Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase I, Open-Label Study of the Relative Bioavailability of Evobrutinib Tablet Manufacturing Batches in Healthy Participants
Study Number:	MS200527_0131
Protocol Version:	08 September 2022/Version 1.0
Merck Compound:	Evobrutinib (M2951)
Merck Registered Compound Name in Japan:	Not applicable
Study Phase:	Phase 1
Brief Title:	Relative Bioavailability of Evobrutinib Tablet Batches
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 Strasse 250 Darmstadt, 64293, Germany
Regulatory Agency Identifying Numbers:	EudraCT: 2022-002755-19
Keywords:	Pharmacokinetics

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1 Protocol Summary

1.1 Synopsis

Clinical Study Protocol Title: A Phase I, Open-Label Study of the Relative Bioavailability of Evobrutinib Tablet Manufacturing Batches in Healthy Participants

Brief Title: Relative Bioavailability of Evobrutinib Tablet Batches

Rationale: The purpose of this study is to compare evobrutinib PK profiles for 45-mg tablet (TF2 formulation) batches CCI [redacted]

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To compare the single-dose PK of different manufacturing batches of evobrutinib TF2 formulation relative to a reference batch under fasted conditions in healthy participants	$AUC_{0-\infty}$, C_{max}
Secondary	
To assess the safety and tolerability of evobrutinib administered as a single oral dose of different manufacturing batches of TF2 formulation under fasted conditions in healthy participants	Nature, occurrence, and severity of treatment-emergent adverse events (TEAEs) Absolute values and changes in safety laboratory tests Single 12-lead ECGs evaluated by Investigator (morphology and time intervals). Listing of the ECG description if classified as "abnormal". Vital signs assessed from time of first dose to end of study participation
To further characterize the PK of different manufacturing batches of evobrutinib TF2 formulation	Additional PK parameters, e.g. $AUC_{0-tlast}$, t_{max}, $t_{½}$, CL/F, V_z/F, F_{rel}

ECG = Electrocardiogram, TEAE = Treatment-emergent adverse event, TF2 = Tablet formulation 2.

Overall Design: This is a randomized, open-label, 4-period, 4-sequence, crossover study (Williams design).

Brief Summary:

The purpose of this study is to compare evobrutinib PK profiles for 45-mg tablet (TF2 formulation) batches CCI [redacted] Study details include:

- Study Duration: up to 46 days.
- Treatment Duration: Single oral dose of 45 mg evobrutinib administered in fasted state at Day 1 of each period.
- The washout between administrations of study intervention in each period will be approximately 48 hours.

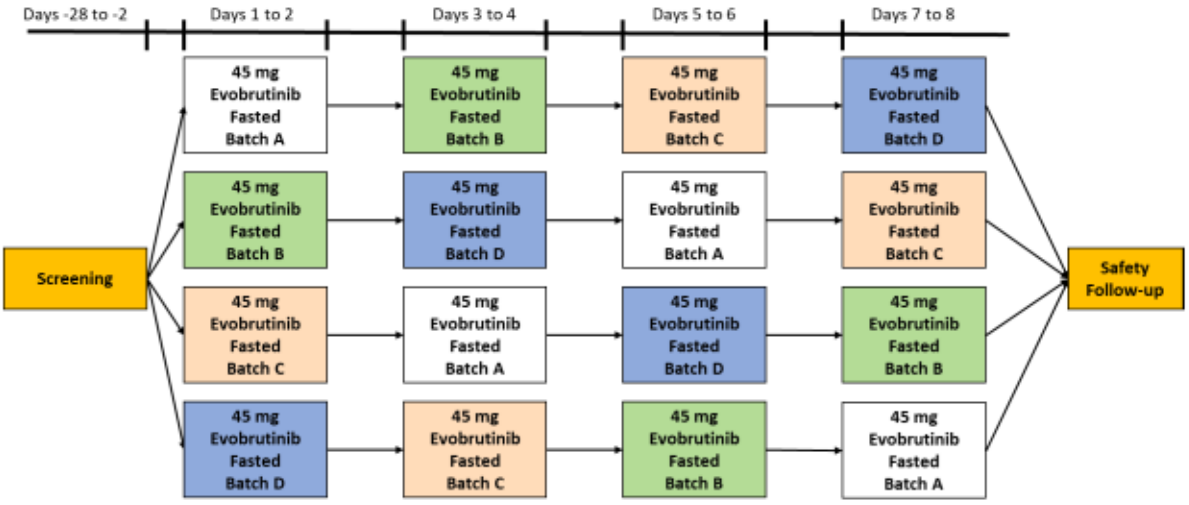
• Visit Frequency: Screening visit will be within 28 days prior to first administration of study intervention. Participants will be resident in the CRU from Day -1 to Day 8.

Number of Participants: CCI [redacted]

Study Intervention Groups and Duration: Single-dose, randomized, 4-period, 4-sequence, 4-way crossover study (Williams design), up to 46 days.

Data and Safety Monitoring /Other Committee: No

1.2 Schema



Batch A = CCI [redacted] (reference), Batch B = CCI [redacted] (lower dissolution bound), Batch C = CCI [redacted] (upper dissolution bound), Batch D = CCI [redacted] (hammer-milled).
Doses are on Days 1, 3, 5, and 7, with an approximate 48-hour washout between doses. Safety follow-up to be approximately 7-10 days after study discharge.

1.3 Schedule of Activities

Assessment	Screening	Treatment									SFU by phone	Comments
		P1			P2		P3		P4			
Study Day(s)	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15 ± 3**	Approximate 48-hour washout between doses on Days 1, 3, 5, and 7.
Period-specific Day(s)	**-28 to -2**	**-1**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**		
Informed consent available	prior to any screening activity											
Study Site Admission		X										
Inpatient visit (on stay)		<==========								=>		Participants are discharged on Day 8
Eligibility criteria	X	X[a]										[a] Recheck of healthy state on Day -1.
Demographics, height, and weight	X											Demography to include, at minimum age (year of birth), sex, race, and ethnicity.
Medical history	X											
FSH and TSH levels	X											FSH only in postmenopausal women.
Pregnancy test	X	X								X		Women of childbearing potential must have a negative serum pregnancy test at the Screening visit. Urine pregnancy test Day -1 and before discharge on Day 8 will also be performed.
QuantiFERON test	X											
eGFR	x											
Viral serology	X											See Appendix 6.
Cotinine, alcohol and drugs of abuse testing	X	X										See Appendix 6.
SARS-Cov-2	X	X										See Appendix 6.
Randomization			X									

