment' will be considered as fixed."

In addition to the model based approach all parameters will be calculated and analysed descriptively.

7.2.3 Secondary endpoint analyses

The secondary endpoint (refer to Section 2.1.3) will be calculated according to the relevant BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints.



7.2.5 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.3. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the assigned treatment will be discussed in the minutes of the Report Planning Meeting).

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used to evaluate 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 time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to the screening period. Those occurring in the run-in period will be assigned to the run-in period, while all others -from first trial medication intake in respective treatment period to end of REP (see Section 1.2.3) will be assigned to the respective treatment period. Events occurring after the REP but prior to end of study examination date will be assigned to follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined in the TSAP in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals, or periods without treatment effects (such as screening and follow-up intervals).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, AESIs (see Section 5.2.6.1), and other significant AEs (according to ICH E3) will be listed separately.

Previous and concomitant therapies will be presented without consideration of time intervals and treatment periods.

Laboratory data will be compared to their reference ranges. Values outside the reference range will be highlighted in the listings. Additionally, differences from baseline will be evaluated.
Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

In general, unless otherwise specified in the TSAP, the last non-missing measurement prior to first trial medication intake will be used as baseline for safety variables (laboratory data, ECG, vital signs).

Relevant ECG findings will be reported as AEs.

Results regarding the C-SSRS will only be listed.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

It is not planned to impute missing values for safety parameters.

7.3.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant BI internal procedures.

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.4 RANDOMISATION

Since no randomisation will be performed in this trial, this Section is not applicable.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned that approximately 32 subjects (including up to 8 drop-outs or non PK evaluable subjects) will participate in the trial and start period 1. This is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The observed intra-individual coefficient of variation (gCV) for EE in previous trials [U13-1189; U12-1031; U09-1393; U07-1867; U03-3408] was roughly 13-20% for C_{max} and 8-15% for AUC. The intra-individual coefficient of variation (gCV) for DRSP reported in the literature [R23-0502]was roughly 16% for C_{max} and 23% for AUC.

Therefore, the following Table 7.5: 1 provides a summary of the precision that is expected with a 95% probability and two-sided 90% confidence interval of various gCVs and gMean ratios (T/R) using sample sizes of 20, 24 and 28.

Table 7.5: 1 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a fixed-sequence crossover trial (N=20, 24, 28).

N	gCV [%]	Precision upper CL** / relative BA estimate	90% CI [%] of respective ratio*		
			94	100	107
20	15	1.11	(84.82; 104.17)	(90.24; 110.82)	(96.55; 118.58)
20	20	1.15	(82.01; 107.74)	(87.25; 114.61)	(93.36; 122.64)
20	25	1.19	(79.34; 111.37)	(84.40; 118.48)	(90.31; 126.77)
24	15	1.1	(85.80; 102.98)	(91.28; 109.56)	(97.67; 117.22)
24	20	1.13	(83.27; 106.11)	(88.59; 112.88)	(94.79; 120.78)
24	25	1.16	(80.85; 109.28)	(86.02; 116.26)	(92.04; 124.40)
28	15	1.09	(86.53; 102.11)	(92.06; 108.63)	(98.50; 116.23)
28	20	1.12	(84.22; 104.92)	(89.59; 111.62)	(95.87; 119.43)
28	25	1.15	(82.00; 107.76)	(87.23; 114.64)	(93.34; 122.66)

*Ratio of geometric means (test/reference) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_R)$.
**Confidence interval limit

The expected 90% confidence interval limits in the table were derived by

$$\text{CI limit}_{\text{upper,lower}} = \exp(\ln(\theta) \pm \omega),$$

with θ being the ratio (T/R) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

The calculation was performed as described by Julious [R11-5230] using R Version 4.1.2.

Thus, based on a sample size of N=24 evaluable subjects and assuming a gCV of 25% for the PK endpoints of EE + DRSP (= COC Yasmin®), the precision of the 90% CI would be 1.16.

Accounting for up to 8 drop-outs or non PK evaluable subjects, a total of N = 32 (24 + 8) subjects are planned to be entered into the trial.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the subject's treating physician.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the CTR.

The terms and conditions of the insurance coverage are made available to the investigator and the subjects and are stored in the ISF.

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, 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 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 retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC 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.

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

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial subject that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the subject, documented in their medical records, would be acceptable.

Before providing any copy of subjects' source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number, and social security number) have properly been removed or redacted to ensure subject confidentiality.

If the subject is not compliant with the protocol, any corrective action (e.g. re-training) must be documented in the subject file.

For the CRF, data must be derived from source documents, for example:

- Subject identification: gender, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator/institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the Clinical Research Associate, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

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

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 and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 7 and 12 of the WHO GCP handbook.

To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a participant identification number instead of the trial participant's name. The code is only available at the site and must not be forwarded to the sponsor. In case participant's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the trial participant will be redacted by the site prior to forwarding. Access to the participant files and clinical data is strictly limited: personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site 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.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs/IECs and trial participants will be informed as appropriate.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples and clinical data, in particular

- Sample and data usage have to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external storage facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (e.g. biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data

- Samples and/or data may be transferred to third parties and other countries as specified in the ICF

8.6 TRIAL MILESTONES

The start of the trial is defined as the date when the first subject in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last subject in the whole trial ('Last Subject Completed').

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the laws of each member state.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last subject (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [redacted], under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required trial activities, in order to

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of local Clinical Trial Mangers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

The trial medication will be provided by the [redacted], or will be obtained by the clinical trial site from public pharmacy (Yasmin®).

Safety laboratory tests and exploratory PD biomarkers measurements will be performed by the local laboratory of the trial site ([redacted]).

Analyses of ethinylestradiol and drospirenone concentrations in plasma will be performed at [redacted]

Address: [redacted]

Analyses of BI 1358894 concentrations in plasma will be performed at [redacted].
Address: [redacted]

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

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

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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9.2 UNPUBLISHED REFERENCES

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c28667517 [redacted]. Safety, tolerability, and pharmacokinetics of multiple rising oral doses of BI 1358894 (double-blind, randomised, placebocontrolled, parallel-group design) and evaluation of midazolam interaction (nested, open, fixed-sequence, intra-individual comparison) in healthy male subjects. CTR 1402-0002. 2020

U03-3408 [redacted]. A single centre, open-label, randomized, parallel group, multiple dose comparison of the effect of Tipranavir 750 mg and Ritonavir 200 mg or Tipranavir 500 mg and Ritonavir 100 mg, administered twice daily, on the pharmacokinetic characteristics of Noret. CTR 1182.22. 2005

U07-1867 [redacted] An open, randomised, two-way cross-over trial to evaluate the effect of multiple doses of flibanserin on the single dose pharmacokinetics of a combination of ethinylestradiol and levonorgestrel. CTR 511.93.2008

U09-1393 [redacted]. An open, two-period, fixed-sequence, phase I trial to evaluate the effect of multiple doses of BI 1356 on the multiple-dose pharmacokinetics of a combination of ethinylestradiol and levonorgestrel. CTR 1218.11. 2009

U12-1031 [redacted]. An open-label, two-period, fixed-sequence trial to evaluate the effect of multiple doses of BI 10773 on the multiple-dose pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in healthy premenopausal female volunteers. CTR 1245.41. 2012

U13-1189 [redacted]. An open-label, two-period, fixed-sequence, phase I trial to evaluate the effect of multiple doses of 240 mg BI 201335 QD on the multiple-dose pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in healthy premenopausal female volunteers. CTR 1220.56. 2013

10. APPENDICES

10.1 COLUMBIA-SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by* [redacted] *and* [redacted] *Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (*[redacted]*Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact [redacted]*, New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu*

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past__ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	___

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime	Past __ Years
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by* [redacted] *and* [redacted] *Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (*[redacted] *Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact [redacted]*, New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu*

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Suicide:	**Yes** **No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		08 May 2023
EU Trial number		2022-502861-78-00
BI Trial number		1402-0019
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		An open-label, fixed-sequence cross-over, two-period, phase I trial to evaluate the effect of multiple doses of BI 1358894 on the pharmacokinetics of a combination of ethinylestradiol and drospirenone in healthy female subjects
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		Flow Chart
Description of change		Follow up to take place on Days 42 - 52
Rationale for change		Request from competent authorities
Section to be changed		Flow Chart, section 5.2.3 Safety laboratory parameters
Description of change		Cotinine test at screening included
Rationale for change		Request from competent authorities
Section to be changed		Section 3.3.3 Exclusion criteria
Description of change		Exclusion criterion 14 was changed to exclude all smokers from the study. The following exclusion criterion was removed since it is not applicable: "Inability to refrain from smoking on specified trial days"
Rationale for change		Request from competent authorities
Section to be changed		Section 4.1.2 Selection of doses in the trial
Description of change		Sentence to the justification of dose selection added
Rationale for change		Request from competent authorities
Section to be changed		Section 8.1 Trial approval, subject information, informed consent
Description of change		Wording referring to the subjects' legally representative deleted
Rationale for change		Request from competent authorities
Section to be changed		Section 8.5 Statement of confidentiality and subject privacy

Description of change		A description of the arrangements to comply with the applicable rules on the protection of personal data was added
Rationale for change		Request from competent authorities

11.2 GLOBAL AMENDMENT 2

Date of amendment		12 Jul 2023
EU Trial number		2022-502861-78-00
BI Trial number		1402-0019
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		An open-label, fixed-sequence cross-over, two-period, phase I trial to evaluate the effect of multiple doses of BI 1358894 on the pharmacokinetics of a combination of ethinylestradiol and drospirenone in healthy female subjects
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		Flow Chart
Description of change		Footnote 8 added at Period 2, Visit 4, Day 1
Rationale for change		Inconsistency
Section to be changed		3.3.3 Exclusion criteria
Description of change		Exclusion criteria number 12, 13, 17, 18 and 25 will have as reference time point the treatment allocation.
Rationale for change		To correct an inconsistency in the previous version of the protocol. Since start of run-in marks the first administration of trial medication, a reference to treatment allocation was necessary. To clarify that the run-in period belongs to the trial per se and, as a consequence, patients need to start adhering to study restrictions already at that time.
Section to be changed		Section 3.3 Selection of trial population, Section 3.3.4 Withdrawal of subjects from treatment or assessments, Section 3.3.5 Replacement of subjects, Section 7.5 Determination of sample size
Description of change		Clarification about the necessity that at least 32 subjects start period 1. Instructions about how to proceed with subjects who stop the trial before starting period 1.
Rationale for change		An adaptation of the description was necessary because it is imperative that at least 32 subjects start period 1 to reach the objectives of the trial and it has consequences on the replacement strategy.

Section to be changed		4.1.1 Identity of the Investigational Medicinal Products
Description of change		Yasmin® is listed as test product 2
Rationale for change		Inconsistency
Section to be changed		Section 4.3 Treatment compliance
Description of change		Compliance will only be checked in treatment periods 1 and 2
Rationale for change		Clarification
Section to be changed		Section 4.1.3 Method of assigning subjects to treatment groups
Description of change		Adaption of text for allocation of Subject Identification Number and implementation of a re-check of inclusion/exclusion criteria prior to run-in
Rationale for change		In line with other changes in this amendment, the allocation will take place prior to run-in and after a re-check of relevant inclusion/exclusion criteria.
Section to be changed		Section 5.3.2.1 Blood sampling for pharmacokinetic analysis of ethinylestradiol and drospirenone
Description of change		Adaption of volume of first aliquot
Rationale for change		Lab request
Section to be changed		Section 5.3.2.2 Blood sampling for pharmacokinetic analysis of BI 1358894
Description of change		Adaption of volume of first aliquot
Rationale for change		Lab request

11.3 GLOBAL AMENDMENT 3

Date of amendment		19 Oct 2023
EU Trial number		2022-502861-78-00
BI Trial number		1402-0019
BI Investigational Medicinal Product(s)		BI 1358894
Title of protocol		An open-label, fixed-sequence cross-over, two-period, phase I trial to evaluate the effect of multiple doses of BI 1358894 on the pharmacokinetics of a combination of ethinylestradiol and drospirenone in healthy female subjects
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		Title page, synopsis
Description of change		Change of PI
Rationale for change		[redacted] will take over the function as PI in the trial
Section to be changed		Section 1.2.1 B I1358894
Description of change		Number of participants in phase I and II updated
Rationale for change		New numbers according to recent update of IB

APPROVAL / SIGNATURE PAGE

Document Number: c41232811 **Technical Version Number:4.0**

Document Name: clinical-trial-protocol-version-04

Title: An open-label, fixed-sequence cross-over, two-period, phase I trial to evaluate the effect of multiple doses of BI 1358894 on the pharmacokinetics of a combination of ethinylestradiol and drospirenone in healthy female subjects

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	23 Oct 2023 15:05 CEST
Approval-Clinical Program [redacted]		23 Oct 2023 15:06 CEST
Approval-Clinical Trial Leader		23 Oct 2023 15:47 CEST
Verification-Paper Signature Completion		24 Oct 2023 11:18 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed