Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase I, Open-Label, Multiple-Dose Study of the Effect of Evobrutinib on the Pharmacokinetics of a Combined Oral Contraceptive in Healthy Female Participants
Study Number:	MS200527_0079
Protocol Version:	20 September 2022/Version 3.0
Merck Compound**:**	Evobrutinib (M2951)
Merck Registered Compound Name in Japan:	Not applicable
Study Phase:	I
Short Title:	Effect of Evobrutinib on Pharmacokinetics of a Combined Oral Contraceptive
Principal Investigator:	PPD
Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KgaA, Darmstadt, Germany an affiliate of Merck KgaA, Darmstadt, Germany Frankfurter Str. 250 64293, Darmstadt, Germany
Regulatory Agency Identifying Numbers:	EudraCT: 2022-000124-38
Keywords:	Drug-drug interaction, clinical pharmacology

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	28 April 2022
2.0	Updated Protocol	30 June 2022
3.0	Updated Protocol	20 September 2022

Protocol Version 3.0 (20 September 2022)

Overall Rationale for the Amendment

This protocol amendment was prepared to allow rescreening of healthy volunteers that had to discontinue due to personal or logistical reasons or due to minor deviations that were not considered clinically relevant.

Section # and Name	Description of Change	Brief Rationale
5.4 Screen Failures	Four exceptions for rescreening were introduced.	To allow rescreening of healthy volunteers that had to discontinue due to personal or logistical reasons or due to minor deviations that were not considered clinically relevant.

Table of Contents

1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase I, Open-Label, Multiple-Dose Study of the Effect of Evobrutinib on the Pharmacokinetics of a Combined Oral Contraceptive in Healthy Female Participants

Short Title: Effect of Evobrutinib on Pharmacokinetics of a Combined Oral Contraceptive (COC)

Rationale: Embryo-fetal toxicity studies in female mice and rabbits indicate a teratogenic potential of evobrutinib. Thus, a study to evaluate the drug-drug interaction potential of evobrutinib on COC components is required according to FDA and EMA guidance.

The intent of this study is to assess the effect of evobrutinib on the pharmacokinetics of the COC ethinyl estradiol/norethisterone in healthy female participants. CCI [redacted]

Objectives and Endpoints:

Objectives	Endpoints	Ref. #
Primary		
To investigate the effect of multiple doses of evobrutinib on EE/NET PK in healthy participants	Plasma EE/NET: $AUC_{0-\infty}$ C_{max}	1
Secondary		
To assess the safety and tolerability of evobrutinib when administered together with EE/NET in healthy participants	Nature, occurrence, and severity of TEAEs Absolute values and changes in safety laboratory tests Single 12-lead ECGs evaluated by Investigator Vital signs assessed from time of first dose to end of study participation	2 3 4 5
To characterize the effect of evobrutinib on EE/NET PK	Plasma EE/NET: t_{max} $t_{½}$ $AUC_{0-tlast}$ CL/F VZ/F	6

ECG=electrocardiogram; EE/NET=ethinyl estradiol/ norethisterone; PK=pharmacokinetics; TEAE=treatment-emergent adverse event.

Overall Design: This will be a nonrandomized, open-label, single-sequence, multiple-dose Phase I study in a maximum of 20 healthy female participants.

Brief Summary:

The purpose of this study is to assess the effect of evobrutinib on the pharmacokinetics of a combined oral contraceptive in healthy female participants. Study details include:

Study Duration: up to 46 days

Treatment Duration: Days 4 to 17 (14 days treatment with evobrutinib); Days 1 and 15 (2 days treatment with COC)

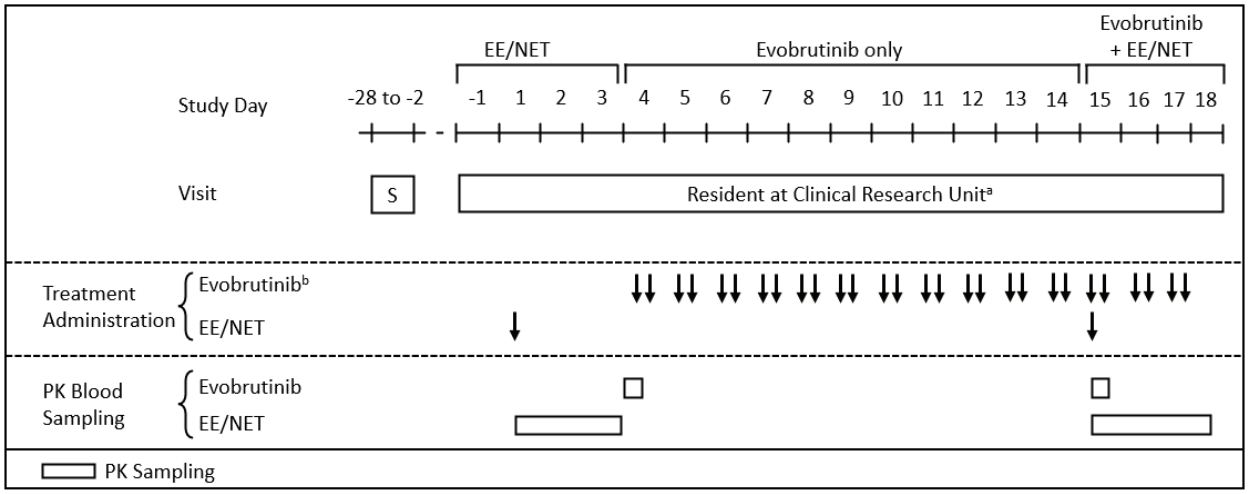
Visit Frequency: Participants will be resident in the Clinical Research Unit from Day -1 to Day 18.

CCI [redacted]

Study Intervention Groups and Duration: single-sequence study, up to 46 days

Involvement of Special Committee(s): No

1.2 Schema



EE/NET=ethinyl estradiol/norethisterone; PK=pharmacokinetic; S=Screening visit.

a Including Safety Follow-up on Day 18 after collection of the last PK sample.

b Twice daily evobrutinib dosing starting on Day 4 under fed conditions.

1.3 Schedule of Activities

Assessments & Procedures	Screen-ing	Intervention Period (Days)																	Safety Follow-up	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Informed consent	X																				Prior to any Screening activity.
Eligibility criteria	X	X[a]																			a: For re-check of eligibility criteria on Day -1, see inclusion (Section 5.1) and exclusion criteria (Section 5.2).
Demography	X																				Demography to include, at minimum, age, sex, race, and ethnicity.
Medical history	X																				
Physical examination	X	X																		X	Brief examination on Day -1 to check eligibility.
Serum pregnancy test	X	X																		X	
Viral serology, TSH and QuantiFERON® test	X																				
Clinical laboratory tests including FSH	X	X														X				X	Details in Appendix 5. FSH in postmenopausal women at Screening only.
Drug screen, alcohol breath test, and SARS-CoV-2	X	X																			
24 hours Holter ECG	X																				At Screening: 24-hour Holter ECG of participants above 45 years of age (± 2 hours time window allowed).
12-lead ECG	X	X	X													X	X			X	On Days -1 and 14 (predose to COC administration on Days 1 and 15); on Days 1 and 15 at 2 hours postdose ± 30 min; and on Day 18.

Assessments & Procedures	Screen-ing	Intervention Period (Days)																	Safety Follow-up	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Vital signs	X	X	X			X										X				X	Includes height and weight (collection at Screening only). Predose and 4 and 6 hours postdose on Days 4 and 14.
CCI [redacted]		[redacted]																			
Participants resident in the CRU		<----------																		---------->	
COC oral administration			X														X				Single dose of EE/NET under fed conditions. For details on dosing see Section 6.1.
PK samples COC			X	X	X	X											X	X	X	X	Days 1-4, 15-18: predose and 20 min, 40 min, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours postdose (see Section 8.4).
Evobrutinib administration						X	X	X	X	X	X	X	X	X	X	X	X	X	X		Evobrutinib to be dosed in the morning and the evening approximately 12 hours apart for twice daily dosing under fed conditions (see Section 6.1).
[redacted]						[redacted]											[redacted]				CCI [redacted]
AE	<----------																			---------->	
Concomitant medication review	<----------																			---------->	

AE=adverse event; COC=combined oral contraceptive; CRU=clinical research unit; ECG=electrocardiogram; EE/NET=ethinyl estradiol/ norethisterone; FSH=follicle stimulating hormone; PK=pharmacokinetic; TSH=thyroid stimulating hormone.

2 Introduction

Evobrutinib is an oral, selective, irreversible inhibitor of BTK that is in clinical development for the treatment of autoimmune diseases, e.g., RMS. Detailed information on the chemistry, pharmacology, efficacy, and safety of evobrutinib is in the IB Version 14.0 dated 20-Oct-2021.

There is extensive clinical experience of the use of the combined oral contraceptive ethinyl estradiol (EE; 0.03 mg) and norethisterone, also referred to as norethindrone (NET; 0.5 mg). See Section 2.2 for details on EE/NET.

2.1 Study Rationale

Embryo-fetal toxicity studies in female mice and rabbits indicate a teratogenic potential of evobrutinib (see Section 2.2). Thus, a study to evaluate the DDI potential of evobrutinib on COC components is required according to FDA and EMA guidance.

The intent of this study is to assess the effect of evobrutinib on the PK of the combined oral contraceptive EE/NET in healthy female participants. CCI [redacted]

2.2 Background

Evobrutinib

Evobrutinib (also known as M2951) is an oral, selective, and irreversible inhibitor of BTK. Bruton's tyrosine kinase is a crucial intracellular kinase in the B cell antigen receptor signaling pathway. The mode of action of evobrutinib via the inhibition of BTK is expected to achieve profound B cell silencing. Thus, BTK inhibition could provide clinical benefit in the treatment of multiple autoimmune diseases including RMS.

In clinical studies with healthy participants, evobrutinib was rapidly absorbed with a t_{max} of 0.5 to 1.5 hours under fasted conditions. Evobrutinib demonstrated dose-proportional PK (i.e., C_{max} and $AUC_{0-\infty}$) over the evaluated dose range of 25 to 500 mg single dose and 25 to 200 mg once daily multiple doses. Median $t_{1/2}$ was approximately 2 hours (range 1.8 to 2.6 hours) at relevant plasma concentrations following a single oral dose of 25 to 200 mg. Accumulation of evobrutinib is minimal with daily dosing (refer to IB).

CCI [redacted]

CCI [redacted]

[redacted]

Ethinyl estradiol/norethisterone

EE and NET are 2 components of many COCs and are substrates of CYP3A4. The co-administration and potential DDIs between evobrutinib and EE/NET could result in lower or higher than desired clinical concentrations of the COC components.

The combined oral contraceptive EE/NET is well characterized (ethinyl estradiol/norethisterone SmPC, June 2021) and has been previously used in similar, published DDI studies (Loi 1999, Garg 2012, Shadle 2000). NET is rapidly and completely absorbed after oral administration, with peak plasma concentrations occurring between 1 and 3 hours. The elimination half-life varies from 5 to 12 hours, with a mean of approximately 8 hours. EE is rapidly and well absorbed from the gastrointestinal tract but is subject to some first-pass metabolism in the gut-wall. The elimination half-life varies from 15 to 20 hours.

2.3 Benefit/Risk Assessment

As of 31 July 2021, 2,041 male and female participants in 16 completed and 4 ongoing clinical studies have been exposed to evobrutinib including healthy participants, participants with RMS, systemic lupus erythematosus, or rheumatoid arthritis, and participants with renal impairment. Evobrutinib was generally safe and well tolerated in all participants. The TEAEs have been primarily mild to moderate in severity. Two Phase III studies with evobrutinib in patients with RMS (MS200527_0080 and MS200527_0082) are currently ongoing.

The evobrutinib treatment duration in this study will be 14 days in total, with 45 mg twice daily dosing of evobrutinib under fed conditions (see Section 4.3). CCI [redacted]

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of evobrutinib may be found in the IB.

Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

2.3.1 Risk Assessment

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) Evobrutinib		
Identified risk: Elevated liver transaminases	Elevated liver transaminases have been observed in patients treated with evobrutinib across the program and is considered an important identified risk (for details refer to current IB Section 6.1). Elevations of liver transaminases were frequent, generally mild (Grade 1), asymptomatic and reversible, and occurred within 6 months of treatment. However, more severe cases were reported. This has not been observed in healthy participants after a single dose nor in patients receiving short treatment with evobrutinib.	Participants with known history of hepatic disorder will not be included in the study. Study participants will be confined, and liver tests will be monitored during the study.
CCI [redacted]	[redacted]	Only female participants who are not of childbearing potential are eligible for participating in the study (see Section 5.1).
Study Intervention(s) EE/NET		
Potential risk: Cardiovascular disease	There is a risk of serious cardiovascular events from COC use. This risk is known to increase with age, particularly in women over 35 years of age, and with the number of cigarettes smoked.	Only nonsmokers will be enrolled, and only 2 doses of COC (separated by 2 weeks) will be administered.
Potential risk: Cardiovascular disease	The use of COC increases the risk of venous thromboembolism. The risk of venous thromboembolism in women using COCs is estimated to be around 3 to 9 per 10,000 woman-years. The risk is highest during the first year of use of a therapy. Use of COCs also increases the risk of cardiovascular events such as strokes and myocardial infarctions, especially in women with other risk factors for these events. The risk of thromboembolic disease due to oral contraceptives gradually disappears after the use is discontinued.	Women with a history of, or current, deep vein thrombosis or pulmonary embolism, cerebrovascular disease, coronary artery disease, cardiac valvular disease, uncontrolled hypertension, headaches with focal neurological symptoms, diabetes mellitus or atrial fibrillation will be excluded from the study.
Potential risk: breast, ovarian, endometrial, cervical and other estrogen- or progestin-sensitive cancer	Most cancers of the female reproductive system are estrogen-or progestin-sensitive cancers and the use of COCs therefore potentially stimulates further growth-expansion.	Women with a history of, or current, breast, endometrial, cervical or other estrogen- or progestin-sensitive neoplastic disease, as well as undiagnosed abnormal uterine bleeding, will be excluded from the study.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Blood draw	Blood draws have the potential to cause AEs such as fainting or hematoma.	Amount of blood drawn will be strictly controlled. Participants will be in a hospital setting with support from highly trained professionals.
ECG	Contact allergies can develop during ECG procedures.	Participants with known contact allergies will not be included in the study.
Other		
Not applicable		

AE = adverse events; COC = combined oral contraceptive; ECG = electrocardiogram; EE/NET = ethinyl estradiol/norethisterone.

2.3.1.1 Potential Risks Associated With the COVID-19 Pandemic Situation

As for the general population, there is a risk of a SARS-CoV-2 infection for study participants as long as the COVID-19 pandemic situation is ongoing.

Evobrutinib is a BTK inhibitor and, as such, works as an immunomodulator. There was some decrease in immunoglobulin M, an increase in immunoglobulin A, and some modest changes in immunoglobulin G following long-term treatment with evobrutinib; these changes were not clinically significant. In addition, duration of the evobrutinib treatment in this study will be limited to 14 days. Although BTK is not required to clear viral infections, apart from enteroviruses, no information is available regarding BTK inhibitors as a class or evobrutinib specifically regarding the risk for either contracting SARS-CoV-2 or severity of COVID-19 at this point. The published data on approved BTK inhibitors (e.g., ibrutinib and acalabrutinib) used in oncology suggest a protective effect of BTK inhibitors for severity and mortality of COVID-19 (Scarfò 2020; Thibaud 2020; Treon 2020).

During the entire study, all recommendations issued by the Robert Koch Institute as well as local guidelines with respect to the minimization of the risk of disease spreading, e.g., social distancing, disinfection, hygiene, and wearing of mouth-nose masks will be followed. During the pandemic situation, further measures according to recommendations and requirements from local health authorities may become necessary and will be followed within the context of this study as far as applicable, to ensure full implementation of the principles of GCP with priority on participant safety in this study also during the COVID-19 pandemic situation. These measures are described in a preventive action plan implemented at the Investigator site.

Due to the constantly evolving nature of the COVID-19 pandemic, the most up-to-date guidelines from the Robert Koch Institute and the applicable federal/local guidelines will be followed. In addition, to minimize the risk coming from a current infection and the risk of getting infected by other participants during the in-house phase (covering the whole treatment phase) of the study, the following measures are implemented:

- Only participants without any symptoms of a respiratory disease and without contact to any known SARS-CoV-2 positive patient or COVID-19 patient will be included into the study.
- Furthermore, as a part of the clinical study procedures, participants will be closely monitored (including for signs of COVID-19) during the entire study duration.
- Continuation of the study in case of a SARS-CoV-2 infection in the study participant or an identified contact to a SARS-CoV-2 positive participant or COVID-19 patient will be done at the Investigator's discretion and agreement with the medical monitoring team.
- The Sponsor will monitor the events related to any SARS-CoV-2 infection reported following evobrutinib regularly and update the recommendations, if necessary.

2.3.2 Benefit Assessment

Healthy participants may expect no direct benefit from participating in clinical studies with evobrutinib.

2.3.3 Overall Benefit: Risk Conclusion

Risk minimization measures routinely implemented in early phase clinical studies are considered adequate, including exclusion criteria (see Section 5.2), close biochemical and hematology laboratory monitoring (see Section 8.2.4), and observation of vital signs and ECGs (see Sections 8.2.2 and 8.2.3). Evobrutinib will be discontinued in case of events that unacceptably endanger the safety of the participant (see Section 7). Participants will be admitted to the study site for the duration of the study to allow continuous safety monitoring.

Considering the measures taken to minimize the risk to participants in this study, the potential risks identified in association with evobrutinib and EE/NET are justified in healthy participants.

3 Objectives and Endpoints

Objectives	Endpoints	Ref. #
Primary		
To investigate the effect of multiple doses of evobrutinib on EE/NET PK in healthy participants	Plasma EE/NET: $AUC_{0-\infty}$ C_{max}	1
Secondary		
To assess the safety and tolerability of evobrutinib when administered together with EE/NET in healthy participants	Nature, occurrence, and severity of TEAEs Absolute values and changes in safety laboratory tests Single 12-lead ECGs evaluated by Investigator Vital signs assessed from time of first dose to end of study participation	2 3 4 5
	Plasma EE/NET:	6

Objectives	Endpoints	Ref. #
To characterize the effect of evobrutinib on EE/NET PK	t_{max} $t_{1/2}$ $AUC_{0\text{-}tlast}$ CL/F VZ/F	
CCI		

ECG=electrocardiogram; EE/NET= ethinyl estradiol/norethindrone; PK=pharmacokinetics; TEAE=treatment-emergent adverse event.

4 Study Design

4.1 Overall Design

Study Design	Open-Label, Multiple-Dose Study of the Effect of Evobrutinib on the Pharmacokinetics of a Combined Oral Contraceptive in Healthy Female Participants (see Section 1.2)
Control Method	None (uncontrolled)
Single or Multicenter	Single center
Control Group	Not applicable
Study Population Type	Healthy female participants not of childbearing potential (see Section 5)
Level and Method of Blinding	Open-label
Bias Minimalization Method(s)	Not applicable
Study Intervention Assignment Method	Not applicable

Involvement of Special Committee(s)	No
Total Duration of Study Participation per Participant	Up to 46 days (see Section 1.3)
Provisions for Study Extension or Entry into Roll-Over Studies	None
Adaptive Aspects of Study Design	Not applicable

4.2 Scientific Rationale for Study Design

This single-sequence design is consistent with the FDA guidance for clinical COC DDI study designs and the EMA Guideline on the investigation of drug interactions and allows for adequate characterization of evobrutinib's potential effect on the PK of EE/NET.

4.2.1 Participant Input into Design

Not applicable.

4.3 Justification for Dose

Evobrutinib

The evobrutinib dose to be used in this study, 45 mg twice daily, with each dose to follow a standardized meal, is the same as for Phase III studies evaluating evobrutinib in participants with RMS. This dosing regimen is anticipated to be well tolerated based on prior clinical experience and is adequate to evaluate the potential clinical DDI effect between evobrutinib and EE/NET.

Evobrutinib exposure increased when given with either a high-fat or low-fat meal relative to fasted conditions (see Section 2.2 for details). The exposure in this study is expected to not exceed that of other studies in healthy participants, in which multiple doses up to 200 mg evobrutinib for 14 days were administered and well tolerated.

Ethinyl estradiol/norethisterone

The dose of the COC to be used in this study, 0.03 mg EE/0.5 mg NET, is the same as a commonly used clinical dose for oral contraception in females and similar to the range of those doses used in DDI studies of this type (Zhang 2018).

4.4 End of Study Definition

The end of the study is defined as the date of last contact (related to this study) with the last participant who participates in this study (last participant's Safety Follow-up Assessment/Early Termination Assessment).

A participant has completed the study if she has completed all study parts, including the Safety Follow-up Assessment shown in Section 1.3.

Study termination criteria

The study will be discontinued or terminated if:

- Unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment is identified. This might include the occurrence of AEs which character, severity or frequency is new in comparison to the existing risk profile.
- One serious unexpected AE suspected to be drug related occurs or ≥ 50% of the participants show AEs of at least moderate severity for which a causal relationship to the study intervention or study-related procedures cannot be excluded.
- Any data derived from other clinical trials or toxicological studies become available which negatively influence the risk/benefit assessment.

General information on study termination is specified in Appendix 2.

5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted. Minor, not clinically relevant excursions (from the normal range) in laboratory findings are allowed at the discretion of the Investigator (see Section 5.2, #16).

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant has provided written informed consent, as indicated in Appendix 2.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Category	Criterion
Age	1. Are 18 to 68 (inclusive) years of age at the time of signing the informed consent.
Type of Participant and Disease Characteristics	2. Are overtly healthy as determined by medical evaluation, including no clinically significant abnormality identified on physical examination or laboratory evaluation and no active clinically significant disorder, condition, infection or disease that would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion.
Weight	3. Have a body weight within 50.0 and 100.0 kg (inclusive) and body mass index within the range 19.0 and 30.0 kg/m^2 (inclusive).
Sex and Contraception/Barrier Requirements	4. Female participants who are **not** a WOCBP See Appendix 3 for definitions.
Informed Consent	5. Capable of giving signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the ICF and this protocol.
Smoking	6. Are nonsmokers for at least 6 months preceding Screening.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Category	Criterion
Medical Conditions	1. History or presence of clinically relevant respiratory, gastrointestinal, renal, hepatic, hematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, dermatological, connective tissue diseases or disorders, as determined by medical evaluation.
	2. Individuals with diagnosis of hemochromatosis, Wilson´s disease, alpha 1 antitrypsin deficiency, or any other chronic liver disease including Gilbert's disease will be excluded from the study.
	3. Prior history of splenectomy or any clinically relevant surgery within 3 months prior to Screening.

Category	Criterion
	4. History of any malignancy.
	5. History of chronic or recurrent acute infection or any bacterial, viral, parasitic or fungal infections within 30 days prior to Screening and at any time between Screening and admission, or hospitalization due to infection within 6 months prior to Screening.
	6. History of shingles within 12 months prior to Screening.
	7. History of drug hypersensitivity, ascertained or presumptive allergy/hypersensitivity to the active drug substance and/or formulation ingredients; history of serious allergic reactions leading to hospitalization or any other hypersensitivity reaction in general, which may affect the safety of the participant and/or outcome of the study per the Investigator's discretion.
	8. History of alcoholism or drug abuse within 2 years prior to Screening, or positive for drugs of abuse or alcohol by the laboratory assays conducted during Screening and Day -1.
	9. History of residential exposure to tuberculosis, or a positive QuantiFERON® test within 4 weeks prior to or at the time of Screening.
	10. Administration of live vaccines or live-attenuated virus vaccines within 3 months prior to Screening. Administration of other types of vaccines (e.g., SARS-CoV-2 vaccines) is allowed until 4 weeks before admission to CRU, thereafter it is prohibited until the end of the study. **Note:** In case of clinical symptoms, the participant should be symptom-free for at least 1 week prior to admission to CRU.
	11. Any condition, including findings in the laboratory tests, medical history, or other Screening assessments, that in the opinion of the Investigator constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study's objectives, conduct, or evaluation.
Prior/Concomitant Therapy	12. Weak, moderate or strong inhibitors or inducers of CYP3A4/5 (table of substrates, inhibitors, and inducers) within 4 weeks prior to the first administration of study intervention.

Category	Criterion
	13. Use of any prescribed medicine or over-the-counter drug or dietary supplement, including herbal remedies, vitamins, and minerals, antacids and dietary supplements such as fish oils within 2 weeks or 5 times the half-life of the respective drug, whichever is longer, prior to the first administration of study intervention. Occasional ibuprofen up to 1200 mg per day is permitted.
Prior/Concurrent Clinical Study Experience	14. Use of any investigational drug in any clinical study within 60 days prior to Study Day 1 administration or have used an experimental monoclonal antibody within the past 1 year prior to Study Day 1 or have participated in a study evaluating a BTK inhibitor within 60 days, or are on extended follow-up in a clinical study, even if last administration of an IMP was more than 60 days ago, or 5 half-lives of the investigational drug, whichever is longer, prior to Screening.
Diagnostic Assessments	15. Medical history and physical examination results that include any ongoing clinically relevant findings as judged by the Investigator.
	16. Clinically relevant findings (excluding minor, not clinically relevant excursions from normal ranges, as judged by the Investigator) at Screening in biochemistry, hematology, coagulation, and urinalysis examinations for the age of the participant, as judged by the Investigator: • Alanine aminotransferase, aspartate aminotransferase: above 1.3-fold upper limit of normal **Note:** Levels of alanine aminotransferase and aspartate aminotransferase may increase physiologically towards early post menopause (Tiwari 2018, Petroff 2022, Matsui 2016). Therefore, inclusion of participants with slight elevations from ULN for alanine aminotransferase and aspartate aminotransferase levels can be justified for postmenopausal women. • Creatinine: above 1.2-fold upper limit of normal • Absolute lymphocyte count, absolute neutrophil count: below limit of reference range

Category	Criterion
	17. Estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (2009) < 75 mL/min at Screening.
	18. Semi-supine systolic blood pressure > 140 mmHg or < 90 mmHg, diastolic blood pressure > 90 mmHg or < 50 mmHg, and pulse rate > 90 or < 50 bpm at Screening. Any abnormal blood pressure results may be repeated once and if the repeat result is within the normal range, it is not considered to have met the exclusion criterion.
	19. 12-lead ECG showing a QTcF > 450 ms, PR > 215 ms, or QRS > 120 ms.
	20. 24-hour Holter ECG at screening for participants above 45 years of age showing clinically relevant abnormalities.
	21. Positive for a) hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, or human immunodeficiency virus I and II tests at Screening; b) SARS-CoV-2 at Screening or Day -1.
	22. Use of hormonal preparations (estrogens and/or progestin and/or androgens including anabolic steroids): • Short-acting hormonal preparations within 8 weeks (oral, transdermal, vaginal) before first study treatment administration until Follow-Up Visit. • Long-acting hormonal preparations within 6 months (intramuscularly/ subcutaneously administered depot preparations, implants, intra-uterine system) before first study treatment administration until Follow-Up Visit.
Other Exclusions	23. Consumption of an average weekly alcohol intake of > 7 units/week for women. One unit is equivalent to 8 g of alcohol: a half pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.

Category	Criterion
	24. Excessive consumption of xanthine-containing food or beverages (> 5 cups of coffee a day or equivalent) or inability to stop consuming caffeine, from 48 hours prior to study intervention administration until after collection of the final PK sample.
	25. Consumption of alcohol from 48 hours prior to first administration of study intervention.
	26. Herbal supplements including, but not limited to, St. John's wort, grapefruit, Seville oranges, cranberries, or juices of these fruits within 14 days prior to the first administration of study intervention.
	27. Donation or loss of more than 450 mL of blood in the 60 days prior to Screening, donation of plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
	28. Travel to a country with a high prevalence of tropical diseases within 3 months prior to Screening.
	29. Inability to communicate reliably with the Investigator or considered by the Investigator to be unable to or unlikely to co-operate with the requirements of the study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Abstain from consumption of the following from 14 days before the start of study intervention until after the final dose: Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, and juices from these fruits.

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid

- During each dosing period, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
- During each dosing period, participants will abstain from alcohol and cannabinoid-containing products for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.

Note: In this study the consumption of alcohol is not allowed from 48 hours prior to first administration of study intervention (see Section 5.2) until after collection of the final PK sample.

- Use of tobacco products will not be allowed from at least 6 months preceding Screening until after the final follow-up visit.

5.3.3 Activity

Participants will abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., watching television or reading).

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened with the following exceptions:

- The participant successfully passed the screening procedures but subsequently could not start the study on schedule.
- Initial screening occurred too early to complete the required washout period after any prior therapy.
- The participant was not included due to transient reasons (e.g., an infection at the time of screening).
- Minor (not clinically relevant, as judged by the principal investigator) excursions of the in-/exclusion criteria may entitle the participant for rescreening.

Rescreening will be limited to 2 rescreenings per participant.

If an individual is to be rescreened, signature of a new ICF will be required.

5.5 Criteria for Temporarily Delaying the Administration of Study Intervention

Not applicable.

6 Study Intervention(s) and Concomitant Therapies

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Intervention(s) Administration

Arm Name	Evobrutinib plus combined oral contraceptive	Evobrutinib plus combined oral contraceptive

Arm Type	Experimental	Experimental
Arm Description	Evobrutinib twice daily (morning and evening, approximately 12 hours apart), Days 4 to 17; and EE/NET single dose on Days 1 and 15	Evobrutinib twice daily (morning and evening), Days 4 to 17; and EE/NET single dose on Days 1 and 15
Intervention Name	Evobrutinib	EE/NET
Type	Drug	Drug
Dose Formulation	Film-coated tablet (TF2)	Film-coated tablet
Unit Dose Strength(s)	45 mg	0.03 mg/0.5 mg
Dose Amount	45 mg	0.03 mg/0.5 mg
Frequency	Twice daily	Single dose on Days 1 and 15
Route of Administration	Oral	Oral
Use	Experimental	Experimental
IMP/NIMP	IMP: Evobrutinib	IMP: EE/NET
Supplier	Merck Healthcare KGaA	Merck Healthcare KGaA
Packaging and Labeling	Study Intervention will be provided in containers. Each container will be labeled per country requirement. Additional details of packaging and labeling of study intervention will be defined in a separate IMP Handling Manual.	Study Intervention will be provided in containers. Each container will be labeled per country requirement. Additional details of packaging and labeling of study intervention will be defined in a separate IMP Handling Manual.

Each participant will receive 45 mg evobrutinib and 0.03 mg/0.5 mg EE/NET as follows (see also Schedule of Assessments in Section 1.3):

- **Day 1 – single dose EE/NET:**
  0.03 mg/0.5 mg EE/NET 0.5 hours after the start of a standard moderate-fat/-calorie breakfast with fasting for 4 hours postdose.
- **Day 4 through Day 14 – evobrutinib twice daily:**
  Morning:
  45 mg evobrutinib 0.5 hours after the start of a standard moderate-fat/-calorie breakfast.

Evening:
45 mg evobrutinib (approximately 12 hours ± 1 hour after morning dose) 0.5 hours after the start of a standardized meal.

- **Day 15 – single dose EE/NET and evobrutinib twice daily:**

  Morning:
  45 mg evobrutinib and 0.03 mg/0.5 mg EE/NET 0.5 hours after the start of a standard moderate-fat/-calorie breakfast with fasting for 4 hours postdose.

  Evening:
  45 mg evobrutinib (approximately 12 hours ± 1 hour after morning dose) 0.5 hours after the start of a standardized meal.

- **Day 16 and Day 17 – evobrutinib twice daily:**

  Morning:
  45 mg evobrutinib 0.5 hours after the start of a standard moderate-fat/-calorie breakfast.

  Evening:
  45 mg evobrutinib (approximately 12 hours ± 1 hour after morning dose) 0.5 hours after the start of a standardized meal.

All doses will be administered with 240 mL water in a standing position. Thereafter, the participants will stay in a semi-recumbent position for at least 1 hour postdose.

Timing of meals

On Day 1, each participant will receive a single dose of EE (0.03 mg) / NET (0.5 mg) 30 min after the start of a standard moderate-fat/-calorie breakfast (490 calories composed of approximately 77 g of carbohydrates, 28 g of protein, and 13 g of fat [Naderer 2015]). Following an overnight fast of at least 10 hours, participants should start breakfast 0.5 hour before the administration of EE/NET. The breakfast should be consumed within 30 min. Start date and time and stop time of the breakfast will be recorded in the participants' eCRFs as well as whether the entire breakfast was consumed. If the entire meal is not consumed, the percentage of meal consumed (in quartiles) should be recorded.

From Day 4 until Day 17, participants will receive twice daily dosing with 45 mg evobrutinib (morning and evening) 0.5 hour after the start of a standardized meal. On Day 4, the 72 hours postdose sample for EE/NET will be collected prior to evobrutinib dosing.

On Day 15, participants will receive EE/NET and evobrutinib in the morning 0.5 hour after the start of a standard moderate-fat/-calorie breakfast. Following an overnight fast of at least 10 hours, participants should start the moderate-fat/-calorie breakfast 30 min prior to administration of EE/NET and evobrutinib, and the breakfast should be consumed within 30 min. Start date and time and stop time of the breakfast will be recorded in the participants' eCRFs as well as whether the entire breakfast was consumed. If the entire meal was not consumed, the percentage of meal consumed (in quartiles) should be recorded.

On Day 1 until Day 17, lunch will be provided approximately 4 hours and dinner approximately 11.5 hours after the morning evobrutinib dose. The other meals will be provided at the usual mealtimes of the study center.

All other meals during the inpatient stay at the study center, will be standardized and no documentation of time and complete consumption is needed.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee will confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the IMP Handling Manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, container numbers, expiry dates, and the participant numbers.
- The Investigator site will maintain records, which adequately document that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) will not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the IMP Handling Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Not applicable as this is a nonrandomized study.

After informed consent procedure, every participant is given a screening number. Only participants who comply with all selection criteria (see Sections 5.1 and 5.2) can be included into the study. Prior to the first administration of the study intervention, the participants enrolled will be assigned to a unique 3-digits assignment number in ascending numerical order.

The Investigator will keep a record relating the participant assignment numbers and the names of all participants (including screening number and the PPD identification number) who have given their informed consent, to allow easy checking of data in participant files, when required. This record will also include the date of participant's enrollment and completion, as well as participants who could not be assigned to study intervention for whatever reason.

6.3.2 Blinding

Blinding Method

Not applicable. This is an open-label study.

Assignment Method Retention

Not applicable.

6.3.3 Emergency Unblinding

Not applicable as this is an open-label study.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5 Dose Modification

Doses will not be modified.

6.6 Continued Access to Study Intervention after the End of the Study

The Sponsor will not provide any additional care to participants after they leave the study because such care would not differ from what is normally expected for healthy participants.

6.7 Treatment of Overdose

For this study, any dose of study intervention greater than the maximum dose in the study that is considered safe and well tolerated within a 24-hour time period will be considered an overdose.

The Sponsor has no specific recommendation for treating an overdose of evobrutinib. The Investigator will use his/her clinical judgment to manage any overdose, considering the symptoms and any site procedures or standards.

Recommendation for treatment of an overdose of EE/NET is described in the summary of product characteristics for EE/NET.

Even if not associated with an AE or a SAE, any overdose is recorded in the CRF and reported to global patient safety in an expedited manner. Overdoses are reported on a SAE and Overdose Report Form, following the procedure in Appendix 4.

6.8 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.8.1 Rescue Medicine

No specific antidote is available for evobrutinib. Symptomatic treatment will be provided in case of a medical emergency.

6.8.2 Permitted Medicines

The only permitted medicines are the following:

- Ibuprofen up to 1200 mg per day, at the discretion of the Investigator.

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

Medications may be given at the Investigator's discretion if deemed necessary for the participant's immediate wellbeing. Medications may be administered to address adverse reactions or anticipated emergency situations.

The Investigator will record all concomitant medications taken by the participants during the study, from the date of signature of informed consent, in the participant source data and in the appropriate section of the eCRF.

6.8.3 Prohibited Medicines

Prohibited medicines at study entry are indicated in the exclusion criteria (see Section 5.2).

The participants are prohibited from using prescription or over-the-counter medications (apart from those described in Section 6.8.2) within 2 weeks or 5 terminal half-lives, whichever is longer, prior to the first administration of study intervention, during the study, and until the Safety Follow-up Assessment (this includes herbal remedies, vitamins, minerals, antacids and dietary supplements such as fish oils).

Weak, moderate or strong inhibitors or inducers of CYP3A4/5 within 4 weeks prior to the first administration of study intervention, and until after the Safety Follow-up Assessment, are prohibited. Also, drugs mainly metabolized by CYP3A4/5 and that have a narrow therapeutic index should be avoided.

6.8.4 Other Interventions

Additional restrictions that study participants should adhere to from Day -1 until the Safety Follow-up Assessment are detailed in Section 5.2.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

A participant is to be discontinued from the study intervention if any of the following apply:

- A participant is enrolled but is subsequently discovered not to have met the inclusion/exclusion criteria at Screening.
- If discontinuation of study intervention is considered necessary by the Investigator and/or desired by the participant after occurrence of an AE. This includes AEs of severe intensity and SAEs regardless of the relationship to study intervention.
- Protocol noncompliance judged as significant by the Investigator (after discussion with the Sponsor).
- Use of a nonpermitted concomitant therapy, if agreed to be clinically relevant by Sponsor and Investigator (defined in Section 6.8), for which the predefined consequence is withdrawal from study intervention.
- Any events that unacceptably endanger the safety of the participant.

If a clinically significant finding is identified (including changes from Baseline in QT interval corrected by Fridericia' formula) after start of study intervention, the Investigator or qualified

designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG at the time of collection will be documented. Any new clinically relevant finding is reported as an AE.

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety. The Schedule of Assessments specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed. Note: If study intervention is discontinued the Safety Follow-Up visit should be performed.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may discontinue from the study at any time, at her own request or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- There will be no replacement of participants who withdraw from the study.
- The participant may be withdrawn by the Investigator due to participation in another clinical study.
- A participant must be withdrawn if any of the following occurs during the study:
  - AEs, if study discontinuation is considered necessary by the Investigator and/or desired by the participant. This includes in particular AEs of severe intensity and SAEs regardless of the relationship to study treatment.
  - Use of nonpermitted concomitant medications, as defined in Section 6.8. However, any medications that are considered necessary for the participant's wellbeing (e.g., ibuprofen up to 1200 mg per day) may be given at the discretion of the Investigator.
  - Protocol noncompliance judged as significant by the Investigator, including noncompliance to the required study considerations (e.g., food/diet requirements), as defined in Sections 5.1, 5.2, 5.3, 6.1, and 8.
  - Pregnancy
  - If a participant has failed to attend scheduled study assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.
- If a participant must be withdrawn from the study, the Medical Monitor as well as Scientific/Medical Lead and Clinical Trial Lead of the Sponsor will be informed immediately.
- If there is a medical reason for the withdrawal, appropriate medical care will be provided.
- At the time of study discontinuation, if possible, a discontinuation visit will be conducted, as listed in the Schedule of Assessments. The Schedule of Assessments specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.

  Note: If the study is discontinued prematurely, the Safety Follow-Up visit should be performed.
- If the participant revokes consent for the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.

- If a participant requests the destruction of any biological samples still remaining, the Investigator will document this in the site study records and inform the Sponsor. The samples will be destroyed.
- The Investigator will secure the safety of the study participants and make every attempt to collect the data.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner or caretaker (where allowed by local regulations) for information. These contact attempts will be documented in the participant's medical record.
- If the participant continues to be unreachable, she will be deemed as "lost to follow-up".

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the Schedule of Assessments.
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.
- All screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the

procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Assessments.

- Safety results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

  Note: This is not applicable in this study, since the study is open-label.

- No more than 100 mL of blood may be drawn in a 24-hour period, and no more than 300 mL of blood in a 4-week period.
- Where allowed by local law/regulations, samples collected during this clinical study may be transferred to a biobank and used for future research outside the clinical protocol when additional consent for this purpose is given. Transfer to the biobank will be documented and any testing of coded biobank samples will not be reported in the CSR.
- The long-term storage of samples after study completion for future research may be performed will all sample types collected in the study (e.g., PK, pharmacogenetics, biomarkers, or immunogenetic) if the participant consents to optional future medical research.

8.1 Efficacy Assessments and Procedures

Not applicable.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, ECGs, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems, and abdomen (liver and spleen).
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Blood pressure and participant's position; pulse; respiratory rate; temperature and location of measurement, weight, and height (at Screening only) will be measured and recorded. Temperature will be measured in the ear.

- Blood pressure and pulse measurements will be preceded by at least 5 min of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and measured with an automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

- A 24-hour Holter ECG will be obtained at Screening for participants above 45 years of age. This Holter ECG will be reviewed prior to treatment start.
- Single 12-lead ECG will be obtained as outlined in the Schedule of Assessments using an ECG machine that automatically measures heart rate, PR, RR, QRS, QT, and corrected QT interval by Fridericia' formula. Documentation of the QTcF is mandatory and will be collected in the eCRF.
- 12-Lead ECGs will be recorded in a supine position following 5 min of rest.

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5 at the time points listed in the Schedule of Assessments. All samples will be clearly identified.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by PPD laboratory; the QuantiFERON® Test will be performed by PPD
- The Investigator will review each laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE, unless it does **not** meet the AE definition, as specified in Appendix 4. The laboratory reports will be filed with the source documents.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

- The definitions of an AE and a SAE are in Appendix 4.
- The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study, as specified in Section 8.3.2.
- Requests for follow-up will usually be made via the Sponsor or CRO-designated study team member, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.

- All AEs and SAEs will be collected from the signing of the ICF until the Safety Follow-up Visit at the time points specified in the Schedule of Assessments (see Section 1.3). Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.
- Investigators are not obligated to actively solicit information on AEs or SAEs after the end of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.1 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.

8.3.2 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AESIs (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Reasonable attempts to obtain this information will be made and documented. It is also the Investigator's responsibility to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is in Appendix 4.

8.3.3 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The

Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Individual Case Safety Reports will be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators within 15 days.

An Investigator or sub-investigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g., Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will review the safety reports and confirm completion of this review. This information will be filed in the Investigator's Site File and the IRB/IEC will be notified, if appropriate, according to applicable local laws/regulations and site SOPs.

8.3.4 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the Safety Follow-up. Note: In this study, only women of nonchildbearing potential will be included.
- If a pregnancy is reported, the Investigator will record the pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of female participant pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Adverse pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered and reported as SAEs. A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date for a healthy newborn. In case of a congenital anomaly or other illness of the newborn, follow-up will continue until the illness has resolved or there is a definite outcome of the event.
- Any post study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.5 Cardiovascular and Death Events

Not applicable.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.7 Adverse Events of Special Interest

For this study, AESI(s) include only the following:

- Infections (serious, severe, and opportunistic, ≥ Grade 3)

  As per its mechanism of action, evobrutinib may impair B cell function which might lead to a decreased humoral immunity and consequently an increased risk of infection. Overall, in completed studies in participants the Medical Dictionary for Regulatory Activities SOC infection was one of the most reported SOCs (e.g., in the MS200527_0086 RMS study approximately 18% to 32% of participants treated with evobrutinib reported infection; a similar rate was reported in the placebo group in the 0 to 24 week period), the individual events were of low grade, mainly Grade 1, nonserious and did not lead to study intervention discontinuation. Treatment of infections must be prompt and done in accordance with local standard of care depending on considerations such as the nature and severity of the infection and participant's overall health status. Any Common Terminology Criteria for Adverse Events Grade ≥ 3 or SAEs of infection and opportunistic infection are considered as an AESI.

- Seizures

  Seizures are more common in patients with MS than in the general population, occurring in 2% to 3% of MS patients (Poser 2003). Convulsions were observed in early studies of evobrutinib in dogs, however the plasma concentration of evobrutinib was approximately 140-fold greater than it is predicted for the dose used in this study. One participant with RMS with significant brain lesion load reported seizure of unclear clinical picture. The PK data for this participant did not exceed the expected values and was similar to other participants in the study. Anticonvulsant therapy was started, and the participant continued treatment with evobrutinib with no reoccurrence. The Investigator did not consider the event to be related to evobrutinib. No event of convulsion/seizure was reported in other indications. Evobrutinib has been administered to approximately 800 patients with MS, rheumatoid arthritis and systemic lupus erythematosus. Moreover, an electroencephalogram study in healthy volunteers did not show an epileptogenic potential for evobrutinib. Any type of seizures/epilepsy of any grade or its consequences are classified as AESIs.

- Elevated lipase, elevated amylase, pancreatitis

  Asymptomatic elevations in amylase or lipase or both in participants treated with evobrutinib have been observed at a variety of time points and reported as TEAEs or noted as laboratory abnormalities. In RMS Study MS200527_0086, the incidence of TEAEs of lipase increased was slightly higher in evobrutinib 75 mg once daily and 75 mg twice daily arms (5 [9.4%] and 5 [9.3%], respectively) when compared to other arms (approximately between 4% to 6%). However, shifts from Baseline to highest grade on treatment were similar across all treatment arms for both amylase and lipase. In evobrutinib studies in other indications and in healthy participants, the incidence of TEAEs of increased amylase or lipase, or both was infrequent and

no clinically meaningful differences were observed across treatment arms. Any elevation of > 2 × ULN of lipase or amylase and any type of pancreatitis are classified as AESIs.

- Liver related events

  The elevations of transaminases observed in participants treated with evobrutinib were frequent, asymptomatic, and reversible on discontinuation of evobrutinib. The mechanism is unknown.

  Evobrutinib liver AESIs will include transaminases (> 3 × ULN), bilirubin elevations (> 1.5 × ULN), biological Hy's Law cases based on laboratory data, any type of acute or chronic hepatitis (any grade), suspected drug-induced liver injury, acute or chronic hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions.

AESIs have to be reported immediately (within 24 hours). For reporting of AESIs, see Appendix 4.

8.4 Pharmacokinetics

- The following PK parameters will be calculated, when appropriate: PK parameters will be calculated for all analytes and unless otherwise noted.

Symbol	Definition
$AUC_{0-\infty}$	The AUC from time zero (= dosing time) up to infinity with extrapolation of the terminal phase.
$AUC_{0-tlast}$	The AUC from time zero (= dosing time) to the time of the last quantifiable concentration (t_{last}).
C_{max}	Maximum observed concentration.
t_{max}	The time to reach the C_{max} in a dosing interval.
$t_{1/2}$	The terminal half-life.
CL/F	The apparent total body clearance following extravascular administration (EE, NET, CCI only).
V_Z/F	The apparent volume of distribution during the terminal phase following extravascular administration (EE, NET, CCI only).
CCI	[redacted]
[redacted]	[redacted]

- Whole blood samples of approximately 4 mL for measurement of plasma concentrations of EE/NET and 3 mL for measurement of CCI and CCI will be collected. Collection times are specified in the Schedule of Assessments (see Section 1.3).
- EE/NET samples will be collected starting on Day 1 and Day 15 with timepoints predose through 72 hours postdose. On Day 4, the 72 hours postdose sample will be collected prior to evobrutinib dosing.

CCI [redacted]

- The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration.

- The quantification of EE/NET and evobrutinib in plasma will be performed using a validated assay method. CCI [redacted]
- Remaining samples collected for analyses of EE/NET and CCI [redacted] concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Additionally, remaining plasma samples may be used for investigation of other CCI [redacted].
- Details on processes for collection and handling of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

The accepted time deviations from planned PK sampling times that will not be considered a protocol violation are listed below. Any deviation from these time windows requires a comment in the eCRF and may be discussed in the data review meeting.

Procedure	Time Point (Relative Time)	Window Allowance
Pharmacokinetics	Predose	Day 1: - 60 min Day 4: - 60 min Day 15: -5 min
	0.25 to 1 hours postdose	± 2 min
	> 1 to 12 hours postdose	± 5 min
	> 12 to 24 hours postdose	± 15 min
	> 24 to 72 hours postdose	± 30 min

CCI [redacted]

8.6 Biomarkers

Not applicable.

8.7 Immunogenicity Assessments

Not applicable.

8.8 Health Economics

Not applicable.

9 Statistical Considerations

All planned analyses defined in this protocol will be described in the IAP that will be finalized before the database lock.

Changes in the conduct of the study or planned analyses, if any, will be reported in the appropriate section of the IAP and in the CSR.

9.1 Statistical Hypotheses

The statistical analysis of study data will be purely descriptive; no hypothesis tests will be performed. A definition of primary and secondary objectives and endpoints can be found in Section 3.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

9.3 Analyses Sets

The analysis sets are specified below.

The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock.

Table 3 Analysis Sets

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's enrollment and study intervention status in the study.
Safety (SAF)	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
Pharmacokinetic (PK)	The PK Analysis Set is a subset of the SAF, and the PK population will include all participants: • Who have completed the study without any relevant protocol deviations and factors likely to affect the comparability of PK results. • With adequate study intervention compliance. • With evaluable PK data, i.e., no missing values for primary endpoints at each PK profile/assessment day (Day 1, Day 15). If participants received prohibited concomitant therapy or medicines, as specified in Section 6.8, they will be excluded from the PK population. All PK analyses will be based on this analysis set.

PK = Pharmacokinetic; SAF = Safety; SCR = Screening.

9.4 Statistical Analyses

Statistical analysis will be performed using the computer program package SAS®. More details on the statistical analysis will be presented in the IAP prior to database lock. The statistical analysis will not be started until all data have been corrected and checked for plausibility, and until all necessary coding and assessments have been completed.

Medical history and AE terms will be coded with the latest version of the Medical Dictionary for Regulatory Activities (Version 23.0 or later); concomitant medication will be coded with the WHO Drug Dictionary, WHO Drug Reference List and Anatomical Therapeutic Chemical Classification System, latest versions. Versions of dictionaries used for coding will be defined in the Data Management Plan.

All data recorded during the study will be presented in individual data listings.

For demographic (e.g., age, sex, race, etc.), baseline and safety assessments, continuous measurements will be summarized by means of descriptive statistics (i.e., number and percentage of observations, number and percentage of missing observations, mean, standard deviation, median, the Q1 and Q3, Min, and Max) and categorical data will be summarized by means of frequency tables (i.e., count and percentages), if not stated otherwise.

All data will be evaluated as observed, without imputation method for missing values. The handling of concentration values below the limit of quantification will be described in the IAP.

9.4.1 Efficacy Analyses

Not applicable.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis set (see Section 9.3).

Reference #	Endpoint	Statistical Analysis Methods
Primary		
Not Applicable		
Secondary		
2 – Safety	Nature, occurrence, and severity of TEAEs	Adverse event counts and participants with AEs will be summarized for each treatment by SOC and PT. In addition, AEs will be tabulated and listed per participant and analyzed by severity and relationship to study intervention.
3 – Safety	Absolute values and changes in safety laboratory tests	Safety laboratory parameters will be listed for each participant including absolute values and changes from Baseline and flags for measurements outside the reference ranges, if applicable. Laboratory parameters (hematology and clinical chemistry) will be summarized by time point including both absolute values and changes from Baseline.
4 – Safety	Single 12-lead ECGs evaluated by Investigator	Electrocardiogram data will be summarized by absolute values and changes from Baseline values by treatment using descriptive statistics. Clinical noteworthy ECG findings for individual participants will be listed and summarized as appropriate.
5 – Safety	Vital signs assessed from time of first dose to end of study participation	Vital signs by participant, including absolute values and changes from Baseline, will be listed and summarized by treatment and time point using descriptive statistics.
Tertiary/ Exploratory		
Not Applicable		

AEs = adverse events; ECG = electrocardiogram; PT = preferred term; TEAE = treatment-emergent adverse events; SOC = system organ class.

9.4.3 Other Analyses

9.4.3.1 Analysis of Pharmacokinetics

Analysis of primary endpoints

A general linear model with a fixed effect for TREATMENT and a random effect for SUBJECT will be applied to log-transformed PK parameters C_{max} and $AUC_{0-\infty}$ based on the PK analysis set to assess the effect of multiple doses of evobrutinib on EE/NET PK. Treatment differences on the

log scale of EE/NET with evobrutinib vs EE/NET alone (Day 15 vs Day 1) will be estimated for C_{max} and $AUC_{0-\infty}$ together with their 90% CIs.

Point estimates and CIs will be back transformed to the original scale.

Analysis of secondary endpoints

The same analysis model as described for the primary endpoints will be provided for the secondary endpoint $AUC_{0-tlast}$ of EE/NET.

Details on the PK analyses will be in the IAP that will be finalized before database lock.

9.4.4 Sequence of Analyses

All final, planned analyses identified in the clinical study protocol will be performed only after the last participant has completed the last visit, i.e., Safety Follow-up, with all study data in-house, all data queries resolved, and the database locked.

10 References

Conceplan® M Summary of Product Characteristics 500 µg norethisterone/30 µg ethinyl estradiol tablets, Pfizer website. https://www.pfizer.de/sites/default/files/FI-2874.pdf Last accessed in Apr 2022.

FDA. Drug Development and Drug Interactions. Table of Substrates, Inhibitors and Inducers. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers Last accessed in Apr 2022.

Garg V, van Heeswijk R, Yang Y, et al. The pharmacokinetic interaction between an oral contraceptive containing ethinyl estradiol and norethindrone and the HCV protease inhibitor telaprevir. J Clin Pharmacol. 2012;10:1574-83.

Loi CM, Stern R, Koup JR, et al. Effect of Troglitazone on the Pharmacokinetics of an Oral Contraceptive Agent. J Clin Pharmacol. 1999;39:410-7.

Matsui S, Yasui T, Kasai K, et al. Changes of liver enzymes and triglyceride during the menopausal transition in Japanese women. J Obstet Gynaecol. 2016;36(6):806-811.

Naderer O, Jones LS, Zhu J, et al. The effect of food and formulation on the pharmacokinetics, safety, and tolerability of GSK1322322 in healthy volunteers. Clin Pharmacol Drug Dev. 2015;4:49-55.

Petroff D, Baetz O, Jedrysiak K, et al. Age Dependence of Liver Enzymes: An Analysis of Over 1,300,000 Consecutive Blood Samples. Clin. Gastroenterol Hepatol. 2022;3:641-650.

Poser CM, Brinar VV. Epilepsy and multiple sclerosis. Epilepsy Behav. 2003;4(1):6-12.

Scarfò L, Chatzikonstantinou T, Rigolin GM, et al. COVID-19 severity and mortality in patients with chronic lymphocytic leukemia: a joint study by ERIC, the European Research Initiative on CLL, and CLL Campus. Leukemia. 2020;1-10.

Shadle CR, Liu G, Goldberg MR. A double-blind, placebo-controlled evaluation of the effect of oral doses of rizatriptan 10 mg on oral contraceptive pharmacokinetics in healthy female volunteers. J Clin Pharmacol. 2000;3:309-15.

Spence R, Mandagere A, Walker G et al. Effect of steady-state ambrisentan on the pharmacokinetics of a single dose of the oral contraceptive norethindrone (norethisterone) 1 mg/ethinylestradiol 35 microg in healthy subjects: an open-label, single-sequence, single-centre study. Clin Drug Investig. 2010;5:313-24.

Thibaud S, Tremblay D, Bhalla S, et al. Protective role of Bruton tyrosine kinase inhibitors in patients with chronic lymphocytic leukaemia and COVID-19. Br J Haematol. 2020;1-3.

Tiwari S, Adhikari IP. Renal and Liver Profile in Pre and Post Menopause Women Attending OPD of a Tertiary Health Care Level. Glob j res anal. 2018;2:135-137.

Towsend R, Dietz A, Hale C, et al. Pharmacokinetic Evaluation of CYP3A4-Mediated Drug-Drug Interactions of Isavuconazole With Rifampin, Ketoconazole, Midazolam, and Ethinyl Estradiol/ Norethindrone in Healthy Adults. Clin Pharmacol Drug Dev. 2017;1 :44-53.

Treon SP, Castillo JJ, Skarbnik AP, et al. The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. Blood. 2020;135(21):1912-15.

Zhang N, Shon J, Kim M-J, et al. Role of CYP3A in Oral Contraceptives Clearance. Clin Transl Sci. 2018;11:251-260.

11 Appendices

Appendix 1 Abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
BTK	Bruton's Tyrosine Kinase
CI	Confidence Interval
COC	Combined Oral Contraceptive
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	coefficient of variation
CYP3A4/5	Cytochrome P450 3A4/5
DDI	Drug-drug interaction
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EE	Ethinyl Estradiol
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HRT	Hormone Replacement Therapy
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
MS	Multiple Sclerosis
NET	Norethisterone, also referred to as norethindrone
NIMP	Noninvestigational Medicinal Product

PK	Pharmacokinetic(s)
QTcF	Corrected QT interval by Fridericia' formula
QTL	Quality Tolerance Limit
RBC	Red blood cell count
RMS	Relapsing Multiple Sclerosis
SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-emergent Adverse Event
ULN	Upper Limit of Normal
WOCBP	Woman of Childbearing Potential

Appendix 2 Study Governance

Financial Disclosure

- Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act of 1996 requirements, where applicable; and the IRB/IEC or study center.
- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent will also sign the ICF.
- If the ICF is updated during their participation in the study, participants will be reconsented to the most current, approved version.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.
- The participant will be informed that her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

The Principal Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Principal Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the CSR.

- The study will be conducted at a single center, the Clinical Pharmacology Unit of PPD [redacted] will be responsible for the following activities:
  - Clinical conduct and laboratory services
  - Data management
  - Statistical programming and analysis
  - PK analysis
  - Medical writing
  - Independent monitoring
  - Medical monitoring
  - Project management
  - Regulatory services

  Clinical trial supplies will be provided by Thermo Fisher.

Details of structures and associated procedures will be defined in a separate Operations Manual.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines

- Applicable ICH GCP Guidelines
- Applicable laws and regulations

- The protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) will be submitted to an IRB/IEC for review and approve before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.
- When the Investigator is not available, the Phase 1 facility will provide the appropriate means to contact a physician. This includes the provision of a 24-hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions will meet good local standards, as applicable.

Clinical Study Report

After study completion, the Sponsor will write a CSR in consultation with the Principal Investigator and other relevant study-appointed experts of the Sponsor and PPD .

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- A summary of data will be provided to ClinicalTrials.gov as well as to the European Clinical Trial Database, as applicable, and will occur 12 months after the last clinic visit of the final study participant or another appropriate date to meet applicable requirements. Healthy participants might be provided with the results of the medical examinations at request. After finalization of the study, healthy participants might be provided with the information published on ClinicalTrials.gov and/or the European Clinical Trial Database at request.
- After completion of the study, a CSR will be written by the Sponsor in consultation with the Principal Investigator following the guidance in ICH Topic E3 and will be submitted in accordance with local regulations.
- Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff who had been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.
- The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study intervention and therefore may be disclosed as required to other clinical Investigators, to the FDA, EMA, and to other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study. No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Data Management Plan.

- The Investigator will maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- QTLs will be predefined in the Operational Manual to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

  Note: QTLs will not be defined in this Phase I study as neither the limited number of planned participants nor the short duration of the study support the collection of meaningful QTLs.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.
- Study Monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator will maintain source documents that support the data recorded in the CRFs.
- Data recorded on CRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records will be available.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.

- Definition of what constitutes source data is found in Source Data Location Form.

Study and Site Start and Closure

The study start date is when the first participant signs the Informed Consent Form.

Study and Site Closure

The Investigator may initiate site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended closure.

Reasons for the early closure of a study site by the Sponsor or Investigator may include:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further development of the Sponsor’s compound
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any third-party service providers of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Contraception and Barrier Requirements

Note: This study includes women of nonchildbearing potential only (see Section 5.1). Study participants who use hormonal preparations may not participate in the study (see Section 5.2). However, please see the definition for a WOCBP below for information on criteria to be used.

Definitions:

WOCBP:

A woman is of childbearing potential (fertile) following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

Postmenopause:

Postmenopause is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
- A female on HRT and whose menopausal status are in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization:

For this study, permanent sterilization includes:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Documentation can come from the site personnel's review of the individual's medical records, medical examination, or medical history interview.

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline and are judged to be more severe than expected for the participant's condition are considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease, but may be leading to study intervention discontinuation). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or a SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or a SAE if they fulfil the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied within the expectedness for participant's condition, as judged by the Investigator. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

SAE Definition

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE will be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
- However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization must be documented and reported as SAEs.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is **not** intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may

require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually considered as serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission of an infectious agent via a study intervention is also considered an SAE for reporting purposes, as specified below for reporting SAEs or AESIs.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- As needed, the Sponsor/designee may ask for copies of certain medical records (e.g., autopsy reports, supplemental lab reports, documents on medical history/concomitant medications, discharge letters), as supporting source documentation. All participant identifiers, except the participant number, will be redacted on these copies before submission to the Sponsor/designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Specific guidance is in the CRF Completion and Monitoring Conventions.

Assessment of Intensity

The Investigator will assess the intensity of each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. Do not confuse an AE that is assessed as severe with a SAE. Severe is a category used to rate the intensity of an event; both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least 1 of the predefined criteria specified in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator will assess the relationship between study intervention and each AE/SAE occurrence:
  - Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention. A reasonable alternative explanation will be available.
  - Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator will document in the medical notes that he/she has reviewed the AE/SAE and assessed causality.
- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.
- The Investigator may change his/her causality assessment after considering follow-up information and send a SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the Sponsor/designee to elucidate the nature and/or causality of the AE or SAE, as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor/designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor/designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting by a Paper Form

- SAE reporting on a paper report form may be used in single center studies in addition to the standard electronic CRF and as a back-up method for an electronic data capture system failure. The form includes completion instructions for the Investigator, names, addresses, and telephone and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the form within 24 hours after becoming aware of the event.
- Additional documents (e.g. laboratory reports, autopsy report, hospital discharge letter) and relevant pages from the CRF may be required in addition (e.g. medical history, concomitant medication). The data provided will be consistent with the information in the CRF.

Reporting of AESIs

- For a nonserious AESI, the site will complete the specific AESI report form and notify the Sponsor immediately (within 24 hours), using the same process for reporting SAEs, as specified above.
- For a serious AESI, the site will complete an SAE report form, using the SAE reporting process, specified above.

Reporting of Pregnancies

- Pregnancy will be reported whether related to the study intervention using the applicable paper form.
- The applicable form will be used to report if an abnormal outcome of the pregnancy occurs and the child/fetus sustains an event.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

Appendix 5 Clinical Laboratory Tests

The protocol-required clinical laboratory assessments are in the following table:

Laboratory Assessments	Parameters			
Hematology	Platelet count		Mean corpuscular volume (MCV)	White Blood Cell Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Hemoglobin		Mean corpuscular hemoglobin (MCH)	
	Hematocrit			
	Erythrocytes (RBC)			
Biochemistry	Blood Urea Nitrogen	Potassium	Aspartate aminotransferase	Bilirubin (total)
	Creatinine	Sodium	Alanine aminotransferase	Protein
	Glucose	Calcium	Alkaline phosphatase	Triglycerides
	Uric acid	Chloride	Gamma Glutamyl Transferase	Lipase
	C Reactive Protein		Lactate dehydrogenase	Amylase
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood (hemoglobin), ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal/dipstick is positive for blood or protein). Note: In case of a positive result for hemoglobin, leukocyte esterase, protein or nitrite, a flow cytometry count and classification will be performed.			
Coagulation	• Prothrombin Intl. Normalized Ratio • Activated Partial Thromboplastin Time			
Pregnancy Testing	• Serum human chorionic gonadotropin pregnancy test at all time points listed in the SoA (see Section 1.3)			
Other Screening Tests	• Follicle Stimulating Hormone (postmenopausal women only) • Urine drug screen (to include at minimum: Amphetamine, Methamphetamine, barbiturates, 3,4-methylenedioxymethamphetamine, cocaine, opiates, cannabinoids, Benzodiazepine, methadone, phencyclidine, oxycodone, and tricyclic antidepressants): Screening and Day 1 • Serology (HIV-1 Antibody, HIV-2 Antibody, Hepatitis B Virus Surface Antigen, Hepatitis B Virus Core Antibody, Hepatitis C Virus Antibody, QuantiFERON® Test) • SARS-CoV-2 Antigen (rapid test) at Screening and SARS-CoV-2 RNA (PCR) at admission on Day -1 • Thyroid stimulating Hormone • Alcohol breath test: Screening and Day -1 Estimated Glomerular Filtration Rate based on Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (2009). All study-required laboratory assessments will be performed by a central laboratory (i.e., PPD clinical laboratory).			

HIV=human immunodeficiency virus, PCR=polymerase chain reaction, RNA=ribonucleic acid, SARS-CoV-2=severe acute respiratory syndrome coronavirus type 2, RBC=red blood cell count, SoA=Schedule of Assessments.

CCI [redacted]

[redacted]

Appendix 7 Protocol Amendment History

The information for the current amendment is on the title page.

Protocol Version 2.0 (30 June 2022)

Overall Rationale for the Amendment

This protocol amendment was requested by the German competent authority. On this occasion, an additional clinical laboratory test was added as this was missing in protocol v1.0.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	A 24-hour Holter ECG was added for participants above 45 years of age at screening (see Section 5.2).	For clarification of the ECG measurement at Screening.
1.3 Schedule of Activities 12-Lead ECG	In the notes added, that on Day -1, at predose to COC administration on Day 1, an ECG measurement will be done. On Day 14, at predose to COC administration on Day 15, an ECG measurement was added. On COC administration Days 1 and 15, an ECG measurement was added at 2 hours ± 30 min postdose.	For clarification of ECG measurements on COC administration days.
1.3 Schedule of Activities Vital Signs	Rewording of note for vital signs measurement.	For clarification.
5.2 Exclusion Criteria	Exclusion criterion was added: '24-hour Holter ECG at screening for participants above 45 years of age showing clinically relevant abnormalities.'	For clarification of the ECG measurement at Screening.
6.1 Study Intervention(s) Administration	Timing of meals on Day 15: 'and the breakfast should be consumed within 25 to 30 minutes' was reworded to 'and the breakfast should be consumed within 30 minutes'.	For clarification. The evobrutinib predose pharmacokinetic sample on Day 15 shall be taken as close as possible to the planned dosing (within 5 min prior to dosing). Thus, for logistical reasons, the time period for the breakfast was adapted.
	Timing of meals on Day 1: 'The breakfast should be consumed within 25 to 30 min.' was reworded to 'The breakfast should be consumed within 30 min.'	For alignment with timing of meals on Day 15.
8.2.2 Vital Signs	'weight and height (at baseline only)' was reworded to 'weight and height (at Screening only)'	For consistency with the wording in Section 1.3 Schedule of Assessments.
8.2.3 Electrocardiograms	A bullet point was added:	For clarification of the ECG measurement at Screening.

Section # and Name	Description of Change	Brief Rationale
	'A 24-hour Holter ECG will be obtained at Screening for participants above 45 years of age. This Holter ECG will be reviewed prior to treatment start.'	
8.4 Pharmacokinetics	Table with accepted time deviations from planned PK sampling times: Time window allowance at predose was specified for Days 1, 4, and 15: Day 1: - 60 min Day 4: - 60 min Day 15: -5 min	For clarification of predose time window.
Appendix 5 Clinical Laboratory Tests (Hematology Parameters)	Adding 'Erythrocytes (RBC)' to hematology parameters.	For completion of the safety laboratory parameters. Red blood cell count (erythrocytes) was measured in all safety laboratory tests as part of the hematology panel but this was not stated in the protocol version v1.0.

Appendix 8 Sponsor Signature Page

Study Title:	A Phase I, Open-Label, Multiple-Dose Study of the Effect of Evobrutinib on the Pharmacokinetics of a Combined Oral Contraceptive in Healthy Female Participants
Regulatory Agency Identifying Numbers:	EudraCT: 2022-000124-38
Clinical Study Protocol Version:	20 September 2022/Version 3.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, Academic Degree:	PPD
Function/Title:	Medical Responsible
Institution:	Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany
Address:	Frankfurter Str. 250, 64293 Darmstadt, Germany
General Merck Phone Number:	Office: PPD Mobile: PPD
General Merck Fax Number:	Not applicable

Global Version ID: CCI

Appendix 9 Principal Investigator Signature Page

Study Title:	A Phase I, Open-Label, Multiple-Dose Study of the Effect of Evobrutinib on the Pharmacokinetics of a Combined Oral Contraceptive in Healthy Female Participants
Regulatory Agency Identifying Numbers:	EudraCT: 2022-000124-38
Clinical Study Protocol Version:	20 September 2022/Version 3.0
Site Number:	Not applicable

I approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, ICH GCP (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

Name, academic degree: PPD

Function/Title: Principal Investigator

Institution:
Address:
Telephone number:
Fax number:
E-mail address:

PPD

Global Version ID: CCI