Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	Phase I Open-label, Single Dose Study to Investigate the Effect of Hepatic Impairment on the Pharmacokinetics (PK) of Evobrutinib (M2951)
Study Number:	MS200527_0059
Amendment Number	Not Applicable
Merck Compound Number:	M2951
Study Phase:	Phase I
Short Title:	Effect of hepatic impairment on evobrutinib PK
Principal Investigator:	PPD
Sponsor Name and Legal Registered Address:	Merck Healthcare KGaA an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 Darmstadt, Germany Medical Responsible: Name: PPD Address: As above General Merck Phone Number: PPD Mobile: PPD General Merck Fax Number: Not applicable Email: PPD
Regulatory Agency Identifying Numbers:	EudraCT: 2020-001920-32
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Medical Monitor Name and Contact Information:	PPD Phone: PPD Mobile: PPD Email: PPD

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	22-May-2020

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

Phase I, Open-label, Single Dose Study to Investigate the Effect of Hepatic Impairment on the Pharmacokinetics (PK) of Evobrutinib (M2951)

Short Title:

Effect of hepatic impairment on evobrutinib PK

Rationale:

The purpose of the study is to describe the evobrutinib pharmacokinetics (PK) in participants with different stages of hepatic impairment compared to a control group of participants with normal hepatic function. The results of this study will contribute to the understanding of the evobrutinib metabolism and inform recommendations on dose adjustments in participants with hepatic impairment.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To investigate the PK of evobrutinib after a single dose to participants with hepatic impairment compared to participants with normal hepatic function	$AUC_{0-\infty}$, and C_{max}
Secondary	
To assess the safety and tolerability of evobrutinib when administered as a single dose to participants with normal hepatic function and with impaired hepatic function	Occurrence of treatment-emergent adverse events (TEAEs), changes from Baseline in laboratory safety tests, 12-lead electrocardiogram (ECG) morphology and time intervals (PR, QRS, RR, QT, and QTcF), and vital signs from time of first dose to the End of Study
To characterize the effect of hepatic function on the PK of evobrutinib through secondary PK endpoints	t_{max}, $t_{½}$, AUC_{0-12} and AUC_{0-24}, AUC_{0-t}, CL/f, V_Z/f, unbound fraction in plasma (f_u), AUC for unbound drug from time zero to infinity ($AUC_{0-\infty,u}$), unbound C_{max} ($C_{max,u}$), and unbound apparent oral clearance ($CL_{,u}$/f)

Overall Design:

This is an open-label, nonrandomized, parallel-group, single-center, single oral dose, Phase I study to investigate the PK and safety of evobrutinib in participants with different degrees of hepatic impairment compared to participants with normal hepatic function. Participants will be assigned to one of 3 groups: normal hepatic function (Group 1), mild hepatic impairment (Group 2), or moderate hepatic impairment (Group 3). Participants of Group 2 (8 participants with mild hepatic impairment) will be recruited in parallel with participants of Group 3 (8 participants with moderate hepatic impairment). After completion of enrollment of both Group 2 and Group 3, Group 1 consisting of 8 healthy participants will be recruited to match the group mean value to the participants of Group 2 and Group 3 regarding age (± 10 years; ≥ 18 years old and ≤ 79 years old), and weight (± 10%; ≥ 50 kg and ≤ 120 kg). Efforts will also be made to have adequate sex representation in Group 1 (+ 2/- 2 male or female participants) that is similar to Groups 2 and 3. Up to 4 additional participants may be recruited in Group 1 for matching purpose.

Disclosure Statement:

This is an open-label, parallel group PK study with 3 arms.

Number of Arms: 3

Blinding: No blinding

Number of Participants:

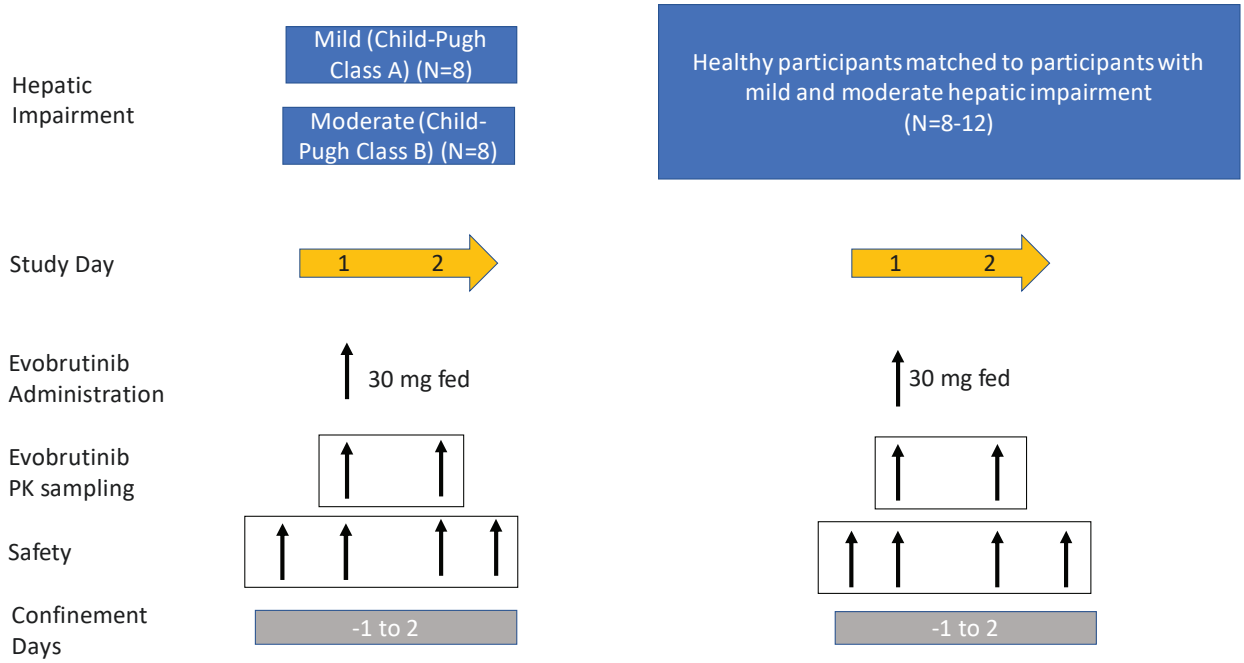
A maximum of 28 participants will be assigned to study intervention such that approximately 24 to 28 evaluable participants complete the study. Each of the 3 groups is planned to include 8 participants. Up to 4 additional participants may be added into Group 1 for matching purpose. Based on the observed total variability of the primary PK endpoints for similar doses of evobrutinib in the most recent Phase I studies, the coefficient of variation (CV) of the geometric mean for AUC and C_{max} is expected to be between 30% and 60%.

Study Intervention Groups and Duration:

The duration of the study will be up to 33 days: Participants will be screened between Day -28 to Day -2, dosing will occur on Day 1, PK sampling and safety assessments will occur on Day 1 through to Day 2 and the Follow-Up visit between Day 4 and Day 6.

Involvement of Special Committee(s): No

1.2 Schema



Abbreviations: PK= Pharmacokinetics

1.3 Schedule of Activities

Assessments & Procedures	Screening (Baseline if Day -1 value not available)	Study Day			Follow-Up/ Discontinuation	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**4 to 6**	**Day -1 value will be used as baseline if available. For ECG and vital sign, Day 1 predose value will be used as baseline.**
Informed Consent	X					Prior to any screening activity
Inclusion and Exclusion Criteria	X	X				
Demography	X					
Hospitalization		X	X	X		Participants may be discharged 32 hours after administration of study intervention
Full Physical Examination	X	X				
Medical History (includes substance usage)	X					Substances: drugs, smoking history, alcohol intake, use of caffeine or xanthine-containing beverages
Ultrasound and Assessment of Encephalopathy	X					For participants with hepatic impairment only
Serum Pregnancy Test (WOCBP only)	X	X			X	
Drug and Alcohol Test	X	X				See Appendix 5
Clinical Laboratory Tests	X	X		X	X	See Appendix 5
12-lead ECG	X		X		X	Single ECG assessments will be conducted; Day 1: at predose (as baseline) and 1 hour postdose
Vital Signs	X	X	X	X	X	Includes height & weight collected at Screening only Day 1: at predose (as baseline) and 1 hour postdose; Day 2 at 32 hours postdose. See Section 8.2.2.
CCI						

Assessments & Procedures	Screening (Baseline if Day -1 value not available)	Study Day			Follow-Up/ Discontinuation	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**4 to 6**	**Day -1 value will be used as baseline if available. For ECG and vital sign, Day 1 predose value will be used as baseline.**
Administration of Study Intervention			X			Administration will occur 30 mins after starting a standard breakfast
AE & SAE Review	X	X	X	X	X	
Concomitant Medication Review	X	X	X	X		
PK sampling			X	X		Predose, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 32.0 hours postdose. See Section 8.5.
PK sampling for free fraction			X			1.5, 4, and 12 hours postdose. No separate blood collected. Backup samples will be used See Section 8.5

Abbreviations: AE = Adverse event; ECG = Electrocardiogram; PK= Pharmacokinetics; SAE = Serious adverse event; WOCBP = woman of childbearing potential

2 Introduction

Evobrutinib is an oral, selective, irreversible inhibitor of Bruton's tyrosine kinase (BTK) which is in clinical development for the treatment of autoimmune diseases, e.g., multiple sclerosis (MS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE).

Detailed information on the chemistry, pharmacology, efficacy, and safety of evobrutinib is in the current version of the Investigator's Brochure (IB).

2.1 Study Rationale

The purpose of the study is to describe the evobrutinib pharmacokinetics (PK) in participants with different stages of hepatic impairment compared to a control group of participants with normal hepatic function. The results of this study will contribute to the understanding of the evobrutinib metabolism and inform recommendations on dose adjustments in participants with hepatic impairment.

2.2 Background

Evobrutinib (also known as M2951 and MSC2364447C) is an oral, selective, irreversible inhibitor of BTK. Bruton's tyrosine kinase is a crucial intracellular kinase in the B cell antigen receptor (BCR) signaling pathway. The mode of action of evobrutinib and nonclinical data support clinical development in a broad spectrum of autoimmune and inflammatory disorders involving aberrant B cell and myeloid cell activity. Inhibition of BTK is expected to achieve profound B cell silencing. Thus, BTK inhibition could provide clinical benefit in the treatment of multiple autoimmune diseases including RA, SLE, and MS.

CCI [redacted]

CCI [redacted]

Additional details of the safety, efficacy, and PK of evobrutinib may be found in the current version of the IB.

2.3 Benefit/Risk Assessment

As of July 31, 2019, approximately 1,214 adults have been exposed to evobrutinib including healthy participants, participants with relapsing multiple sclerosis (RMS), SLE, or RA, and participants with renal impairment. Evobrutinib was generally well tolerated in all participants. The treatment-emergent adverse events (TEAE)s have been primarily mild to moderate in severity.

The aim of the study is to describe PK of evobrutinib in participants with different stages of hepatic impairment compared to a healthy control group. The results of this study will contribute to the understanding of the evobrutinib metabolism and inform recommendations on dose adjustments in participants with hepatic impairment.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AE)s of evobrutinib may be found in Section 4.2 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

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) [evobrutinib]		
Identified risks: 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 see 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 within a week of treatment with evobrutinib.	As a single low dose of evobrutinib will be administered in this study, and given the short half-life of evobrutinib, worsening of liver function is unlikely to occur. Study participants will be confined, and liver tests will be monitored during the study.
Potential risks: Embryo-fetal toxicity	Based on nonclinical findings, embryo-fetal toxicity is considered as an important potential risk in participants exposed to evobrutinib.	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 120 days after the last dose and agree not to donate eggs for reproduction.

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

2.3.2 Benefit Assessment

The aim of the study is to describe the PK of evobrutinib in participants with different stages of hepatic impairment compared to a healthy control group. The results of this study will contribute to the understanding of the evobrutinib metabolism and inform recommendations on dose adjustments in participants with hepatic impairment. Therefore, participants will contribute to the process of developing new therapies in areas of unmet need where evobrutinib could be used.

2.3.3 Overall Benefit: Risk Conclusion

The risk minimization proposed in this study includes a low dose of evobrutinib, single dosing and site admission of the study participant for the duration of the study to allow continuous safety monitoring. This clinical study will be conducted in compliance with the clinical study protocol, International Council for Harmonization and Good Clinical Practices (ICH GCP), and any additional applicable regulatory requirements.

Considering the potential risks and the measures taken to minimize risk to participants in this study, the conduct of the study is considered as justified in the participants with hepatic impairment.

3 Objectives and Endpoints

Objectives	Endpoints
Primary	
To investigate the PK of evobrutinib after a single dose to participants with hepatic impairment compared to participants with normal hepatic function	$AUC_{0-\infty}$, and C_{max}
Secondary	
To assess the safety and tolerability of evobrutinib when administered as a single dose to participants with normal hepatic function and with impaired hepatic function	Occurrence of treatment-emergent adverse events (TEAEs), changes from Baseline in laboratory safety tests, 12-lead ECG morphology and time intervals (PR, QRS, RR, QT, and QTcF), and vital signs from time of first dose to the End of Study
To characterize the effect of hepatic function on the PK of evobrutinib through secondary PK endpoints	t_{max}, $t_{½}$, AUC_{0-12} and AUC_{0-24}, AUC_{0-t}, CL/f, V_Z/f, unbound fraction in plasma (f_u), AUC for unbound drug from time zero to infinity ($AUC_{0-\infty,u}$), unbound C_{max} ($C_{max,u}$), and unbound apparent oral clearance ($CL_{,u}$/f)
Tertiary/Exploratory	
Not applicable.	

4 Study Design

4.1 Overall Design

This is an open-label, nonrandomized, parallel-group, single-center, single oral dose, Phase I study to investigate the PK and safety of evobrutinib in participants with different degrees of hepatic impairment compared to participants with normal hepatic function.

Participants with hepatic impairment will be assigned to a group of mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment at Screening by use of the Child-Pugh system (Table 1 and Table 2) and, in addition to participants with normal hepatic function, assigned to one of the following groups:

- Group 1: normal hepatic function
- Group 2: mild hepatic impairment
- Group 3: moderate hepatic impairment

Participants of Group 2 (8 participants with mild hepatic impairment) will be recruited in parallel with participants of Group 3 (8 participants with moderate hepatic impairment). After completion

of enrollment of both Group 2 and Group 3, Group 1 consisting of 8 healthy participants will be recruited to match the group mean value to the participants of Group 2 and Group 3 regarding age (± 10 years; ≥ 18 years old and ≤ 79 years old), and weight (± 10%; ≥ 50 kg and ≤ 120 kg). Efforts will also be made to have adequate sex representation in Group 1 (+2/-2 male or female participants) that is similar to Groups 2 and 3. Up to 4 additional participants may be recruited in Group 1 for matching purpose.

Table 1 Child-Pugh Grades/Class of Hepatic Impairment

Child-Pugh Score	Child-Pugh Grade/Class	Severity of Hepatic Impairment
5-6	A	Mild
7-9	B	Moderate
10-15	C	Severe[a]

a Participants with severe hepatic impairment will not be included in this study.

Table 2 Child-Pugh Criteria (FDA – Guidance for Industry, 2003)

	Points Scored for Observed Findings		
	1	2	3
Encephalopathy grade[a]	none	1 or 2	3 or 4
Ascites[b]	absent	slight	moderate
Serum bilirubin (mg/dL)	< 2	2 to 3	> 3
Serum albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prothrombin time, sec prolonged	< 4	4 to 6	> 6

a Encephalopathy will be assessed by an experienced physician at Screening using the following criteria:
- Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
- Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2 to 3 cycles per second delta activity.

b Ascites will be assessed by an experienced physician by physical examination as well as ultrasound examination at Screening using the following criteria:
- Absent: No ascites is detectable by manual and also not by ultrasound investigation.
- Slight: Ascites palpitation doubtful, but ascites measurable by ultrasound investigation.
- Moderate: Ascites detectable by palpitation and by ultrasound investigation.

Grading of hepatic impairment with the Child-Pugh system, including ultrasound examination for detection and classification of ascites as well as assessment of hepatic encephalopathy, will only be performed on participants with hepatic impairment.

The duration of the study will be up to 33 days: Participants will be screened between Day -28 to Day -2, dosing will occur on Day 1, PK sampling and safety assessments will occur on Day 1 through to Day 2 and the Follow-Up visit between Day 4 and Day 6.

4.2 Scientific Rationale for Study Design

A parallel design with a small number of participants with hepatic impairment and controls with normal hepatic function is the standard design for hepatic impairment studies, in line with the FDA and EMA guidance/guidelines (FDA Guidance for Industry 2003, EMA Guideline CPMP/EWP/2339/02 2005).

In a CYP3A4 drug-drug interaction (DDI) study with evobrutinib (study MS200527-0054, a Phase I, open-label, single-sequence, three-period trial to investigate the effect of CYP3A4 inhibitors on the PK of M2951 in 16 healthy participants), an approximately 3-fold decrease of clearance was observed in participants receiving evobrutinib concurrently with the moderate (fluconazole) and the strong (itraconazole) CYP3A4 inhibitor. Assuming similar magnitude of increase in half-life for evobrutinib in the moderate hepatic impairment group, the predicted half-life would be 6 hours (increased 3 folds from 2 hours under normal condition) for the moderate hepatic impairment group. Therefore, sampling until 32 hours is sufficient for this study. Since evobrutinib showed concentration independent protein binding in human plasma, limited samples will be taken for free fraction measurement at 1.5 hours (anticipated peak concentration) and 12 hours (anticipated trough concentration when given BID). Considering the PK profile of evobrutinib, free trough concentration at 12 hours (anticipated trough concentration when given BID) may not be measurable, therefore one additional sample will be taken at 4 hours in order to have measurable free concentration at lower concentration range. Since there is no pharmacologically active metabolite, metabolite PK profile will not be evaluated in this study.

4.3 Justification for Dose

Evobrutinib exposure increased when given with either a high-fat or low-fat meal. Mean $AUC_{0-\infty}$ and C_{max} following administration of the tablet formulation increased by 70% and 27%, respectively, following a high-fat meal, and 50% and 25%, respectively, following a low-fat meal. The oral dose of 30 mg evobrutinib 30 minutes after a standard meal in this study is expected to have an exposure similar to the exposure achieved at 50 mg dosed under fasted condition, which was the dose used in the moderate (fluconazole) CYP3A4 inhibitor group in the CYP3A4 DDI study. Based on published data (de Jong 2015, de Jong 2017, de Jong 2018) for ibrutinib (a similar BTK inhibitor), the effect of mild/moderate hepatic impairment on exposure (~4-fold higher AUC for mild hepatic impairment and ~10-fold higher AUC for moderate hepatic impairment) was similar to the effect of a moderate CYP3A4 inhibitor (6-fold higher AUC with voriconazole). Therefore, assuming a similar effect for evobrutinib, the CYP3A4 DDI study outcome can be used to predict the change of exposure in participants with impaired hepatic function for evobrutinib. Given the ~3-fold increase in evobrutinib exposure observed with concurrent administration of a moderate CYP3A4 inhibitor (fluconazole) (MS200527-0054), a similar fold increase in evobrutinib exposure is expected in the mild/moderate hepatic impairment groups. The dose of 30 mg under fed conditions is lower than the intended commercial dose (45 mg under fed conditions). It was selected for this study in consideration of the potential 3-fold increase of exposure in mild/moderate hepatic impairment participants to ensure evobrutinib exposure remains below the level observed at the highest single dose of 500 mg and the highest multiple dose of 200 mg under fasted conditions in the first in human study.

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study parts, including the last scheduled procedure shown in Section 1.3.

The end of the study is defined as the date of the last scheduled procedure shown in Section 1.3 for the last participant in the study.

A clinical study protocol may not be considered closed as long as:

- Any participant is still receiving any study intervention.
- Visits specified by the protocol are still taking place.
- Procedures or interventions according to the protocol are still being undertaken in any participant.
- The postintervention follow-Up period, defined in the clinical study protocol as being part of the study, has not yet been completed for any participant.

5 Study Population

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

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

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

5.1 Inclusion Criteria

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

Age

1. Are between 18 and 79 (inclusive) years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. **For participants with normal hepatic function only:** 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.

   OR

For participants with moderately impaired hepatic function only: Is considered to have moderately (Child-Pugh class B and confirmed liver cirrhosis) impaired hepatic function and has been clinically stable for at least 1 month prior to Screening.

OR

For participants with mildly impaired hepatic function only: Is considered to have mildly (Child-Pugh class A and confirmed liver cirrhosis) impaired hepatic function and has been clinically stable for at least 1 month prior to Screening.

Weight

3. Have a body weight within 50.0 and 120.0 kg (inclusive) and body mass index (BMI) within the range 19.0 and 36.0 kg/m^2 (inclusive).

Sex

4. Are male or female

Contraceptive use by females will be consistent with local regulations on contraception methods for those participating in clinical studies.

a. Female Participants:

- Are **not** pregnant or breastfeeding, and at least one of the following conditions applies:
  - **Not** a woman of childbearing potential (WOCBP)

  OR

  - If a WOCBP, use 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:
    - 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.

      AND
      - A barrier method, as described in Appendix 3.
    - During the intervention period
    - After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 120 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.

- Have a negative serum pregnancy test, as required by local regulations, within 24 hours before the first dose of study intervention.

- Additional requirements for pregnancy testing during and after study intervention are in Section 8.2.4.
- 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. Capable of giving signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

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

Medical Conditions

1. Clinical history of autoimmune disorder with hepatic influence (Hashimoto thyroiditis and rheumatic diseases allowed).
2. Diseases and surgeries of the gastrointestinal tract, which could influence the gastrointestinal anatomy and mobility. Prior history of cholecystectomy or inflammatory bowel disease, and any clinically relevant surgery within 6 months prior to Screening.
3. History of any malignancy.
4. History of chronic or recurrent acute infection or any bacterial, viral, parasitic or fungal infections within 30 days prior to Screening and at any time between Screening and admission, or hospitalization due to infection within 6 months prior to Screening.
5. History of shingles within 12 months prior to Screening.
6. History of drug hypersensitivity, ascertained or presumptive allergy/hypersensitivity to the active drug substance and/or formulation ingredients; history of serious allergic reactions leading to hospitalization or any other hypersensitivity reaction in general, which may affect the safety of the participant and/or outcome of the trial per the Investigator's discretion.
7. History of alcoholism within 6 months prior to Screening or drug abuse within 2 years prior to Screening.
8. History of heavy smoking (more than 10 cigarettes a day) within 3 months prior to Screening.
9. Renal dysfunction (estimated glomerular filtration rate < 60 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease equation).

10. History of residential exposure to tuberculosis, or a positive QuantiFERON® or T SPOT® test within 4 weeks prior to Screening.
11. Administration of live vaccines or live-attenuated virus vaccines within 3 months prior to Screening.
12. Significant central nervous system disease (e.g., seizures) which the Investigator considers will interfere with the informed consent, conduct, and completion of the study or constitutes an unacceptable risk to the participants.
13. History of Grade >2 esophagus varices with gastrointestinal bleeding within 3 months prior to Screening.
14. **For participants with impaired hepatic function**: Primary and secondary biliary cirrhosis.
15. **For participants with impaired hepatic function**: Clinical evidence of severe ascites.
16. **For participants with impaired hepatic function**: Hepatic encephalopathy Grade >1.

Prior/Concomitant Therapy

17. Moderate or strong inhibitors or inducers of CYP3A4 and substrates of CYP3A4 within 4 weeks prior to the first administration of study intervention.
18. H2-blocker and proton pump inhibitors within 48 hours of the first study intervention administration.
19. Inhibitor or inducers of P-gp, BCRP, OATPs and OCT1 within 5 days prior to the first study intervention administration.
20. **For participants with normal hepatic function**: Use of any prescribed medicine or over-the-counter drug (other than occasional paracetamol or ibuprofen) or dietary supplement including herbal remedies, vitamins, and minerals within 2 weeks or 5 times the half-life of the respective drug, whichever is the longer, prior to the first administration of study intervention.
21. **For participants with impaired hepatic function**: Addition of new prescribed medicine or over-the-counter drug (other than occasional paracetamol or ibuprofen) or dietary supplement including herbal remedies, vitamins, and minerals within 2 weeks or 5 times the half-life of the respective drug, whichever is the longer, prior to the first administration of study intervention.

Prior/Concurrent Clinical Study Experience

22. Use of any investigational drug in any clinical study within 30 days or 5 half-lives of the investigational drug, whichever is longer, prior to Study Day 1 administration, or have used an experimental monoclonal antibody within the past 1 year prior Study Day 1, or have participated in any study evaluating a BTK inhibitor, regardless of duration since participation, 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 Screening.

Diagnostic Assessments

23. **For participants with normal hepatic function:** Supine systolic blood pressure > 139 mmHg or < 95 mmHg if ≤ 65 years old or > 159 mmHg or < 95 mmHg if > 65 years old, diastolic blood pressure > 90 mmHg or < 50 mmHg and pulse rate > 100 or ≤ 50 bpm, at admission (Day -1) (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).
24. **For participants with impaired hepatic function:** Supine systolic blood pressure > 170 mmHg or < 95 mmHg, diastolic blood pressure > 95 mmHg or < 50 mmHg and pulse rate > 100 or ≤ 50 bpm, at admission (Day -1) (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).
25. **For participants with normal hepatic function**: 12-Lead ECG showing a QTcF > 470 ms, PR > 220 ms, or QRS > 120 ms.
26. **For participants with impaired hepatic function:** 12-Lead ECG showing a QTcF > 480 ms, PR > 220 ms, or QRS > 120 ms.
27. Platelet count less than 50 x 10^9 L.
28. Positive for human immunodeficiency virus 1 and 2 antibodies at Screening.
29. Positive QuantiFERON® or T SPOT® test within 4 weeks prior to Screening.
30. **For participants with normal hepatic function**: Liver function tests (i.e., ALT, AST, GGT, total bilirubin, lipase and amylase) > 1.5x upper limit of normal (ULN).
31. **For participants with normal hepatic function**: Positive for hepatitis B surface antigen (HBsAg), hepatitis B core antibody, hepatitis C antibody at Screening.
32. **For participants with impaired hepatic function**: Evidence of recent infection with hepatitis B and/or hepatitis C within 6 months. Participants with chronic hepatis B or C (duration > 6 months) are eligible for enrollment.

Other Exclusions

33. Consumption of an average weekly intake of > 14 drinks/week for men or > 7 drinks/week for women. One drink is equivalent to (12 g alcohol) = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of 80 proof distilled spirits.
34. Positive for drugs of abuse or alcohol on Screening or at admission (Day -1).
35. 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.
36. Herbal supplements including, but not limited to, St. John's wort, grapefruit, Seville oranges, cranberries, or juices of these fruits within 14 days prior to the first administration of study intervention.
37. Donation or loss of more than 250 mL of blood in the 60 days prior to Screening.

38. 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.
39. Any condition, including findings in the laboratory tests, medical history, or other screening assessments, that in the opinion of the Investigator constitutes an inappropriate risk or a contraindication for participation in the trial or that could interfere with the trial's objectives, conduct, or evaluation.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, cranberries or cranberry juices, and St. John's wort from 14 days before the start of study intervention until after the final dose.

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic (PD) sample.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or PD sample and will abstain from cannabinoid-containing products from Screening until after collection of the final PK and/or PD sample.
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

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). This restriction lasts until the Follow-Up/Discontinuation visit.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants will be assigned a new participant number.

6 Study Intervention(s)

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

6.1 Study Intervention(s) Administration

ARM name	Group 1: normal hepatic function Group 2: mild hepatic impairment Group 3: moderate hepatic impairment
Intervention Name	Evobrutinib
Type	Drug
Dose Formulation	Film-coated tablet
Unit Dose Strength(s)	10 mg
Dose Amount	Participants will receive a single evobrutinib dose of 30 mg as three 10 mg film-coated tablets. For further details, see Section 6.6.
Frequency	Single dose
Route of Administration	Oral
Use	Experimental
Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP)	IMP: evobrutinib
Manufacturer/supplier:	The Sponsor will supply evobrutinib.
Packaging and Labeling:	Evobrutinib will be provided in PE-bottles. Each PE-bottle will be labeled per country requirement.

6.1.1 Medical Device(s)

Not applicable.

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 Pharmacy 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 Pharmacy manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

On Day 1 participants will be assigned a unique number (participant number) in ascending numerical order at the study site. The participant number encodes the participant's assignment to one of the 3 arms of the study. Participants will be assigned to each of the treatment groups based on their level of hepatic function and, thus, no randomization procedures will be applied.

6.3.2 Blinding

Blinding Method

Not applicable as this is an open-label study.

Assignment Method Retention

Not applicable.

6.3.3 Emergency Unblinding

Not applicable as this is an open-label study.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the Case Report Form (CRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. The Investigator will ensure that the information entered into the electronic Case Report Form (eCRF) regarding study intervention administration is accurate for each participant. Any reason for noncompliance should be documented.

Noncompliance is defined as a participant missing 1 dose of study intervention.

6.5 Concomitant Therapy

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

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

Additional information on prohibited medicines is provided in Section 6.5.3.

6.5.1 Rescue Medicine

The study site will not supply rescue medication.

6.5.2 Permitted Medicines

The only permitted medications are the following:

- Paracetamol up to 1,500 mg daily or ibuprofen up to 800 mg daily, at the discretion of the Investigator.

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

For participants with mild and moderate hepatic impairment, treatment with chronic stable medications necessary for maintaining the clinical status of the participant will be permitted if prescribed by the participant's personal physician and approved by the Investigator, in consultation with the Sponsor or designee as needed. Administration of medications should be withheld for at least 2 hours predose and 4 hours postdose as clinically appropriate, except for the prohibited medications as described in Section 6.5.3.

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

6.5.3 Prohibited Medicines

The following treatments and therapies are not permitted during this study:

- H2-blocker and proton pump inhibitors within 48 hours prior to the first study intervention administration until 6 hours after study intervention administration.
- Antacids within 2 hours of dosing (2 hours prior to dosing and 2 hours after the dosing).
- Herbal supplements including, but not limited to, St. John's wort; grapefruit, Seville oranges, cranberries, or juices of these fruits within 2 weeks prior to the first study intervention administration until the Follow-Up visit.
- Moderate or strong inhibitors or inducers of CYP3A4 within 4 weeks prior to the first administration of study intervention until the Follow-Up visit.
- Inhibitor or inducers of P-gp, BCRP, OATPs and OCT1 within 5 days prior to the first study intervention administration until the Follow-Up visit.
- **For participants with normal hepatic function**: The participants are prohibited from using prescription or over-the-counter medications (apart from paracetamol or ibuprofen, as judged appropriate by the Investigator) or dietary supplement including herbal remedies, vitamins, and minerals within 2 weeks or 5 half-lives, whichever is longer, prior to the first study intervention administration during the study, and until the Follow-Up visit.
- **For participants with impaired hepatic function:** Addition of any medication is prohibited, which includes prescribed medicine, over-the-counter drug (other than occasional paracetamol or ibuprofen) or dietary supplement including herbal remedies, vitamins, and minerals within 2 weeks or 5 times the half-life of the respective drug, whichever is the longer, prior to the first administration of study intervention and until the Follow-Up visit.

6.5.4 Other Interventions

Additional restrictions that study participants should adhere to from Day -1 until the Follow-Up/Discontinuation visit are detailed in Section 5.2.

6.6 Dose Selection and Modification

The participants will receive the following treatment during the study:

- A single oral administration of 3 x 10 mg film-coated tablets of evobrutinib under fed conditions

All participants will receive the study intervention after they have completed a standard breakfast. Drug administration will be 30 minutes after start of the intake of a standard breakfast with 240 mL of water. Participants should eat this meal within 25 minutes. The participants will remain fasting for 2 hours when a standardized snack will be provided and at 4 hours a standardized lunch will be served.

The standard breakfast will contain approximately 500 calories and will be balanced in macronutrients (approximately 50% carbohydrates, 25% protein, and 25% fat). The menu must be approved by the Sponsor. The participant will be expected to eat the entire meal. The percentage consumed will be recorded for all participants. A deviation will be recorded if the participant eats less than 90% of the meal. Participants will not be excluded from dosing if they are unable to complete the entire meal.

6.7 Study Intervention after the End of the Study

After a participant with hepatic impairment has completed the study or has withdrawn early, the pre-study treatment will be continued, if required, in accordance with generally accepted medical practice. In the healthy participants, no further treatment or medical care is planned or required after the end of the study.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Not applicable since evobrutinib is administered only once in the study.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time, at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of discontinuing from the study, if possible, a discontinuation visit will be conducted, as listed in the Schedule of Activities (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 withdraws consent for future involvement in 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.

- A participant has the right at any time to request destruction of any biological samples taken. The investigator will document this in the site study records.

In case a participant must be withdrawn from the study, the Medical Monitor and clinical study leader for the Sponsor will be informed immediately.

If there is a medical reason for the withdrawal, appropriate medical care will be provided.

Participants who withdraw from the study prior to the first administration of study intervention or for any reason do not have a full PK dataset may be replaced. A discussion should occur between the Investigator and the Sponsor regarding whether a replacement may be considered.

7.3 Lost to Follow-Up

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

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

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

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA (Section 1.3).
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the 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 and were performed within the time frame defined in the SoA (Section 1.3).
- A maximum of 200 mL of blood will be collected in any one-month period from each participant in the study, including any extra assessments that may be required.

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, 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 8.3.1.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators will pay special attention to clinical signs related to previous serious illnesses.
- Any physical examination abnormality findings which are clinically significant, before the ICF is signed, will be captured on the eCRF. After the ICF is signed, new physical exam abnormality findings will be captured on the AE form.

8.2.2 Vital Signs

- Height and weight will be measured at Screening and recorded.
- Tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

- 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).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. ECG assessments will be done after 5 minutes rest in supine position.

8.2.4 Clinical Safety Laboratory Assessments

Blood samples will be collected in a fasted condition (after a fast of at least 8 hours).

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5 at the time points 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 the local laboratory.
- The Sponsor will receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study will be forwarded to the Sponsor or designated organization.
- The Investigator will review each laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports will be filed with the source documents.
- Additional serum or highly sensitive urine pregnancy tests may be conducted, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study.

8.2.5 Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

8.3 Adverse Events and Serious Adverse Events

- The definitions of an AE and a Serious Adverse Event (SAE) are in Appendix 4.
- The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious or that caused the participant to discontinue the study, as specified in Section 8.3.3.

- Requests for follow-up will usually be made via the Study Monitor, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

- All SAEs will be collected from the signing of the ICF until the Follow-Up Visit/Discontinuation Visit at the time points 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 AEs will be collected from the signing of the ICF until Follow-Up Visit/Discontinuation Visit at the time points specified in the SoA.
- AEs/SAEs that begin before the start of study intervention but after obtaining ICF will be recorded on the Medical History/Current Medical Conditions CRF, not on the AE CRF.
- 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 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.

8.3.2 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.

8.3.3 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 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.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Individual Case Safety Reports will be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

An Investigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g., Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will review and then file it along with the Investigator Brochure in the Investigator's Site File and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the end of the reporting period defined in Section 8.3.1.
- If a pregnancy is reported, the Investigator will inform the Sponsor within 24 hours of learning of the pregnancy and will follow the procedures specified below for collection of pregnancy information.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Collection of Pregnancy Information

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while she is in the study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of the pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to

8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- 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.
- 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 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.4 Treatment of Overdose

For this study, any dose of evobrutinib greater than the maximum dose in the study within a 24-hour time period will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

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

8.5 Pharmacokinetics

The following PK parameters will be calculated from the individual plasma concentration-time data, when appropriate:

Symbol	Definition
$AUC_{0\text{-}tlast}$	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0\text{-}12}$ and $AUC_{0\text{-}24}$	The area under the concentration-time curve (AUC) from time zero (= dosing time) to 12 or 24 hours at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0\text{-}\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at $t_{last,}$ as estimated using the linear regression from λ_z determination. $AUC_{0\text{-}\infty} = AUC_{0\text{-}tlast} + C_{last\ pred}/\lambda_z$.
C_{max}	Maximum observed concentration.
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (i.e., 1st occurrence in case of multiple/identical C_{max} values).
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$.

Symbol	Definition
CL/F	Apparent total plasma clearance after oral administration. CL/F = Dose $_{p.o.}$ /$AUC_{0-\infty}$.
V_Z/F	Apparent volume of distribution during terminal phase after oral administration. V_z/F = Dose/($AUC_{0-\infty}$*λ_z) following single dose.
f_u	Free or unbound fraction of evobrutinib calculated as free concentration/total concentration (For each participant, 3 samples will be analysed to determine a percent of free fraction or unbound evobrutinib. The values from these samples if measurable will be used to estimate a mean percentage).
$AUC_{0-\infty,u}$	Calculated as f_u * $AUC_{0-\infty}$
$C_{max, u}$	Calculated as f_u * C_{max}
$CL_{,u}$/F	Calculated as Dose $_{p.o.}$ /$AUC_{0-\infty,u}$

Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of evobrutinib. Collection times are specified in the SoA (Section 1.3). The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration. The sampling timing may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

The quantification of evobrutinib in plasma will be performed using a validated LC-MS/MS assay. Concentrations will be used to evaluate the PK of evobrutinib. The free fraction of evobrutinib sample will not be drawn separately but will be analyzed from the PK back up samples at 1.5, 4 and 12 hours.

Remaining samples collected for analyses of evobrutinib concentrations may also be used to evaluate safety or PD aspects related to concerns arising during or after the study. Full details of the bioanalytical methods will be described in a separate bioanalytical report.

Details on processes for collection and handling of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the End of Study are specified in the respective ICF.

PK parameters will be derived using noncompartmental methods with the validated computer program Phoenix® WinNonlin® (version 6.4 or higher; Certara, L.P., Princeton, New Jersey, USA).

The exact date/time of sample collection and drug administration (24-hour clock time) must be recorded in the eCRF and will be used in the calculation of PK parameters. The accepted time deviations from planned PK times that will not be considered a protocol violation are listed below:

Procedure	Time Point (Relative Time)	Window Allowance
PK	Predose	- 60 min
	0.25 to 1 h postdose	- 2 / + 2 min
	> 1 h to 12 h postdose	- 5 / + 5 min
	> 12 h to 32 h postdose	- 15 / + 15 min

The predose sample will be considered as if it had been taken simultaneously with the administration of study intervention.

8.6 Pharmacodynamics

Not applicable.

CCI

[redacted]

8.8 Biomarkers

Not applicable.

8.9 Immunogenicity Assessments

Not applicable.

8.10 Health Economics

Not applicable.

9 Statistical Considerations

Details of the statistical analyses will be described in a separate Integrated Analysis Plan.

9.1 Statistical Hypotheses

No formal statistical hypothesis will be tested, as the study is designed to be descriptive.

9.2 Sample Size Determination

It is of note that the number of participants in special population studies should be limited due to feasibility constraints, since participants with hepatic impairment are in general difficult to recruit. Thus, the sample size is partially based on experience from previous Phase I studies with other candidate drugs to obtain adequate safety, tolerability, and PK data to achieve the objectives of the study while exposing as few participants as possible to the study intervention and procedures.

The aim of the comparison between participants with moderate (or mild) hepatic impairment and healthy participants is to characterize possible differences in the PK primary endpoints $AUC_{0-\infty}$ and C_{max} in the hepatic impaired and normal participants.

CCI

CCI

A maximum of 28 participants will be assigned to study intervention such that approximately 24 to 28 evaluable participants complete the study. Each of the 3 groups is planned to include 8 participants. Up to 4 additional participants may be added into Group 1 for matching purpose.

9.3 Populations for Analyses

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

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 Population is a subset of the Safety Analysis Population 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 (BLQ) is considered a valid measurement. Participants will be analyzed according to the actual treatment they received. All PK analyses will be based on the PK Analysis Population.

9.4 Statistical Analyses

Statistical analysis will be performed using the computer program package SAS® System for Windows™ (release 9.4 or later version; SAS Institute, Cary NC, USA).

All data will be evaluated as observed; no imputation method for missing values will be used. If not otherwise specified, 'baseline' refers to the last scheduled measurement before administration of the study intervention. If no baseline exists, then the baseline value will be treated as missing.

All data recorded during the study will be presented in individual data listings performed on the Safety Analysis Set, as appropriate.

Further details on the statistical analysis will be presented in the Integrated Analysis Plan that will be finalized prior to database lock.

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 intervention. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Participants who prematurely withdrew from the study will be displayed in a by-participant listing, and summarized by primary withdrawal reason.

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, coagulation and clinical chemistry) will be summarized by time point including both absolute values and changes from baseline. Urinalysis parameters will be listed.

Vital signs and ECG parameters will be listed by participant including changes from baseline, and summarized by treatment and time point using descriptive statistics.

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

Endpoint	Statistical Analysis Methods
Primary	No primary safety endpoints
Secondary	
Nature, occurrence, and severity of treatment-emergent adverse events (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 Medical Dictionary for Regulatory Activities 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 and data listings of abnormalities.
12-lead electrocardiograms (ECGs) (morphology and time intervals [PR, QRS, RR, QT and corrected QT intervals based on Fridericia formula, QTcF])	ECG data will be summarized by changes-from-baseline values by treatment using descriptive statistics. Clinical noteworthy ECG findings for individual participants will be listed and summarized as appropriate.
Vital signs assessed from time of first dose to end of study participation	Vital signs data will be summarized by changes-from-baseline values using descriptive statistics.
Tertiary/Exploratory	Not applicable

9.4.3 Other Analyses

Details on the PK analyses will be specified in the Integrated Analysis Plan that will be finalized before database lock. Integrated analyses across studies, such as the population PK analysis and PD analyses will be presented separately from the main clinical study report (CSR).

9.4.3.1 Analysis of Pharmacokinetics

An analysis of variance (ANOVA) model including hepatic function group as a fixed effect will be applied to log-transformed PK parameters $AUC_{0-\infty}$, and C_{max} of evobrutinib of the hepatic impairment groups (Child-Pugh class A and Child-Pugh class B) and control group (normal hepatic function). Separate models will be fitted for the comparison between the hepatic impairment groups (Child-Pugh class A and Child-Pugh class B) and the control group. For each parameter, differences between the hepatic impairment groups and the control group will be estimated on the log scale (group mean ratio) together with corresponding 90% CIs. The geometric least square means together with corresponding 95% CIs by hepatic function group will also be estimated. Point estimates and CIs will be back-transformed to the original scale.

The relationship between $AUC_{0-\infty}$ and C_{max} of evobrutinib and the hepatic function parameters (e.g., albumin-bilirubin score as continuous variable) will additionally be explored with a linear regression.

For secondary PK endpoints such as CL/f, $AUC_{0-\infty,u}$, $C_{max,u}$, and $CL_{,u}/f$, the same ANOVA and linear regression analyses like for the primary endpoints will be performed.

All primary and secondary PK endpoints (parameters) will be listed and will be descriptively summarized by hepatic impairment group using: number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max), geometric mean (Geomean), geometric coefficient of variation (GeoCV%) and graphically displayed. Individual plasma and mean concentration time plots will be provided for each treatment using linear (± SD) and semi-logarithmic scales.

The analysis of all primary and secondary PK endpoints of evobrutinib will be performed using the PK Analysis population.

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., Follow-Up/Discontinuation visit with all study data in-house, all data queries resolved, and the database locked.

There are no planned formal interim analyses.

10 References

de Jong J, Skee D, Murphy J, et al. Mannaert E. Effect of CYP3A perpetrators on ibrutinib exposure in healthy participants. Pharma Res Per. 2015;3:e00156.

de Jong J, Skee D, Hellemans P, et al. Single-dose pharmacokinetics of ibrutinib in subjects with varying degrees of hepatic impairment. Leukemia & Lymphoma. 2017;58:185-94.

de Jong J, Hellemans P, de Wilde S, et al. A drug–drug interaction study of ibrutinib with moderate/strong CYP3A inhibitors in patients with B-cell malignancies. Leukemia & Lymphoma. 2018;59:2888-95.

11 Appendices

Appendix 1 Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
BCR	B cell antigen receptor
BMI	Body mass index
BTK	Bruton's tyrosine kinase
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
CI	Confidence interval
CV	Coefficient of variation
CCI	[redacted]
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Council for Harmonization
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MS	Multiple sclerosis
PD	Pharmacodynamics
PK	Pharmacokinetics
RA	Rheumatoid arthritis
RMS	Relapsing multiple sclerosis
SAE	Serious Adverse Event
SLE	Systemic lupus erythematosus
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reactions

TEAE	Treatment-emergent adverse event
WOCBP	Woman of childbearing potential

Appendix 2 Study Governance

Financial Disclosure

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

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants or their legally-authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) 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 re-consented to the most current, approved version.
- A copy of the ICF(s) will be provided to the participant.
- The original signed and dated consent will remain at the Investigator's site and will be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date

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 his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

The study is planned to be conducted at a single site in Germany. This site is a clinical pharmacology unit.

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 appear in the following clinical studies registries: EU Clinical Trials Register and ClinicalTrials.gov.

Details of structures and associated procedures will be defined in a separate Standard Operation Procedures. The Clinical Research Organization (CRO), Covance, will be responsible for the following activities:

- Site management
- Data management
- Statistical programming and analysis
- PK analysis
- Medical writing
- Independent monitoring
- Medical monitoring
- Project management
- Regulatory services
- Safety management

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The Investigator will submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC will review and approve them 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 Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
  - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
  - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- 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 I 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.

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. In this case, a coordinating Investigator will be designated by agreement.
- 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 www.ClinicalTrials.gov as well as to the European Clinical Trial Database, if applicable. 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 drug and therefore may be disclosed as required to other clinical Investigators, to the US Food and Drug Administration, 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.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.
- Study Monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator will keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file will identify each participant, contain the following demographic and medical information for the participant, and will be as complete as possible:
  - Participant's full name, date of birth, sex, height, and weight
  - Medical history and concomitant diseases
  - Prior and concomitant therapies (including changes during the study)
  - Study identifier (i.e., the Sponsor's study number) and participant's study number.
  - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
  - Any medical examinations and clinical findings predefined in the protocol
  - All AEs

  - Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.
- All source data will be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document will have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records will be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic 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.
- The Study Monitors will use printouts of electronic files for source data verification. These printouts will be signed and dated by the Investigator and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in Source Data Identification Form.

Study and Site Start and Closure

First Act of Recruitment

- The study start date is the date when the clinical study will be open for recruitment.
- The first act of recruitment is when the site is opened and will be the study start date.

Study Closure and Site Termination

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further development of the Sponsor's compound
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study 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

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered 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.

A WOCBP is **not**:

1. Premenarchal
2. A premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

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

   For a female 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.
3. A postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
   - A female on HRT and whose menopausal status is 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.

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
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a 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.

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 is evaluated in relation to the duration of the study.

Acceptable Methods

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide. Male condom and female condom cannot be used together (due to risk of failure with friction)
- Cervical cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)

Contraceptive use by men or women is consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

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

Hormonal contraception may be susceptible to interaction with the study intervention(s), which may reduce the efficacy of the contraceptive method. As such, male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Acceptable methods are considered effective, but **not** highly effective (i.e., have a failure rate of ≥1% per year). Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are **not** acceptable methods of contraception.

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

AE Definition

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.
• **Events Meeting the AE Definition**
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • 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 a SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or a SAE if they fulfil the definition of an AE or SAE.
• **Events NOT Meeting the AE Definition**
• Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied. • 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).

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or 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 (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

d. Results in persistent disability/incapacity

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

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually considered as serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

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

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

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

If death occurs, the primary cause of death or event leading to death will be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

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 Investigator Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator will document in the medical notes that he/she has reviewed the AE/SAE and assessed causality.
- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.
- The Investigator may change his/her causality assessment after considering follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the Sponsor or its 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 Sponsor or its designee with a copy of any post-mortem findings including histopathology, if possible.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to Sponsor or its 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 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 data collection tool, specified below, to report the event within 24 hours.
- The site will enter the SAE data into the electronic system 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 is used 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 Pregnancies

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

Appendix 5 Clinical Laboratory Tests

Table 4 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelets		Mean Corpuscular Volume (MCV)	WBC Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Reticulocytes			
	Hemoglobin		MCH	
	Hematocrit Red blood cell count White blood cell counts			
Biochemistry	Blood Urea Nitrogen	Potassium	Aspartate Aminotransferase	Bilirubin
	Creatinine	Sodium	Alanine Aminotransferase	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Cholesterol
	Uric acid	Chloride	γ-Glutamyl-transferase	Triglycerides
	C-reactive protein	Inorganic Phosphate	Lactate dehydrogenase	Amylase
	Albumin			
	Urea	Magnesium	Creatinine phosphokinase	Lipase
Coagulation	• INR • PT			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	Serum at Screening, Day -1, and Follow-Up/Discontinuation assessment.			
Other Tests	• Follicle -stimulating hormone (FSH) and estradiol (as needed if **not** a WOCBP **only**) • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for a WOCBP). • Urine drug screen (to include at minimum: amphetamines, methamphetamines, barbiturates, ecstasy, cocaine, opiates, cannabinoids, benzodiazepines, methadone, phencyclidine, oxycodone, and tricyclic antidepressants) • Urine Microscopy, only if blood, protein, nitrite, or leukocyte esterase are positive on the dipstick • Serology (HIV I and II antibodies, hepatitis B surface antigen, hepatitis B core antibody, hepatis C antibody, Quantiferon® Test) • Thyroid stimulating hormone (TSH) • Alcohol breath test			


CCI

Appendix 7 Sponsor Signature Page

Study Title:	Phase I, Open-label, Single Dose Study to Investigate the Effect of Hepatic Impairment on the Pharmacokinetics (PK) of Evobrutinib (M2951)
Regulatory Agency Identifying Numbers:	EudraCT: 2020-001920-32
Clinical Study Protocol Version:	22 May 2020/Version 1.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	Medical Responsible
Institution:	Merck Healthcare KGaA an affiliate of Merck KGaA, Darmstadt, Germany
Address:	Frankfurter Str. 250, Darmstadt, Germany
Telephone number:	PPD Mobile: PPD
Fax number:	Not Applicable
E-mail address:	PPD

Appendix 8 Principal Investigator Signature Page

Study Title:	Phase I, Open-label, Single Dose Study to Investigate the Effect of Hepatic Impairment on the Pharmacokinetics (PK) of Evobrutinib (M2951)
Regulatory Agency Identifying Numbers:	EudraCT: 2020-001920-32
Clinical Study Protocol Version:	22 May 2020/Version 1.0
Site Number:	

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, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD PPD

Signature

PPD

Date of Signature

PP D

Name, academic degree:	PPD
Function/Title:	
Institution:	
Address:	
Telephone number:	
Fax number:	
E-mail address:	