Assessment	Screening	Treatment									SFU by phone	Comments
		P1			P2		P3		P4			
Study Day(s)	-28 to -2	-1	1	2	3	4	5	6	7	8	15 ± 3	Approximate 48-hour washout between doses on Days 1, 3, 5, and 7.
Period-specific Day(s)	-28 to -2	-1	1	2	1	2	1	2	1	2		
Administration of study intervention			X		X		X		X			Washout period of 48 hours.
Physical examination	X	X								X		A full physical examination will be performed at Screening and before discharge on Day 8, and a brief physical examination will be performed on Day -1.
Vital signs	X	X	X		X		X		X	X		Vital signs will be assessed on the days of dosing (Day 1, 3, 5, and 7) at predose and at 2 hours postdose. At visits where assessment time points coincide with each other, the following sequence of activities will be followed: 12-lead ECG followed by vital signs within 30 minutes before the specified time point preceding the PK sampling, which will be performed at the specified time point.
Safety ECG	X	X	X		X		X		X	X		12-lead ECG will be performed on the days of dosing (Day 1, 3, 5, and 7) at predose and at 2 hours postdose. See Vital signs (row above) for assessments that coincide.
Clinical laboratory safety tests	X	X					X			X		On Day 5, tests will be performed predose. Blood samples for the clinical laboratory safety assessments will be collected in a fasted condition.
PK sampling			X	X	X	X	X	X	X	X		Plasma samples for PK analysis will be collected on the days of dosing (i.e., Days 1, 3, 5, and 7) at predose and 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, and 24.0 hours postdose. See Vital signs (row above) for assessments that coincide.
Previous medication	X											
Concomitant medication monitoring	X	<==========									X	
AE monitoring	X	<==========									X	

AE=Adverse Event, Day = Study Day, ECG = Electrocardiogram, eGFR = estimated Glomerular Filtration Rate;FSH = Follicle stimulating hormone, P=Period, PK=Pharmacokinetics.

2 Introduction

Evobrutinib is an oral, selective, irreversible inhibitor of BTK which is in clinical development for the treatment of autoimmune diseases, including RMS.

Detailed information on the chemistry, pharmacology, efficacy, and safety of evobrutinib is in the IB.

2.1 Study Rationale

The purpose of this study is to compare evobrutinib PK profiles for 45-mg IR tablet (TF2 formulation) batches that have shown varying dissolution profiles in vitro. The relative bioavailability of the batches will be assessed in reference to a reference batch. The choice of the reference and test batches is based on in vitro dissolution profiles: 1 each of lower and upper dissolution bounds (termed side batches), 1 batch as a reference (all 3 batches being conical sieve milled), and a 4th batch which is hammer-milled. This approach, referred to as mapping methodology, is described in the FDA guidance on dissolution testing for immediate release solid oral dosage forms (Guidance for industry, Dissolution testing of immediate release solid oral dosage forms, 1997). Primary PK parameters assessed include evobrutinib plasma C_{max} and $AUC_{0-\infty}$.

2.2 Background

Evobrutinib (also known as M2951 and MSC2364447C) is an oral, selective, irreversible inhibitor of BTK. Evobrutinib inhibits primary B cell functions, such as proliferation and antibody and cytokine release, without directly affecting T cells. Indirect effects on T cells can be mediated by BTK inhibition by blocking the B cell antigen presentation function. In addition, BTK inhibition blocks the activation of innate immune cells by immune complexes downstream of FcR activation. All 3 mechanisms may play a role in the pathogenesis of various autoimmune diseases. Thus, BTK inhibition could provide clinical benefit in the treatment of multiple autoimmune diseases including RMS.

2.3 Benefit/Risk Assessment

As of 31 July 2021, approximately 2,041 adult participants in 16 completed and 5 ongoing clinical studies have been exposed to evobrutinib, including healthy participants (243), participants with RMS (943), systemic lupus erythematosus (437), or rheumatoid arthritis (363), and participants with renal impairment (31) and hepatic impairment (24). Evobrutinib was generally safe and well tolerated in all participants. The TEAEs have been primarily mild to moderate in severity.

Each participant in this study will receive up to 4 doses of evobrutinib at 45 mg under fasted conditions, 2 days apart. This regimen is not expected to exceed exposures reached in first-in-human clinical study EMR200527_001, where single doses of evobrutinib from 25 up to 500 mg and 14 days of dosing with 25, 75, and 200 mg/day were tested and shown to be well tolerated.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of evobrutinib may be found in Section 2.3.1 and 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

Safety Risks Applicable to Healthy Participants

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Important 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). 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 transaminases will be adequately monitored during the study.
CCI [redacted]	[redacted]	Female participants of childbearing potential must not be pregnant, must have a negative pregnancy test at the time of enrollment and use highly effective contraception (Section 5.1) during the study period and for 30 days after the last dose and agree not to donate eggs for reproduction during this period.
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-like setting with support from highly trained professionals.
ECG	Contact allergies can develop during ECG procedures.	Participants with known contact allergies to ECG electrodes will not be included in the study.

AE = adverse event, IB = Investigator's Brochure, ECG = electrocardiogram.

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 IgM, an increase in IgA, 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 8 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, in order 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.

In order 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

The healthy participants participating in this study will not obtain any clinical benefit from the treatments. The data obtained from this study will guide further development of evobrutinib.

2.3.3 Overall Benefit: Risk Conclusion

Risk minimization measures routinely implemented in early phase clinical studies are considered adequate, including exclusion criteria (Section 5.2), adequate biochemical and hematology laboratory monitoring (Section 8.2.4), and observation of vital signs and ECGs (Sections 8.2.2 and 8.2.3). Evobrutinib will be discontinued in case of events that unacceptably endanger the safety of the participant (Section 8.3). 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 risk to participants in this study, the potential risks identified in association with evobrutinib are justified in healthy participants.

3 Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the single-dose PK of different manufacturing batches of evobrutinib TF2 formulation relative to a reference batch under fasted conditions in healthy participants	$AUC_{0-\infty}$, C_{max}
Secondary	
To assess the safety and tolerability of evobrutinib administered as a single oral dose of different manufacturing batches of TF2 formulation under fasted conditions in healthy participants	Nature, occurrence, and severity of treatment-emergent adverse events (TEAEs) Absolute values and changes in safety laboratory tests Single 12-lead ECGs evaluated by Investigator (morphology and time intervals). Listing of the ECG description if classified as "abnormal". Vital signs assessed from time of first dose to end of study participation
To further characterize the PK of different manufacturing batches of evobrutinib TF2 formulation	Additional PK parameters: e.g. $AUC_{0-tlast}$, t_{max}, $t_{½}$, CL/F, V_z/F, F_{rel}

ECG = Electrocardiogram, TEA = Treatment-emergent adverse event, TF2 = Tablet formulation 2.

4 Study Design

4.1 Overall Design

Study Design	Randomized, open-label, 4-period, 4-sequence, crossover design
Control Method	Not applicable
Single or Multicenter	Single center
Study Population Type	Healthy participants
Level and Method of Blinding	Not applicable
Bias Minimalization Method(s)	Randomization
Study Intervention Assignment Method	Not applicable
Data and Safety Monitoring /Other Committee:	No
Total Duration of Study Participation per Participant	Up to 43 days
Provisions for Study Extension or Entry into Roll-Over Studies	Not applicable
Adaptive Aspects of Study Design	Not applicable

A study scheme and a detailed Schedule of Assessments are provided in Section 1.2 and Section 1.3 respectively.

4.2 Scientific Rationale for Study Design

This study will compare the single-dose evobrutinib PK of different tablet manufacturing batches relative to a reference batch under fasted conditions in healthy participants. Results of this study are planned to provide data to support ongoing clinical development and post-approval activities.

The study utilizes a randomized crossover design to ensure all participants who complete the study receive each treatment and hence allows within participant comparisons, and that no bias is introduced or confounds the conclusions of the study. CCI [redacted].

The study endpoints are based on the regulatory guidance of the FDA (Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations, 2014) and the EMA (Guideline on the Investigation of Bioequivalence, 2010).

4.2.1 Participant Input into Design

Not applicable.

4.3 Justification for Dose

The evobrutinib dose to be used in this study is 45 mg under fasted conditions. 45 mg is the same dose as in the Phase 3 studies evaluating evobrutinib in participants with RMS. The Phase 3 dose is being administered under fed conditions, whereas fasted conditions are being used in this study as recommended in the FDA guidance for bioavailability studies.

The exposure in this study is expected to not exceed that of other studies in healthy participants, in which a single dose up to 500 mg and multiple doses up to 200 mg evobrutinib for 14 days were administered and well tolerated.

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).

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

Study Termination Criteria

The study will be terminated if:

- unacceptable risk, any relevant toxicity, or a negative change in the benefit/risk assessment is identified. This might include the occurrence of AEs whose character, severity or frequency is new in comparison to the existing risk profile.

- any data derived from other clinical trials or toxicological studies become available which negatively influence the benefit/risk 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 individuals who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether an individual 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.

Before performing any study assessments that are not part of the individual's routine medical care, the Investigator will confirm that the individual 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 between 18 and 55 (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 BMI within the range 19.0 and 30.0 kg/m^2 (inclusive).
Sex and Contraception/ Barrier Requirements	4) Male or female The Investigator confirms that each participant agrees to use appropriate contraception and barriers, if applicable. The contraception, barrier, and pregnancy testing requirements are below. Male participants: No contraception needed. Female participant: • Is **not** breastfeeding. • Is **not** pregnant (i.e., has a negative serum or highly sensitive urine pregnancy test, as required by local regulations, within 24 hours before the first dose of study intervention). If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. • Is **not** a WOCBP • If a WOCBP, uses a highly effective contraceptive method (i.e., with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods: 1) Before the first dose of the study intervention(s), if using hormonal contraception: Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses; **OR**, Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay. 2) During the study intervention period 3) After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 30 days after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period. The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention. Negative pregnancy test, as required by local regulations, at Screening and within 24 hours before the first dose of study intervention. The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.
Informed Consent	5) Are 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 stable non-smokers for at least 3 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, musculoskeletal, genitourinary, immunological, dermatological, connective tissue, psychiatric (due to rare risk of hallucinations, agitation and activation of psychosis), and other diseases or disorders, and epilepsy, 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. Prior history of cholecystectomy or splenectomy, and any clinically relevant surgery within 6 months prior to the first administration of study intervention.
	3. History of any malignancy.
	4. History of seizures.
	5. History of pharmacologically treated psychiatric disease.
	6. 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 the first administration of study intervention.
	7. History of shingles within 12 months prior to Screening.
	8. History of drug hypersensitivity (e.g. quinolones and 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 including contact hypersensitivity to ECG electrodes, which may affect the safety of the participant and/or outcome of the study per the Investigator's discretion.
	9. History of alcoholism or drug abuse within 2 years prior to the first administration of study intervention, or positive for drugs of abuse, nicotine/cotinine or alcohol by the laboratory assays conducted during Screening and Day -1.
	10. History of residential exposure to tuberculosis, or a positive QuantiFERON® test within 4 weeks prior to or at the time of Screening.
	11. Positive for a) hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, or HIV I and II tests at Screening; b) SARS-CoV-2 at Screening and Day -1.
	12. Any condition, including findings in the laboratory tests, medical history (e.g. heart failure, hypokalemia, family history of Long QT Syndrome), 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.

Category	Criterion
	13. Administration of live vaccines or live-attenuated virus vaccines within 3 months prior to Day 1. Administration of other types of vaccines is allowed until 14 days before the first administration of study intervention, thereafter it is prohibited until the end of the study. However, for SARS-CoV-2 mRNA vaccine is not permitted 42 days prior to Day1. Note: In case of clinical symptoms, the participant should be symptom-free for at least 1 week prior to the first administration of study intervention.
Prior/Concomitant Therapy	14. Moderate or strong inhibitors or inducers of CYP3A4/5 or Pgp within 4 weeks prior to the first administration of study intervention.
	15. 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 paracetamol (acetaminophen) up to 2 g per day or hormonal contraceptives/HRT is permitted.
Prior/Concurrent Clinical Study Experience	16. Use of any investigational drug in any clinical study within 60 days prior to Day 1 administration, or have used an experimental monoclonal antibody within the past 1 year prior to 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 a study intervention was more than 60 days ago, or 5 half-lives of the investigational drug, whichever is longer, prior to the first administration of study intervention.
Diagnostic Assessments	17. Medical history and physical examination results that include any ongoing clinically relevant findings as judged by the Investigator.
	18. 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 ULN • Creatinine: above normal limits • Absolute lymphocyte count, absolute neutrophil count: below limit of reference range. • Amylase and lipase above normal ranges; minor deviations are allowed, if not clinically relevant.
	19. eGFR according to the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (2009) < 90 mL/min at Screening. In case of a borderline result between ≥ 80 and < 90 mL/min, Cystatin C will be determined in addition, and the participant will only be included if the Cystatin C value is below the upper limit of normal.
	20. 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.
	21. 12-lead ECG showing a QT interval corrected for heart rate according to Fridericia's formula (QTcF) > 450 ms, PR > 215 ms, or QRS > 120 ms at Screening.
	22. Any other abnormal laboratory results that the Investigator believes should preclude the participant's participation in the study.

Category	Criterion
Other Exclusions	23. Consumption of an average weekly alcohol intake of > 14 units/week for men or > 7 units/week for women. One unit (12 g) of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
	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 in each period.
	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 (hypericum perforatum), 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 the first administration of study intervention, donation of plasma from 2 weeks prior to the first administration of study intervention, or platelets from 6 weeks prior to the first administration of study intervention.
	28. Travel to a country with a high prevalence of tropical diseases within 3 months prior to the first administration of study intervention.
	29. Inability to communicate reliably with the Investigator or considered by the Investigator to be unable to or unlikely to cooperate with the requirements of the study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants will abstain from consuming energy drinks, herbal supplements including, but not limited to, St. John's wort (hypericum perforatum), Seville oranges, grapefruits, pomelos, exotic citrus fruits, grapefruit hybrids, cranberries, and juices from these fruits from 14 days before first administration of evobrutinib until after collection of the final PK sample.

The following general instructions on meals and dietary restrictions and timing of meals apply to the study:

During the in-house period at the CRU, on dosing Days 1, 3, 5, 7, participants should follow an overnight fast of at least 10 hours prior to evobrutinib administration. Four hours after evobrutinib administration, a standardized lunch will be served. An afternoon snack will be provided approximately 8 hours and dinner approximately 12 hours postdose. On other days participants will receive meals at customary times.

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

On each dosing day, study intervention will be administered with 240 mL of water in a standing position at the study center following an overnight fast of at least 10 hours. Participants will remain fasting until 4 hours postdose. Participants will not be allowed any liquid from 1 hour predose until

1 hour postdose, except for the 240 mL water required to consume the dose with. Participants should thereafter consume at least 1.5 L of water per day (no documentation of volume is needed).

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid

- During the 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 sample.
- During the dosing period participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- During the dosing period participants will abstain from cannabinoid-containing products for 24 hours before the start of dosing until after collection of the final PK sample.
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted from at least 3 months preceding Screening until after final Follow-up visit (phone call).

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).

On dosing Days 1, 3, 5, and 7, participants will stay in a semi-recumbent position until completion of the 1-hour procedures. Participants are allowed to get up for going to the bathroom as needed.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened.

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

Study Intervention(s) Administered

Intervention Label	Evobrutinib
Intervention Name	Evobrutinib
Intervention Description	Participants will receive a 45-mg dose of evobrutinib once each on Days 1, 3, 5, and 7. Study intervention will be administered with 240 mL of water in a standing position at the study center following an overnight fast of at least 10 hours. Participants will remain fasting until 4 hours postdose. Details in 5.3.1.
Type	Drug

Dose Formulation	Tablet (TF2)
Unit Dose Strength(s)	45 mg
Dose	45 mg single dose
Dosage Regimen	Single tablet on Days 1, 3, 5, 7
Route of Administration	Oral
Use	Experimental
IMP or NIMP/AxMP	IMP
Sourcing	Provided by 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 Arm(s)

Arm Name	Evobrutinib 45 mg Batch A	Evobrutinib 45 mg Batch B	Evobrutinib 45 mg Batch C	Evobrutinib 45 mg Batch D
Arm Type	Experimental	Experimental	Experimental	Experimental
Arm Description	Single dose in each treatment period	Single dose in each treatment period	Single dose in each treatment period	Single dose in each treatment period
Associated Intervention Labels	Evobrutinib	Evobrutinib	Evobrutinib	Evobrutinib

Batch A = CCI (reference), Batch B = CCI (lower dissolution bound), Batch C = CCI (upper dissolution bound), Batch D = CCI (hammer-milled).

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 documents 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

This will be an open-label, randomized study. Participants will be randomly assigned to 1 of the following 4 treatment sequences, with a maximum of 7 participants assigned to each treatment sequence (ratio 1:1:1:1), using a Williams design for a 4-treatment, 4-period crossover study:

Sequence no.	Actual Sequence	Period			
		1	2	3	4
1	A-B-C-D	A	B	C	D
2	B-D-A-C	B	D	A	C
3	C-A-D-B	C	A	D	B
4	D-C-B-A	D	C	B	A

Batch A = CCI (reference), Batch B = CCI (lower dissolution bound), Batch C = CCI (upper dissolution bound), Batch D = CCI (hammer-milled).

After informed consent procedure, every participant is given a screening number. Only participants who comply with all eligibility criteria (see Sections 5.1 and Section 5.2) can be included into the study.

On Day 1, prior to first administration, the participants enrolled will be assigned a unique 3-digits assignment number (randomization number) in ascending numerical order at the study site. The

randomization number encodes the participant's assignment to 1 of the 4 treatment sequences of the study, per the randomization schedule generated prior to the study by PPD CTS Department.

The Investigator will keep a record relating the participant assignment numbers and the names of all participants (including screening number and the PPD randomization 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.

6.4 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. A member of the study site staff other than the person administering the study intervention will confirm the study intervention dose and study participant identification at the time of dosing. 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 evobrutinib 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.

Even if not associated with an AE or SAE, any overdose is recorded in the CRF and reported to global patient safety in an expedited manner. Overdoses are reported on an 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 signing of the ICF until Safety Follow-up Visit (phone call), 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. For nondrug interventions, record the name, the indication, and dates administered.

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

6.8.1 Rescue Medicine

No antidote is available specifically for evobrutinib. Symptomatic treatment will be provided in case of a medical emergency. Any kind of toxicity occurring during the study will be treated symptomatically.

6.8.2 Permitted Medicines

The only permitted medicines are the following:

1. Paracetamol (acetaminophen) up to 2 g per day, at the discretion of the Investigator

2. Hormonal contraceptives and HRT (see Appendix 3).

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.

6.8.3 Prohibited Medicines

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

The participants are prohibited from using prescription or over-the-counter medications (apart from those described above) 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).

Inhibitors or inducers of CYP3A4/5 or P-gp within 4 weeks prior to the first administration of study intervention, and until after the Safety Follow-Up assessment, are prohibited.

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 5.3.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the entire study is specified in Appendix 2.

7.1 Discontinuation of Study Intervention

A participant must be withdrawn from administration of study intervention if any of the following occur:

- Participant withdraws consent.
- A participant is enrolled but is subsequently discovered not to have met inclusion/exclusion criteria at Screening.
- AEs, if discontinuation of study intervention 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 intervention.
- Pregnancy (see Section 8.3.4).
- Protocol noncompliance judged as significant by the Investigator (after discussion with the Sponsor).
- Use of a nonpermitted concomitant drug if clinically relevant as agreed by Sponsor and Investigator, as defined in Section 6.8 where the predefined consequence is withdrawal from study intervention.
- Any events that unacceptably endanger the safety of the participant.

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety.

The SoA specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed.

If study intervention is discontinued, the safety assessments of Day 8 and follow-up phone call should be performed.

7.1.1 Liver Clinical Safety Laboratory Tests Stopping Criteria

The Investigator will consider discontinuation of study intervention for abnormal liver function when a participant meets one of the conditions outlined in the algorithm or if the Investigator believes that it is in best interest of the participant.

- All confirmed events of ALT or AST $\geq 5 \times$ ULN triggers stopping criteria.
- All confirmed events of ALT or AST $\geq 3 \times$ ULN and total bilirubin $> 2 \times$ ULN triggers stopping criteria.

These events will be reported as an AESI.

7.1.2 Cardiac Safety Stopping Criteria

If a clinically significant finding is identified (including changes from baseline in QT interval corrected using Fridericia's formula (QTcF > 60 ms and QT/QTcF > 500 ms) 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.

7.1.3 Rechallenge

7.1.3.1 Study Intervention Restart or Rechallenge After Liver Stopping Criteria Are Met

Study intervention restart or rechallenge after liver clinical safety laboratory test stopping criteria are met by any participant in this study are not allowed.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may discontinue from the study at any time, at their own request or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons (e.g., disruption of operations due to natural disasters, interruption of lab or facility accreditation, participant moving to another country, resignation of key staff").
- At the time of study discontinuation, if possible, a discontinuation visit will be conducted, as listed in the SoA. The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.
- 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.

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 will 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, he/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 SoA.
- 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 will continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, 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, were performed within the time frame defined in the SoA, and if reviewed and approved by the Sponsor.
- About 165 mL of blood total will be taken throughout the study. Up to about 45 mL of blood may be drawn at certain visits. These blood samples will be used for the following purposes: PK and clinical laboratory tests.

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.

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, respiratory, 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 during measurement; pulse; respiratory rate; temperature and location of measurement, weight, and height (at baseline only) will be measured and recorded. Vital signs will be measured in supine position. Tympanic temperature will be measured.
- Blood pressure and pulse measurements will be preceded by at least 5 minutes 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

- 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 QTcF. ECG abnormalities will be documented as clinically significant or not clinically significant in the eCRF together with a description of the abnormality.
- 12-lead ECGs will be recorded in a supine position following 5 min of rest.

8.2.4 Clinical Safety Laboratory Tests

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 6 at the timepoints listed in the SoA. 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.
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the end of relevant systemic exposure of the study intervention and correspond with the time frame for female participant contraception in Section 5.1.

- Additional serum or urine pregnancy testing may be conducted at any time during the study to establish the absence of pregnancy, at the Investigator's discretion or if local regulations require them.

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

- The definitions of an AE and SAE are in Appendix 4.
- The Investigator and any qualified designees (e.g., Subinvestigators) 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 Safety Follow-up Visit (phone call) at the timepoints specified in the SoA (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 toward 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 Subinvestigator 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 read it and confirm completion of this activity. 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 and female partners of male participants will be collected after the start of study intervention and until 120 days after the last dose of evobrutinib.
- 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 or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) 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 /pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant /pregnant female partner 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 /pregnant female partner, 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 and/or opportunistic and/or ≥ 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 commonly 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 patients with MS (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 ECG study in healthy participants 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 $> 2 \times$ 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 ($> 3 \times$ ULN), bilirubin elevations ($> 1.5 \times$ 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

8.4.1 Blood Sampling and Bioanalysis

- Samples are collected only where allowed by local law/regulations.
- The actual date and time (24-hour clock time) of:
  - Each sample collection
  - Study intervention administration prior to sample collection
- will be recorded in the eCRF to determine the elapsed time of sampling in relation to the administration of study intervention.

- Blood samples for measurements of evobrutinib concentrations will be collected. Collection times are specified in the SoA. The accepted time deviations from planned PK sampling times that will not be considered a protocol violation are listed in Table 1.
- The quantification of evobrutinib in plasma will be performed using a validated assay method.
- Remaining samples collected for bioanalytical measurements may also be used for exploratory assessment of metabolites of evobrutinib or exploratory biomarkers during or after the study. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- Details on processes for collection and handling of these samples are in Laboratory Manual.

Table 1 Time Deviations from PK Sampling Times

Procedure	Time Point (Relative Time)	Window Allowance
PK	Predose	- 60 min
	15 min	± 2 min
	30 min	± 2 min
	1 hr	± 2 min
	1.5 hr	± 5 min
	2 hr	± 5 min
	2.5 hr	± 5 min
	3 hr	± 5 min
	4 hr	± 5 min
	6 hr	± 5 min
	8 hr	± 5 min
	12 hr	± 5 min
	16 hr	± 15 min
	24 hr	± 15 min

Any deviation from the above-mentioned time windows requires a comment in the eCRF and may be discussed in the data review meeting.

8.4.2 PK Parameters

- The following PK parameters for evobrutinib will be calculated, when appropriate:

Symbol	Definition
$AUC_{0\text{-}tlast}$	The AUC from time zero (= dosing time) to the time of the last quantifiable concentration (t_{last}).
$AUC_{0\text{-}\infty}$	The AUC from time zero (= dosing time) up to infinity with extrapolation of the terminal phase.
CL/F	The apparent total body clearance following extravascular administration.
C_{max}	Maximum observed concentration.

Symbol	Definition
F_{rel}	Relative Bioavailability [%] of Test Treatment in relation to Reference Treatment.
$t_{1/2}$	Terminal half-life.
t_{lag}	The time prior to the first concentration at or above LOQ.
t_{max}	The time to reach the C_{max} in a dosing interval.
V_z/F	The apparent volume of distribution during the terminal phase following extravascular administration.
λ_z	Terminal first order (elimination) rate constant.

LOQ = Limit of quantification.

Other PK parameters might be added based on emerging data. Details will be in the IAP.

- Concentration data may be used for integrated data analyses across studies, such as population PK, and reported separately from the main CSR.

8.5 Genetics and/or Pharmacogenomics

Not applicable.

8.6 Biomarkers

Not applicable.

8.7 Immunogenicity Assessments

Not applicable.

8.8 Health Economics

Not applicable.

9 Statistical Considerations

9.1 Statistical Hypotheses

The statistical analysis of study data will be purely descriptive; no hypothesis tests will be performed.

CCI [redacted]

[redacted]

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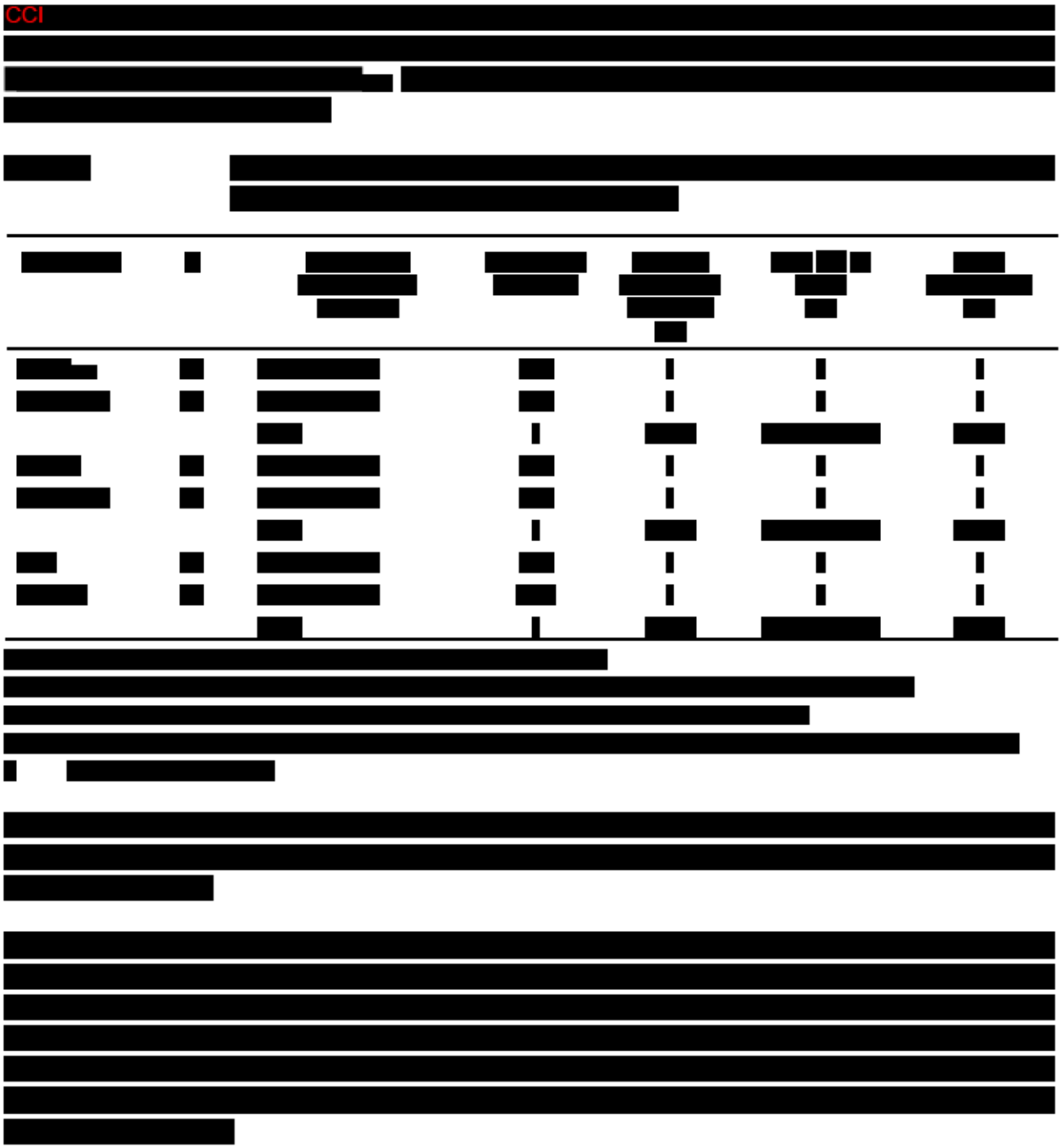

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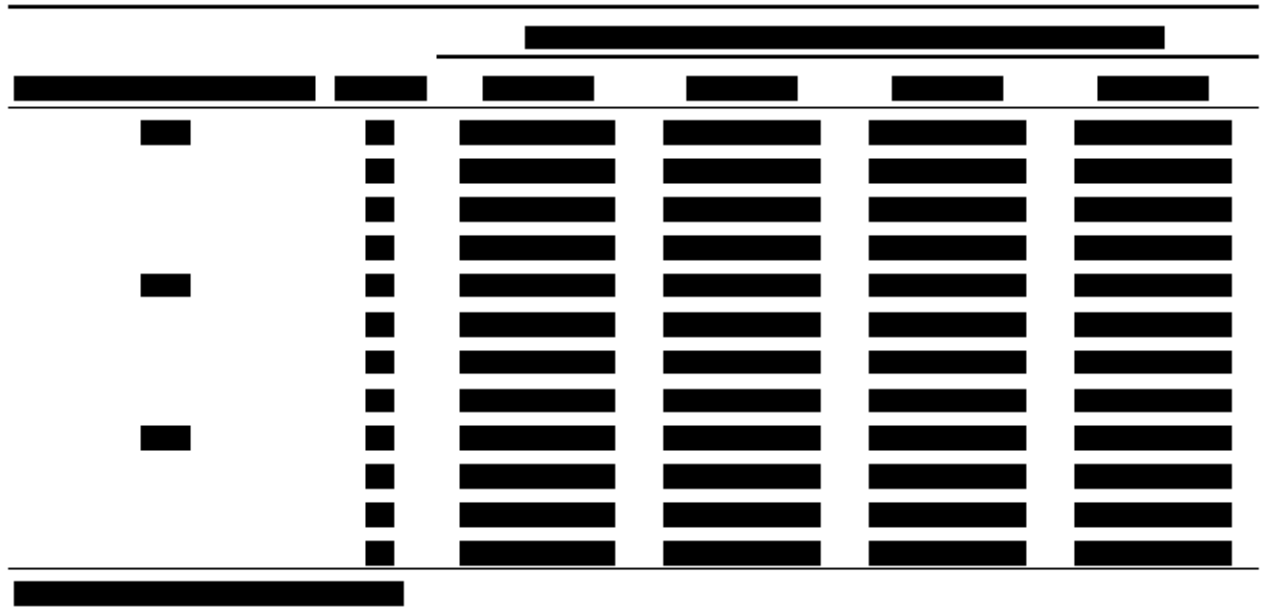

9.3 Analysis Sets

The analysis sets are specified below.

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's randomization 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.
PK	The PK Analysis Set is a subset of the Safety Analysis Set and will consist of all participants who receive at least one dose of active IMP and provide at least one measurable postdose concentration. A measurement below lower limit of quantification is considered a valid measurement. Participants will be analyzed according to the actual treatment they received in each period. All PK analyses will be based on the PK Analysis Set.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

Not applicable.

9.4.2 Safety Analyses

In general, for the evaluation of safety parameters, the numerical values will be summarized descriptively (N, arithmetic mean, median, standard deviation, minimum and maximum values). Categorical variables will be presented in frequency tables by the number of observations and percentages.

Adverse Event counts and participants with AEs will be summarized for each treatment by system organ class and preferred term. In addition, AEs will be tabulated and listed per participant and analyzed by severity and relationship to study drug.

Participants who prematurely withdrew from the study or from treatment will be displayed in a by-participant listing and summarized by primary withdrawal reason for each treatment sequence.

Safety laboratory parameters will be listed for each participant including changes from baseline and flags for measurements outside the reference ranges, where applicable. Laboratory parameters (hematology and clinical chemistry) will be summarized by time point including both absolute values and changes from baseline.

Vital signs by participant, including changes from baseline, will be listed and summarized by treatment and time point using descriptive statistics. Electrocardiogram parameters and physical examination assessments will be listed for each participant.

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

Endpoint	Statistical Analysis Methods
Primary	No primary safety endpoints
Secondary	
Nature, occurrence, and severity of TEAEs	The number and percentage of participants experiencing at least 1 TEAE will be summarized by treatment as well as the number of events. Tables by relationship to study drug and by severity will be generated. AEs will be coded using MedDRA terminology.
Absolute values and changes in safety laboratory tests	All laboratory data will be reported with SI units. Laboratory parameters will be summarized using descriptive statistics for absolute values, changes from baseline (predose for the respective period) and data listings of abnormalities.
Single 12-lead electrocardiograms (ECGs) (morphology and time intervals PR, QRS, RR, QT and QTcF)	ECG data will be summarized by changes from baseline (predose for the respective period) values by treatment using descriptive statistics. Clinical noteworthy ECG findings for individual participants will be listed and summarized as appropriate.

Endpoint	Statistical Analysis Methods
Vital signs assessed from time of first dose to end of study participation	Vital signs data will be summarized by changes from baseline (predose for the respective period) values using descriptive statistics.
Tertiary/Exploratory	Not applicable

9.4.3 Other Analyses

Category/Endpoint	Statistical Analysis Methods
Primary	
$AUC_{0-\infty}$ C_{max}	PK parameters are listed in Section 8.4. Summary statistics will be provided. A linear mixed model with BATCH, PERIOD, and SEQUENCE as fixed effects and SUBJECT within SEQUENCE as a random effect will be applied to log-transformed primary endpoints C_{max}, and $AUC_{0-\infty}$ based on the PK analysis set. Differences between batches on the log scale for each comparison will be estimated for the parameters together with their 90% CIs. Point estimates and CIs will be back transformed to the original scale for presentation. All PK analyses will be performed on the PKAS.
Secondary	
PK parameters (in Section 8.4)	Summary statistics of PK parameters will be provided. All PK analyses will be performed on the PKAS.

PKAS = PK analysis set.

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. Interim analyses for early decision making may take place with restricted and documented access to the data and results, without impact on the study design.

10 References

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.

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.

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):1912-5.

11 Appendices

Appendix 1 Abbreviations

AE	adverse event
AESI	adverse events of special interest
ALT	alanine transaminase
AST	aspartate transaminase
BTK	Bruton's tyrosine kinase
CRF	case report form
CRO	clinical research organization
CSR	clinical study report
CT	clinical trials
CV	Coefficient of variation
Day	Study Day (unless otherwise indicated)
DRE	disease-related events
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medical Agency
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IAP	integrated analysis plan
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IFU	information for use
Ig	immunoglobulin
IMP	investigational medicinal product
INR	international normalized ratio
IR	immediate release
IRB	Institutional Review Board
IRC	Independent Review Committee
LOQ	limit of quantification
PK	pharmacokinetic
PKAS	pharmacokinetic analysis set
QTcF	corrected QT interval by Fridericia' formula
RMS	Relapsing multiple sclerosis
SAE	serious adverse event
SAF	safety

SCR	screening
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse events
TF	Tablet formulation
ULN	upper limit of normal
WHO	World Health Organization
WOCBP	woman of childbearing potential

Appendix 2 Study Governance

Financial Disclosure

Investigators and Subinvestigators 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 their representative will explain the nature of the studyincluding the risks and benefits, 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; privacy and data protection 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 their 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 clinical study report.

The study will be conducted at a single center, the Clinical Pharmacology Unit of PPD, Germany. PPD 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 separately (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 CIOMS 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 clinical study report 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 not be predefined in this study because neither the limited number of planned participants nor the short duration of the study support the collection of meaningful quality tolerance limits.
- Monitoring details describing strategy, including definition of study critical data items and processes (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 or contracts.
- 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 and its origin is found in the 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.

- Sponsor discontinuation of the study due to an unacceptable risk, any relevant toxicity, or negative change in the risk/benefit assessment.

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

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 non-estrogen 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.

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

Implantable progestogen-only hormone contraception associated with inhibition of ovulation

- IUD
- IUS
- Bilateral tubal occlusion.

Azoospermic partner (vasectomized or due to a medical cause)

- Azoospermia is a highly effective contraceptive method provided the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.
- Documentation can come from the site personnel's review of the individual's medical records, medical examination, or medical history interview.

Highly Effective Methods That Are User Dependent
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

- Oral
- Intravaginal
- Transdermal
- Injectable.

Progestogen-only hormone contraception associated with inhibition of ovulation

- Oral
- Injectable.

Sexual abstinence: a highly effective method **only** if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Notes:

Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants.

Highly effective methods are those with a failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

If locally required, in accordance with Clinical Trials Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are **not** acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure from friction).

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 (e.g., 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 per the Investigator's medical and scientific judgment, are considered clinically significant in the medical and scientific judgment of the Investigator (e.g., not related to progression of underlying disease, but may be leading to study intervention discontinuation). • Exacerbation of a chronic or intermittent pre-existing 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 SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or 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 pre-existing 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).

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death.
a) 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.
b) 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 fulfills 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 pre-existing 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.
c) 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.
d) Is a congenital anomaly/birth defect.
e) 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 and AESIs.

In this clinical study, any late spontaneous abortion, fetal death in utero, ectopic pregnancy, chronic fetal distress, stillbirth, neonatal death or prematurity-related complication more than is typical for prematurity will be considered as an SAE.

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, 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 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: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Do not confuse an AE that is assessed as severe with an 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 an 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 an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE in multicenter studies to the Sponsor or its designee will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE form, specified below, to report the event within 24 hours. • The site will enter into the electronic system the SAE data within 24 hours after becoming aware of the event. It is expected that the Investigator/Subinvestigator signs off this data in the system and any relevant associated data (e.g., additional laboratory tests, medical records, diagnostic reports, histopathological examinations, or consultation with other health care professionals) will be entered as soon as it becomes available. • After the study is completed at a site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Sponsor's safety department. • By exception, an SAE (or follow-up information) may be reported by telephone. The site will complete the electronic SAE data entry immediately thereafter.
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 EDC 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 Liver Safety: Suggested Actions and Follow-up Assessments

The Investigator will consider discontinuation of study intervention for abnormal liver function when a participant meets one of the conditions outlined in the algorithm or if the Investigator believes that it is in best interest of the participant.

All confirmed events of ALT or AST $\geq 5 \times$ ULN triggers stopping criteria.

All confirmed events of ALT or AST $\geq 3 \times$ ULN and total bilirubin $> 2 \times$ ULN triggers stopping criteria.

All AEs involving the liver or the gall bladder will be reported as AESI according to the risk profile of evobrutinib.

Appendix 6 Clinical Laboratory Tests

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

All study-required laboratory assessments will be performed by a central laboratory.

Laboratory Assessment	Parameter	Notes
Biochemistry	Albumin	
	Alanine Aminotransferase	
	Alkaline Phosphatase	
	Amylase	
	Aspartate Aminotransferase	
	Bicarbonate	
	Bilirubin	
	C-reactive protein	
	Calcium	
	Chloride	
	Creatinine	
	Cystatin C	
	Glomerular Filtration Rate, Estimated (by CKD-Epi)	
	Gamma Glutamyl Transferase	
	Glucose	
	Lactate dehydrogenase	
	Magnesium	
	Lipase	
	Potassium	
	Sodium	
	Protein	
	Urate	
Coagulation	Prothrombin Intl. Normalized Ratio	
Hematology	Hematocrit	
	Hemoglobin	
	Leukocytes with Differential: Neutrophils (absolute/%) Lymphocytes (absolute/%) Monocytes (absolute/%) Eosinophils (absolute/%) Basophils (absolute/%)	

Laboratory Assessment	Parameter	Notes
	Ery. Mean corpuscular hemoglobin (MCH)	
	Ery. Mean corpuscular volume (MCV)	
	Platelets	
	Erythrocytes	
Hormonal	Follicle stimulating hormone	For postmenopausal women at Screening only
	Thyroid stimulating hormone	
Routine Urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes by dipstick	
	Microscopic examination (if blood or protein is abnormal).	In case of a positive result for hemoglobin, leukocyte esterase, protein or nitrite, a flow cytometry count and classification will be performed.
Pregnancy	Serum human chorionic gonadotropin pregnancy test, urine pregnancy test	Conducted at timepoints listed in the Schedule of Assessments
Alcohol and Drug Screen	Urine drug screen to include: 3,4-methylenedioxymethamphetamine (ecstasy), amphetamine, methamphetamine, barbiturate, cocaine, opiate, cannabinoids, benzodiazepine, methadone, phencyclidine, oxycodone, tricyclic antidepressants, cotinine Ethanol breath test	Screening and Day -1 only
Serology	HIV antibody, Hepatitis B Virus Surface Antigen, Hepatitis C Virus antibody, SARS-CoV-2 Antigen, SARS-CoV-2 RNA, and QuantiFERON® test	Screening only (except SARS-CoV-2 tests, also Day -1)

Appendix 7 Protocol Amendment History

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

Appendix 8 Sponsor Signature Page

Study Title: A Phase I, Open-Label Study of the Relative Bioavailability of Evobrutinib Tablet Manufacturing Batches in Healthy Participants

Regulatory Agency Identifying Numbers: EudraCT number: 2022-002755-19

Clinical Study Protocol Version: 08 September 2022/Version 1.0

I approve the design of the clinical study:

PPD PPD

Signature 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 Study of the Relative Bioavailability of Evobrutinib Tablet Manufacturing Batches in Healthy Participants
Regulatory Agency Identifying Numbers:	EudraCT number: 2022-002755-19
Clinical Study Protocol Version:	08 September 2022/Version 1.0
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: PPD

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Global Version ID: CCI [redacted]