Boehringer Ingelheim

Clinical Trial Protocol

	Document Number: **c38699243-02**
EUCT No.	2022-500050-42-00
BI Trial No.	1346-0036
BI Investigational Medicinal Product	BI 425809 / iclepertin
Title	The effect of multiple doses of BI 425809 on the pharmacokinetics of multiple doses of a combination of ethinylestradiol and levonorgestrel following oral administration in healthy premenopausal female subjects (an open-label, two-period, fixed sequence design trial with run-in period)
Lay Title	A study in healthy women to test whether BI 425809 influences the amount of a contraceptive in the blood
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]
[redacted] **Investigator**	[redacted] Phone: [redacted] Fax: [redacted]
Current Version, Date	Version 2.0, 12 Oct 2022
Original Protocol Date	13 Jul 2022

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	13 Jul 2022
Revision date	12 Oct 2022
BI trial number	1346-0036
Title of trial	The effect of multiple doses of BI 425809 on the pharmacokinetics of multiple doses of a combination of ethinylestradiol and levonorgestrel following oral administration in healthy premenopausal female subjects (an open-label, two-period, fixed sequence design trial with run-in period)
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	The combination of BI 425809 and oral contraceptives containing ethinylestradiol and levonorgestrel may be widely used in a clinical setting. Considering possible effects of BI 425809 on metabolism of oral contraceptives (OC) due to CYP3A4 induction, the investigation of drug-drug interaction should assure the safe and effective use of oral contraceptives if combined with BI 425809.
Trial objective	To investigate the effect of multiple oral doses of BI 425809 on the multiple dose pharmacokinetics of ethinylestradiol (EE) and levonorgestrel (LNG) (Microgynon®)
Trial endpoints	*Primary endpoints:* $AUC_{\tau,ss}$, $C_{max,ss}$ and $C_{min,ss}$ of EE and LNG in plasma for test compared with reference treatment *Secondary endpoint:* Not applicable
Trial design	Open-label, run-in period, two-period, fixed sequence, no wash-out
Number of subjects **total entered** **on each treatment**	 16 16
Diagnosis	Not applicable
Main inclusion criteria	Healthy female premenopausal subjects, age of 18 to 35 years, BMI of 18.5 to 29.9 kg/m² (inclusive)

Test product 1	BI 425809 film-coated tablets, iCF
dose	10 mg q.d.
mode of administration	Oral with 240 mL of water after an overnight fast of at least 10 h
Test product 2	Microgynon® tablets (oral contraceptives)
dose	30 mcg ethinylestradiol (EE) / 150 mcg levonorgestrel (LNG) q.d.
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h on Days 1, 18-21 in Period 1 and Days 1-21 in Period 2. On Days 2-17 in Period 1 fasting is not mandatory.
Duration of treatment	Run-in Period: 1 tablet q.d. of Microgynon® for 21-49 days (depending on duration of menstrual cycle) Reference treatment (Period 1): 1 tablet q.d. Microgynon® on Days 1-21 Test treatment (Period 2): 1 tablet q.d. Microgynon® + 1 tablet q.d. 10 mg of BI 425809 on Days 1-21 No wash-out period between Treatment Periods
Statistical methods	Absolute bioavailability factor (F) of OC will be estimated by the ratios of the geometric means (test/reference=BI 425809+OC / OC) for the primary endpoints $AUC_{\tau,ss}$, $C_{max,ss}$ and $C_{min,ss}$. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range is not specified. The statistical model will be an ANOVA on the logarithmic scale including the fixed effect for 'formulation' and 'subject' as a random effect. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[5]	PK blood, BI 425809[11]	PK blood, OC[11]	Suicidality assessment[16]	12-lead ECG[12]	Vital signs (BP, PR)[13]	Questioning for AEs and concomitant therapy[7]
SCR	1	-91 to -35			Screening (SCR)[1]	A[8]			x	x	x[15]	
Run-in	2	-56 to -8			Dosing OC[10]	B[8]						x
		-7 to -1			Follow up call (OC free interval)							x
Period 1/ Treatment R (oral contraceptives (OC) alone)	3	1	00:00	08:00	Dosing OC (ambulatory)	x[8]		x[9]				x
		2	24:00	08:00	Dosing OC (ambulatory)							x
		3	48:00	08:00	Dosing OC (ambulatory)							x
		4	72:00	08:00	Dosing OC (ambulatory)							x
		5	96:00	08:00	Dosing OC (ambulatory)							x
		6	120:00	08:00	Dosing OC (ambulatory)							x
		7	144:00	08:00	Dosing OC (ambulatory)							x
		8	168:00	08:00	Dosing OC (ambulatory)							x
		9	192:00	08:00	Dosing OC (ambulatory)							x
		10	216:00	08:00	Dosing OC (ambulatory)							x
		11	240:00	08:00	Dosing OC (ambulatory)							x
		12	264:00	08:00	Dosing OC (ambulatory)							x
		13	288:00	08:00	Dosing OC (ambulatory)							x
		14	312:00	08:00	Dosing OC (ambulatory)							x
		15	336:00	08:00	Dosing OC (ambulatory)							x
		16	360:00	08:00	Dosing OC (ambulatory)							x
		17	384:00	08:00	Dosing OC (ambulatory)							x
		18	408:00	08:00	Dosing OC (ambulatory)			x[9]				x
		19	432:00	08:00	Dosing OC (ambulatory)			x[9]				x
		20	456:00	08:00	Dosing OC (ambulatory)			x[9]				x
		21	478:00	06:00	Admission to trial site[2,14]	B[2,3,8]				x[2]	x[2,15]	x[2]
			480:00	08:00	Dosing OC			x[9]				
			480:30	08:30				x				
			481:00	09:00				x				
			481:30	09:30				x				
			482:00	10:00	240 mL fluid intake (mandatory)			x				
			483:00	11:00				x				
			484:00	12:00	240 mL fluid intake (mandatory), Lunch[4]			x				
			486:00	14:00				x				
			488:00	16:00	Snack (voluntary)[4]			x				
			490:00	18:00				x				
			492:00	20:00	Dinner[4]			x				x
		22	504:00	08:00	Breakfast[4], discharge from trial site			x			x	x
		23-28			Follow up call (OC free interval)							x
Period 2/ Treatment T	4	1	00:00	08:00	Dosing BI 425809 + OC (ambulatory)	x[2,8]	x[9]	x[9]	x[2]	x[2]	x[2]	x[2]
		2	24:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		3	48:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		4	72:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		5	96:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		6	120:00	08:00	Dosing BI 425809 + OC (ambulatory)							x

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[5]	PK blood, BI 425809[11]	PK blood, OC[11]	Suicidality assessment[16]	12-lead ECG[12]	Vital signs (BP, PR)[13]	Questioning for AEs and concomitant therapy[7]
Period 2 / Treatment T (BI 425809 + OC)		7	144:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		8	168:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		9	192:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		10	216:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		11	240:00	08:00	Dosing BI 425809 + OC (ambulatory)				x			x
		12	264:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		13	288:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		14	312:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		15	336:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		16	360:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		17	384:00	08:00	Dosing BI 425809 + OC (ambulatory)							x
		18	408:00	08:00	Dosing BI 425809 + OC (ambulatory)		x[9]	x[9]				x
		19	432:00	08:00	Dosing BI 425809 + OC (ambulatory)		x[9]	x[9]				x
		20	456:00	08:00	Dosing BI 425809 + OC (ambulatory)		x[9]	x[9]				x
		21	478:00	06:00	Admission to trial site[2,14]	B[2,3,8]			x	x[2]	x[2,15]	x[2]
			480:00	08:00	Dosing BI 425809 + OC		x[9]	x[9]				
			480:30	08:30				x				
			481:00	09:00				x				
			481:30	09:30				x				
			482:00	10:00	240 mL fluid intake (mandatory)			x				
			483:00	11:00				x				
			484:00	12:00	240 mL fluid intake (mandatory), Lunch[4]			x				
			486:00	14:00				x				
			488:00	16:00	Snack (voluntary)[4]			x				
			490:00	18:00				x				
			492:00	20:00	Dinner[4]			x				x
		22	504:00	08:00	Breakfast[4], discharge from trial site		x	x			x	x
		23-28			Follow up call (OC free interval)							x
EOS	5	32 to 42			End of study (EOS) examination[6]	C[,8]			x	x	x[15]	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, suicidality assessment, check of vital signs, ECG, safety laboratory (including drug screening), 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. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. Urine drug screening and alcohol breath test.
4. If several actions are indicated at the same time, the intake of meals will be the last action.
5. Letters A, B and C define different sets of safety laboratory examinations (for details refer to Table 5.2.3: 1).
6. At the end of study (synonym for end of trial), the EOS examination includes physical examination, suicidality assessment, vital signs, body weight, ECG, safety laboratory, recording of AEs and concomitant therapies. The EOS examination can be done earliest 11 days after the last drug administration of BI 425809 in Period 2.
7. 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.
8. Pregnancy test in serum only at screening and in urine at other time points indicated in the Flow Chart above.
9. Blood collection takes place within 10 minutes before dosing.
10. Details of treatment with oral contraceptives (OC) during Run-in Period are described in Section 3.1 and 4.1.4.
11. For details of PK blood sampling, refer to Section 5.3.2.
12. For details of 12-lead ECG, refer to Section 5.2.4.

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[redacted]

BP

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IPD

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ULN

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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 425809		
• CNS-related effects	• CNS depressant effects indicated by nonclinical data, and also observed in clinical studies with other compounds in the same pharmacological class [R13-4450] • In clinical studies with healthy volunteers, headache, dizziness and fatigue were the most frequently reported AEs in BI 425809 treatment groups • For details refer to Sections 1.2.1.1, and the current IB [c02155957]	• In case of headache, the investigator may initiate symptomatic treatment if deemed necessary • Subjects will be asked to use public transport instead of driving cars and not to operate machines should they experience CNS-related effects that might impair ability to drive or operate machines • In questionable cases neurological tests and testing of driving ability prior to discharge will be initiated by the investigator. In-house stay may be prolonged at any time at the discretion of the investigator • Alcohol is not permitted from 7 days before the first drug administration in Period 1 until the last PK sample of Period 2
• Gastrointestinal effects	• In clinical studies with healthy volunteers, nausea, vomiting and diarrhoea were among the most frequently reported AEs in BI 425809 treatment groups • For details refer to Sections 1.2.1.1, and the current IB [c02155957]	• Clinical gastrointestinal symptoms will be monitored carefully, and symptomatic treatment may be initiated by the investigator if deemed necessary (e.g. fluid replacement in case of diarrhoea)

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 425809		
• Ophthalmological effects	• In the single rising dose trial using powder for oral solution formulation (1346.1), dose-related increases in VAS scores and visual disturbances (blurred vision, photopsia, chromatopsia) were observed around t_{max} [c02820512] • For details refer to the current IB [c02155957]	• Subjects will be advised not to drive cars or operate machines should they experience blurred vision • In questionable cases visual tests will be initiated by the investigator. In-house stay may be prolonged at any time at the discretion of the investigator • In case of ophthalmological AEs, evaluation to be made by an ophthalmologist
• Haematology changes	• Changes in red blood cell parameters (reductions in haemoglobin, haematocrit, etc.) indicated by non-clinical data • In trials with healthy volunteers, no notable decrease in haemoglobin or haematocrit was noted in the BI 425809 treatment groups compared with placebo • A dose-dependent decrease in haemoglobin was noted in the longer term 12-week Phase II trials with patients at doses 10 mg (-2.3%) and 25 mg (-3.2%) at last value on treatment as compared to baseline • For details refer to Sections 1.2.1.1 and the current IB [c02155957]	• Subjects will regularly undergo clinical laboratory testing to monitor potential BI 425809 induced alterations • Administration of BI 425809 is limited to 3 weeks.
• Drug-induced liver injury (DILI)	• Rare but severe event, thus under constant surveillance by sponsors and regulators.	• Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety.

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 425809		
• Drug-drug interaction between BI 425809 and other drugs	• Co-administration with a strong CYP3A inhibitor increased the total exposure of BI 425809 significantly, while it was significantly decreased in the presence of a strong CYP3A4 inducer (for details refer to the current IB [c02155957])	• Subjects will not be allowed to use strong and moderate inhibitors or inducers of CYP3A4 within 30 days before start of trial treatment
Investigational Medicinal Product: Microgynon®		
Increased risk of serious side effects such as cardiovascular diseases (myocardial infarction, cerebrovascular insult, venous thromboembolism), severe hepatic disease and tumors of breast and liver.	The incidence of venous thromboembolic events is 5-10 per 100.000 women in 1 year, if no hormonal contraceptives are used. The incidence is increased to about 20/100.000 after intake of 2nd generation combined oral contraceptives (containing levonorgestrel, e.g. Microgynon®). In contrast, the intake of 3rd generation combined oral contraceptives (containing gestoden or desogestrel) is associated with a higher risk (up to 40/100.000) of thrombembolic events [R12-0033]. Increased risks of tumors of breast and liver are indicated in the SmPC of Microgynon® [R22-2154], see also Section 1.2.2.3.	- Close monitoring of adverse events, safety lab, ECG and vital signs - Subjects with additional risk factors (smoking, obesity, hypertension) are not to be entered in the trial - Thrombophilic testing will be performed on each subject to detect a potential thrombophilic disposition - 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: Microgynon®		
The most frequent side effects (>10%) of Microgynon® are: - Headache - Spotting and intermenstrual bleeding Rare adverse event (less than 0.1% of users) is hypersensitivity Exacerbation of hereditary angioedema was reported in post-marketing research (frequency unknown)	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 Microgynon® [R22-2154], see also Section 1.2.2.3 and the current SmPC for more details.	- Symptomatic treatment of headache if required - Treatment with Microgynon® 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 - Subjects with history of relevant allergy or hypersensitivity, or hereditary angioedema will be excluded from participation
The following undesirable effects have been observed: - Gastric upset, nausea, vomiting, breast tenderness, changes in body weight, changes in libido, breast pain and depression. - In predisposed women, chloasma which is exacerbated by exposure to sunlight. - Individual cases of poor tolerance of contact lenses.	Based on SmPC of Microgynon® [R22-2154], see also Section 1.2.2.3 and the current SmPC for more details.	- Increased awareness of symptoms - Careful monitoring of hydration in subjects with vomiting - Symptomatic treatment if required - If required, further diagnostics and treatment have to be initiated according to local standard of care - Women with a predisposition to pigment changes should avoid prolonged exposure to sunlight - Contact lens wearers who develop changes in lens tolerance should be assessed by an ophthalmologist

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: Microgynon®		
Drug-drug interaction between BI 425809 and Microgynon®	Due to induction of CYP3A4 by BI 425809 (Section 1.2.1.4), a decrease in OC exposure is expected but an increase cannot be ruled out. Whereas an increase may increase the number and intensity of side effects of ethinylestradiol and levonorgestrel (see above), a decrease would result in reduced efficacy of OC. The impact of OC on BI 425809 exposure as result of interaction with CYP3A4 is expected to be minimal (Section 1.3).	A possible reduced efficacy would not put the subjects at risk since additional contraceptive measures are mandatory per study protocol
Drug-drug interaction between Microgynon® 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 Microgynon® in accordance to the SmPC within 30 days before start of run-in period (including moderate and strong CYP3A4 inhibitors, CYP3A4 inducers, St. John's wort (Hypericum perforatum), etc.)
Trial procedures		
Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paraesthesia, 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

The total volume of blood withdrawn per subject during the entire trial will not exceed the volume of a normal blood donation (500 mL) and will be approx. 320 mL. On Day 21 of Period 1 and 2, the volume of blood withdrawn will not exceed 100 mL per day; and will be approx. 20 mL at screening and approx. 10 mL on the other trial days (see below). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

Table 1.4.2: 2 Overview of blood sampling in the trial

Trial Period	**Day**	**Number of blood samplings**	**Amount of blood (ml)**
Safety blood sampling			
Screening	Day -91 to -35	x 1	20,4
Run-in	Day -56 to -28	x 1	8,8
Period 1	Day 21	x 1	8,8
Period 2	Day 21	x 1	8,8
End of Trial	Day 32 to 42	x 1	11,8
Total number of safety blood samplings: x 5 Total amount of blood for safety evaluation: 58,6 ml			
PK blood sampling (oral contraceptives)			
Period 1	Day 1	x 1	7,5
	Day 18	x 1	7,5
	Day 19	x 1	7,5
	Day 20	x 1	7,5
	Day 21	x 11	82,5
	Day 22	x 1	7,5
Period 2	Day 1	x 1	7,5
	Day 18	x 1	7,5
	Day 19	x 1	7,5
	Day 20	x 1	7,5
	Day 21	x 11	82,5
	Day 22	x 1	7,5
Total number of PK blood samplings (OC): x 32 Total amount of blood for PK evaluation (OC): 240,0 ml			
PK blood sampling (BI 425809)			
Period 2	Day 1	x 1	2,7
	Day 18	x 1	2,7
	Day 19	x 1	2,7
	Day 20	x 1	2,7
	Day 21	x 1	2,7
	Day 22	x 1	2,7
Total number of PK blood samplings (BI 425809): x 6 Total amount of blood for PK evaluation (BI 425809): 16,2 ml			
Total number of blood samplings in the trial: x 43 **Total amount of blood withdrawn in the trial: 314,8 ml**			

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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 q.d. Microgynon® on Days 1-21 (R) in Period 1.

Test (T): one tablet q.d. Microgynon® and one tablet q.d. 10 mg of BI 425809 on Days 1-21 in Period 2.

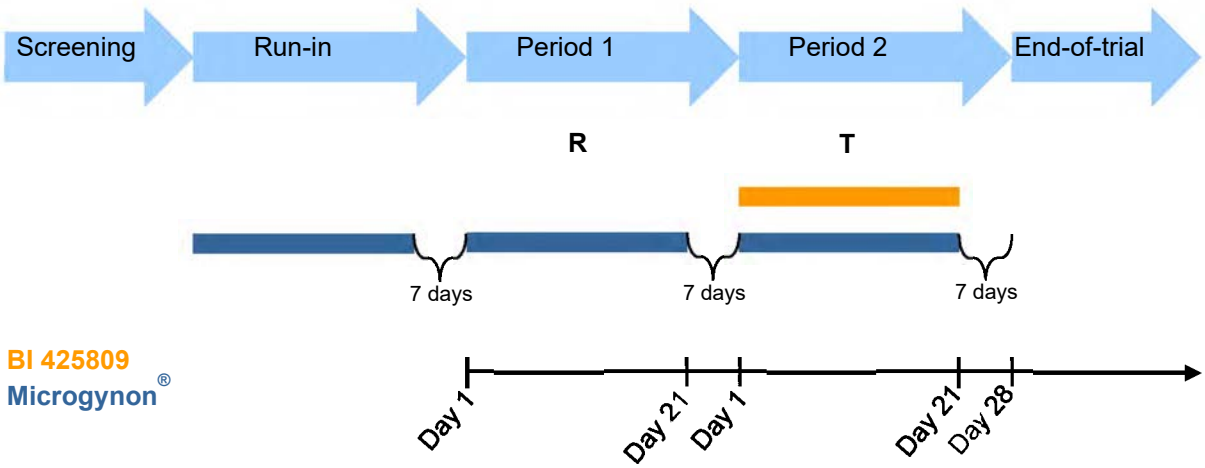
On Days 1, 18-21 in Period 1 and Days 1-21 in Period 2, the treatments will be given under fasting conditions. On Days 2-17 in Period 1 fasting will be not mandatory. The Reference Treatment will always be followed by the Test Treatment in a fixed sequence. There will be no wash-out period between the 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 Microgynon® 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 withdrawal 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 Sections 6.1 and 6.2, respectively.



Abbreviations: R = Reference Treatment (Microgynon®); T = Test Treatment (Microgynon® and BI 425809)

Figure 3.1: 1 Trial design

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R09-5728

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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 on a first-come, first-served basis prior to first administration of oral contraceptives in the morning of the first day of the run-in period (Visit 2).

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. For discussion of trial-associated risks and safety measures, see Section 1.4).

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
T (Test)	Microgynon®	Tablet	30 µg EE /150 µg LNG	1 tablet qd (Period 2, Days 1-21)*	30 µg EE /150 µg LNG
	BI 425809	Tablet	10 mg	1 tablet (10 mg) qd (Period 2, Days 1-21)*	10 mg
R (Reference)	Microgynon®	Tablet	30 µg EE /150 µg LNG	1 tablet qd (Period 1, Days 1-21)*	30 µg EE /150 µg LNG

* - no Microgynon® tablets are to be taken in the last 7 days of each of Period 1 and Period 2 (i.e. Days 22-28).

Run-in period (Visit 2):

The Microgynon® tablets for the run-in period (duration depends on the actual menstrual cycle of the subject) will be dispensed to the eligible subjects. The administration during the run-in period is done by the subjects and documented in a diary. The subjects are advised to take the Microgynon® tablets with a cup of water at the same in the morning, no fasting is required prior to intake. No Microgynon® tablets are to be taken in the last 7 days of the run-in period. The next day will be Day 1 of the study.

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

Administration of trial medication on Day 21 in both treatment periods will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing.

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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
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	--	X
	Prothrombin time – Quick	X	--	X
	Prothrombin time – INR (International Normalization Ratio)	X	--	X
	Thrombophilic testing (Lupus anticoagulant / Anti-cardiolipin antibody (ACA) (IgM, IgG) / Protein C / Protein S /antithrombin III /anti-beta2 Glycoprotein I antibody (IgM, IgG) / Plasminogen / Activated protein C (APC) Resistance (Factor V Leiden)	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	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	--	--	--
Hormones	Thyroid Stimulating Hormone	X	--	--
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	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	--	--
	Triglyceride	X	--	--
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Calcium	X	X	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C
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 RBC/Erythrocytes (qual)	X	--	X
	Urine WBC/Leucocytes (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 at Visit 2 on the 1st day of the Run-in period, and on Day 21 of Visits 3 and 4 (Treatment periods 1 and 2). 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 in women will be performed at screening in serum, and in urine on the 1st day of Run-in period and on Days 1 and 21 of Treatment periods 1 and 2 (i.e., prior to each treatment period, and prior to each admission to trial site), and as part of the end of trial examination. Drug screening will be performed at screening and prior to each admission to trial site. For time points refer to Flow Chart.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/Ecstasy Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)
COVID-19 (nasopharyngeal swab)[1]	SARS CoV-2 PCR test
Pregnancy test (serum/urine)[2]	Beta human chorionic gonadotropin (beta-HCG)

[1] if needed due to the current status of the pandemic, evaluation will be performed shortly (two tests on different days within 72 hours) before admission to trial site in each treatment period as per Flow Chart
[2] pregnancy tests in serum only at screening and in urine at each other time point as per Flow Chart

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. Alcotest® [redacted]) will be performed prior to each treatment period, 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]. Laboratory data will be transmitted electronically from the laboratory to the trial site. The pregnancy test in urine will be conducted as indicated in the Flow Chart using a marketed test, TestPack+Plus hCG Urine OBC; [redacted], or comparable test systems. Drug screening will be performed using SureStep ML 10 Scr Test Device; [redacted] or comparable test systems. Drug screening and pregnancy testing in urine will be analysed at 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.

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For various assumptions around the gCV of 25% , Table 7.5: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

Table 7.5: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a two-period, fixed sequence trial *(N=12 evaluable subjects)*

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
20	1.21	80	65.88	97.15
20	1.21	100	82.35	121.43
20	1.21	125	102.94	151.79
20	1.21	150	123.53	182.15
25	1.27	80	62.84	101.85
25	1.27	100	78.55	127.31
25	1.27	125	98.19	195.13
25	1.27	150	117.83	190.96
30	1.33	80	95.99	106.68
30	1.33	100	74.99	133.36
30	1.33	125	93.73	166.69
30	1.33	150	112.48	200.03

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

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 4.0.3.

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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] *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] *inquiries and training requirements contact* [redacted]

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	___	___

 C-SSRS—Baseline/Screening [Version 1/14/09] Page 1 of 2

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* _____

 C-SSRS—Baseline Screening (Version 1/14/08) Page 2 of 2

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] *(Oquendo M. A.,* [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] *inquiries and training requirements contact* [redacted]

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	____

 C-SSRS—Since Last Visit (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:	Yes ☐ No ☐ Total # of Attempts: _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	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* _____

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		12 October 2022
EUCT No.		2022-500050-42-00
BI Trial number		1346-0036
BI Investigational Medicinal Product(s)		BI 425809 / iclepertin
Title of protocol		The effect of multiple doses of BI 425809 on the pharmacokinetics of multiple doses of a combination of ethinyl estradiol and levonorgestrel following oral administration in healthy premenopausal female subjects (an open-label, two-period, fixed sequence design trial with run-in period)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		1. Flow Chart 2. 1.4.2: 1 3. 1.4.2 4. 1.4.2: 2 5. 3.3.2 6. 3.3.3 7. 3.3.4.3 8. 5.2.3: 1 9. 7.5: 1 10. 8.1 11. 8.5
Description of change		1. Body weight added to EoS examination (ft.6) 2. Mentioning of low therapeutic dose removed 3,4. Details about amounts of blood withdrawn added 5. Inclusion criteria clarified 6. Exclusion criteria clarified 7. Trial discontinuation criteria clarified 8. Name of Factor V Leiden test clarified 9. Confidence intervals clarified 10. Reference to legally authorized representatives deleted 11. Pseudonymization is described

Rationale for change		1,2,6. Correction of typos and mistakes 2-7, 10. Request from the competent authority 8. Update of local safety lab specifications 9. Values updated for paired data 11. Request from the ethical committee

APPROVAL / SIGNATURE PAGE

Document Number: c38699243 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-02

Title: The effect of multiple doses of BI 425809 on the pharmacokinetics of multiple doses of a combination of ethinyl estradiol and levonorgestrel following oral administration in healthy premenopausal female subjects (an open-label, twoperiod, fixed sequence design trial with run-in period)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	12 Oct 2022 17:04 CEST
Author-Trial Statistician		12 Oct 2022 17:10 CEST
Approval-Clinical Program [redacted]		12 Oct 2022 18:13 CEST
Verification-Paper Signature Completion		12 Oct 2022 18:15 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed