Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of Evobrutinib on the QTc (Corrected QT) Interval in Healthy Adult Participants
Study Number:	MS200527_0070
Protocol Version:	01 December 2022/Version 3.0
Merck Compound:	Evobrutinib
Merck Registered Compound Name in Japan:	Not applicable
Study Phase:	Phase 1
Brief Title:	A TQT Study of Effect of Evobrutinib on Cardiac Repolarization
Principal Investigator:	PPD PPD
Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Strasse 250 Darmstadt, 64293, Germany In the US and Canada: EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA
Regulatory Agency Identifying Numbers:	EudraCT: 2022-002664-78

Keywords	Not applicable

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
3.0	Updated Protocol	01-December-2022
2.0	Updated Protocol	24-October-2022
1.0	Original Protocol	29-August-2022

Protocol Version 3.0 (01 December 2022)

Overall Rationale for the Amendment

This non-substantial protocol amendment was prepared to allow rescreening of participants that were not previously enrolled in the study due to personal or logistical reasons or due to minor deviations that were not considered clinically relevant. Additional, wording of inclusion criteria was changed to have more flexibility regarding ratio of sexes.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Wording regarding enrolment of women changed form ‘at least 30% of each sex’ to ‘approx. 30% or more of each sex’	Wording of inclusion criteria was changed to have more flexibility regarding ratio of sexes.
5.4 Screen Failures	Four exceptions for rescreening were introduced.	To allow rescreening of participants that were not previously enrolled in the study due to personal or logistical reasons or due to minor deviations that were not considered clinically relevant.

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1 Protocol Summary

1.1 Synopsis

Clinical Study Protocol Title: A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of Evobrutinib on the QTc (Corrected QT) Interval in Healthy Adult Participants

Brief Title: A TQT Study of Effect of Evobrutinib on Cardiac Repolarization

CCI This study is being conducted to assess potential effects of evobrutinib on cardiac repolarization (i.e. prolongation of QT interval).

CCI

Objectives and Endpoints:

Objectives	Endpoints	Ref. #
Primary		
To evaluate whether evobrutinib administered as a single oral dose (as solution) of 45 mg or 225 mg prolongs QT/QTc in comparison to placebo control	ΔΔQTcF (placebo-corrected change from baseline QTcF) for evobrutinib; with concentration-QTc analysis as primary analysis	1
Secondary		
To demonstrate QTc assay sensitivity	ΔΔQTcF (placebo-corrected change from baseline QTcF) for moxifloxacin	2
To assess the safety and tolerability of evobrutinib	Nature, occurrence, and severity of TEAEs Absolute values and changes in safety laboratory tests Vital signs assessed from time of first dose to end of study participation Single 12-lead ECGs evaluated by Investigator	3
To assess the effect of evobrutinib on other ECG parameters	QT, QTcB, QTcI, PR, QRS, RR, HR, cardiologist assessment including T-wave morphology, and U-wave	4
To determine the PK of evobrutinib CCI [redacted] at 45 mg and 225 mg oral dose (solution) under fasting conditions and moxifloxacin at 400 mg oral dose	AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, and t_{max} for evobrutinib and major metabolite AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, and t_{max} for moxifloxacin	5

Overall Design: This will be a Phase 1, single-center, randomized, double-blinded, placebo- and positive-(moxifloxacin) controlled, single-dose, 4-period crossover study.

Brief Summary: The purpose of this study is to assess potential effects of evobrutinib on cardiac repolarization (i.e. prolongation of QT interval). Study details include:

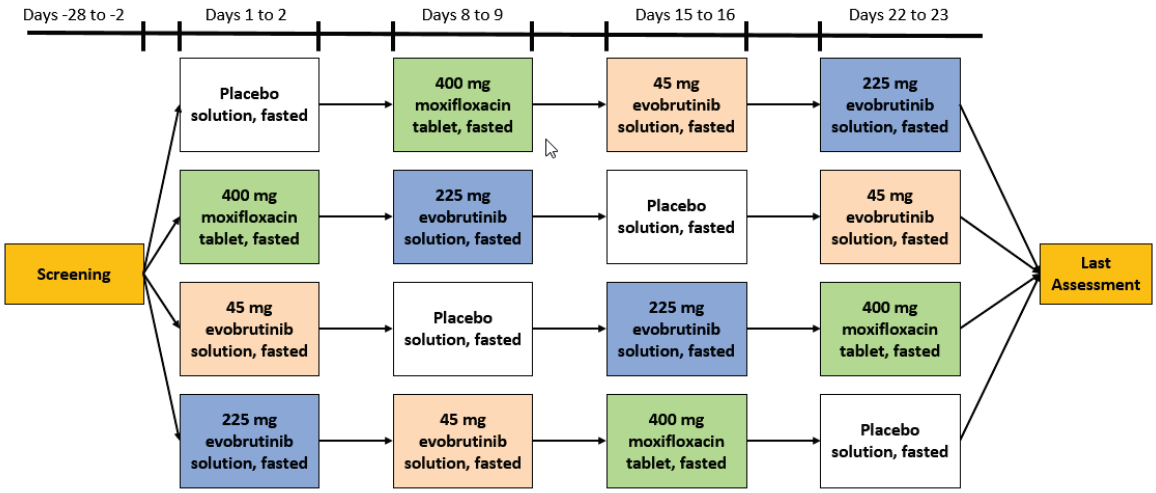
- Study Duration: up to 57 days
- Treatment: Single oral dose of 45 or 225 mg evobrutinib, 400 mg moxifloxacin or placebo administered in fasted state at Study Day 1 of each period.
- The washout between administrations of study intervention between each period will be at least 7 days.
- Visit Frequency: Screening visit will be within 28 to 2 days prior to first administration of study intervention. Participants will be resident in the Clinical Research Unit from Day -1 to Day 2 of each period.

CCI [redacted]

Study Intervention Groups and Duration: Single-dose, 4-way crossover study, up to 57 days

Data and Safety Monitoring /Other Committee: No

1.2 Schema



[a] End of Treatment assessment

Treatment A, B, C, and D are used to denote placebo (solution, fasted), moxifloxacin 400 mg (tablet, fasted), evobrutinib 45 mg (solution, fasted) and evobrutinib 225 mg (solution, fasted), but not necessarily in that respective order. The assignment of actual treatments to the labels will be made when generating the randomization list.

1.3 Schedule of Activities

Assessments & Procedures	Screening	Treatment												Safety Follow-up call	Comments
		P1			P2			P3			P4				
Study Day(s)	**-28 to -2**	**-1**	**1**	**2**	**7[a]**	**8**	**9**	**14[a]**	**15**	**16**	**21[a]**	**22**	**23[b]**	**29**	[a] Assuming 7 days washout between treatment periods. [b] End of Treatment assessment.
Period-specific Day(s)	**-28 to -2**	**-1**	**1**	**2**	**-1**	**1**	**2**	**-1**	**1**	**2**	**-1**	**1**	**2**		
Informed consent	X														Prior to any screening activity
Participants resident at CRU		X	X	X	X	X	X	X	X	X	X	X	X		Discharge on Day 2 of each period
Eligibility criteria	X	X[c]			X[c]			X[c]			X[c]				[c] Recheck of health status on Day -1.
Demography, height & weight	X														Demography to include, at minimum age (year of birth), sex, race, and ethnicity.
Medical history	X														
Serum pregnancy test	X	X			X			X			X				
Viral serology, TSH, eGFR, QuantiFERON® test	X														
Cotinine, alcohol and drugs of abuse testing, SARS-CoV-2	X	X			X			X			X				
Randomization			X												
Physical examination	X	X			X			X			X		X		Brief examination on Days -1 of each period to recheck eligibility/ healthy state after return to CRU and on the End of Treatment assessment visit.
Vital signs	X[d]	X	X[d]	X	X	X[d]	X	X	X[d]	X	X	X[d]	X[d]		Vital signs will be assessed on Day -1 of each period and on the days of dosing (Day 1 of each period) at predose and 1, 2, 6, and 24 h postdose. [d] Body temperature will be assessed at Screening, predose, and the End of Treatment assessment visit. At visits where assessment time points coincide with each other, the following sequence of activities will be followed: safety ECG followed by vital signs within 30 minutes before the specified time point preceding the PK sampling, which will be performed at the specified time point.
Safety ECGs	X		X			X			X			X			Safety ECG at 2 h postdose in each period.

Assessments & Procedures	Screening	Treatment												Safety Follow-up call	Comments
		P1			P2			P3			P4				
Study Day(s)	**-28 to -2**	**-1**	**1**	**2**	**7[a]**	**8**	**9**	**14[a]**	**15**	**16**	**21[a]**	**22**	**23[b]**	**29**	[a] Assuming 7 days washout between treatment periods. [b] End of Treatment assessment.
Period-specific Day(s)	**-28 to -2**	**-1**	**1**	**2**	**-1**	**1**	**2**	**-1**	**1**	**2**	**-1**	**1**	**2**		
Holter recordings			X	X		X	X		X	X		X	X		Holter recordings starting 1 hour prior to first timepoint on Day 1 and lasting at least until last timepoint of PK sampling on Day 2 (24 h postdose) of each period.
Triplicate ECGs from Holter recordings			X	X		X	X		X	X		X	X		On each dosing day 12-lead ECGs extracted in triplicates from Holter recordings at 3 timepoints before dosing (-1 h, -30 min, and -10 min), and at 15 and 30 min and 1, 1.5, 2, 2.5 3, 4, 6, 8, 12,16 h and at 24 h postdose.
Clinical laboratory safety tests	X	X			X			X			X		X		Blood samples for the clinical laboratory safety assessments will be collected in a fasted condition.
PK sampling (evobrutinib, evobrutinib major metabolite, and moxifloxacin)			X	X		X	X		X	X		X	X		Plasma samples for PK analysis will be collected on the days of dosing (i.e., Days 1, 8, 15, and 22) at predose and 15 and 30 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 h postdose. At visits where assessment time points coincide with each other, the following sequence of activities will be followed: PK sample to be collected shortly (within time windows specified) after ECG.
Study intervention administration			X			X			X			X			
Previous/concomitant medication monitoring	X	<==========													Section 6.8.
AE monitoring	X	<==========													Section 8.3.

CRU=clinical research unit; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FSH=follicle stimulating hormone; PK=pharmacokinetics; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; TSH=thyroid stimulating hormone.

2 Introduction

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

CCI [redacted]

This study is being conducted to assess potential effects of evobrutinib on cardiac repolarization (i.e., prolongation of QT interval).

CCI [redacted]

[redacted]

2.2 Background

Evobrutinib

Evobrutinib (also known as M2951 and MSC2364447C) is an oral, selective, irreversible inhibitor of BTK. Evobrutinib inhibits primary B cell responses, such as proliferation and antibody and cytokine release, without directly affecting T cells. Indirect effects on T cells can be mediated by BTK inhibition by blocking the B cell antigen presentation function. In addition, BTK inhibition

blocks the activation of innate immune cells by immune complexes downstream of Fc receptor activation. All 3 mechanisms may play a role in the pathogenesis of various autoimmune diseases. Thus, BTK inhibition could provide clinical benefit in the treatment of multiple autoimmune diseases including RMS.

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

Moxifloxacin

Moxifloxacin 400 mg film-coated tablets are indicated for the treatment of bacterial infections in patients 18 years and older caused by bacteria susceptible to moxifloxacin. Following oral administration, moxifloxacin is rapidly and almost completely absorbed. The absolute bioavailability is approximately 91%. Its pharmacokinetics are linear in the range of 50 to 800 mg single dose and up to 600 mg once daily dosing over 10 days. Following a 400 mg oral dose, peak concentrations of 3.1 mg/L are reached within 0.5 to 4 h after dosing. Moxifloxacin is frequently used in thorough QT studies as a positive control because it induces small and consistent prolongations of QT/QTc but is not considered as having a proarrhythmic activity (refer to moxifloxacin approved product information).

QT Interval

The QT interval (time from the beginning of the QRS complex to the end of the T wave) of the ECG is a measure of the duration of ventricular depolarization and repolarization. When ventricular repolarization is delayed and the QT interval is prolonged, there is an increased risk of ventricular tachyarrhythmia, which can, usually in conjunction with other factors (e.g. hypokalemia, atrial fibrillation and structural heart disease), lead to TdP, a frequently fatal form of polymorphic ventricular tachyarrhythmia. Hence, much emphasis has been placed on the potential proarrhythmic effects of pharmaceuticals associated with QT interval prolongation.

2.3 Benefit/Risk Assessment

As of 31 July 2021, approximately 2,041 adult participants in 16 completed and 4 ongoing clinical studies have been exposed to evobrutinib, including healthy participants (243), participants with RMS (943), systemic lupus erythematosus (437), or rheumatoid arthritis (363), and participants with renal impairment (31) and hepatic impairment (24). Evobrutinib was generally safe and well tolerated in all participants. The TEAEs have been primarily mild to moderate in severity.

Evobrutinib treatment will be administered as a single dose of 45 mg or 225 mg (oral solution) under fasting conditions. These doses are within the range of doses that were previously tested in healthy participant studies and do not exceed exposures reached in first-in-human clinical Study EMR200527-001, where single doses of evobrutinib from 25 up to 500 mg and 14 days of dosing with 25, 75, and 200 mg/day were tested and shown to be well tolerated.

The positive control used, single-dose moxifloxacin, should induce a QTc prolongation of more than 5 ms as evidenced by the lower bound of the two-sided 90% CI in the mean placebo-corrected change from baseline in QTcF (ΔΔQTcF) exceeding 5 ms at the mean peak moxifloxacin concentration. The risk to induce a dysrhythm or TdP by moxifloxacin is very low and this risk is known and is considered acceptable in the scientific community. CCI [redacted]

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

CCI [redacted]

2.3.1 Risk Assessment

Identified and Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Study Intervention(s) Evobrutinib		
Identified risk: Elevated liver transaminases	Elevated liver transaminases have been observed in patients treated with evobrutinib across the program and is considered an important identified risk (for details refer to current IB Section 6.1). Elevations of liver transaminases were frequent, generally mild (Grade 1), asymptomatic and reversible, and occurred within 6 months of treatment. However, more severe cases were reported. This has not been observed in healthy participants after a single dose nor in patients receiving short treatment with evobrutinib.	Participants with known history of hepatic disorder will not be included in the study. Study participants will be confined, and liver tests (e.g. ALT, AST) will be adequately monitored during the study.
Important potential risk: Embryo-fetal toxicity	Based on nonclinical findings, embryo-fetal toxicity is considered as an important potential risk in women of childbearing potential exposed to evobrutinib.	Only women of nonchildbearing potential are included in this study.
Moxifloxacin		
Aortic aneurysm and dissection	This risk applies for the long-term use of the medicine only.	Not applicable as this is single-dose use only.
Prolonged, disabling and potentially irreversible serious adverse drug reactions (musculoskeletal, nervous, psychiatric and senses)	This risk applies for the long-term use of the medicine only.	Exclusion of participants with medical history of psychiatric disorders.

Hypersensitivity and allergic reactions	Hypersensitivity and allergic reactions have been reported for fluoroquinolones including moxifloxacin after first administration. Anaphylactic reactions can progress to a life-threatening shock, even after the first administration.	Suitable emergency treatment will be available (e.g. treatment for shock).
ECG: QTc interval prolongation	QTc prolongations can result in clinically relevant arrhythmias.	Suitable emergency treatment will be available.
Liver: hepatitis	Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with moxifloxacin.	Liver enzyme monitoring and strict stopping rules.
CNS: seizures	Quinolones are known to trigger seizures.	Exclusion of participants with medical history of seizures.
Photosensitivity reactions	Quinolones have been shown to cause photosensitivity reactions in patients.	Participants should be advised to avoid exposure to either UV irradiation or extensive and/or strong sunlight during treatment with moxifloxacin.
Study Procedures		
Blood draw	Blood draws have the potential to cause AEs such as fainting or hematoma.	Amount of blood drawn will be strictly controlled. Participants will be in a hospital setting with support from highly trained professionals.
ECG	Contact allergies can develop during ECG procedures.	Participants with known contact allergies will not be included in the study.
Other		
Not applicable		

2.3.1.1.1 Potential Risks associated with the COVID-19 Pandemic Situation

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

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

During the entire study, all recommendations issued by the Robert Koch Institute as well as local guidelines with respect to the minimization of the risk of disease spreading, e.g. social distancing,

disinfection, hygiene, and wearing of mouth-nose masks will be followed. During the pandemic situation, further measures according to recommendations and requirements from local Health Authorities may become necessary and will be followed within the context of this study as far as applicable, in order to ensure full implementation of the principles of GCP with priority on participant safety in this study also during the COVID-19 pandemic situation. These measures are described in a preventive action plan implemented at the Investigator site.

To minimize the risk coming from a current infection and the risk of getting infected by other participants during the in-house period (covering the whole treatment phase) of the study, the following measures are implemented: Only participants without any symptoms of a respiratory disease and without contact to any known SARS-CoV-2 positive patient or COVID-19 patient in the previous 7 days will be included into the study. Furthermore, as a part of the clinical study procedures, participants will be closely monitored (including for signs of COVID-19) during the entire study duration. Continuation of the study in case of a SARS-CoV-2 infection in the study participant or an identified contact to a SARS-CoV-2 positive participant or COVID-19 patient will be done at the Investigator's discretion and agreement with the medical monitoring team. The Sponsor will monitor the events related to any SARS-CoV-2 infection reported following evobrutinib regularly and update the recommendations, if necessary.

2.3.2 Benefit Assessment

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

2.3.3 Overall Benefit: Risk Conclusion

Risk minimization measures routinely implemented in early phase clinical studies are considered adequate, including exclusion criteria (see Sections 5.1 and 5.2), adequate biochemical and hematology laboratory monitoring (see Section 8.2.4), and observation of vital signs and ECGs (see Sections 8.2.2 and 8.2.3). Participants will be admitted to the study site for the duration of the study to allow continuous safety monitoring. Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with evobrutinib and moxifloxacin are justified in healthy participants.

3 Objectives and Endpoints

Objectives	Endpoints	Ref. #
Primary		
To evaluate whether evobrutinib administered as a single oral dose (as solution) of 45 mg or 225 mg prolongs QT/QTc in comparison to placebo control	ΔΔQTcF (placebo-corrected change from baseline QTcF) for evobrutinib; with concentration-QTc analysis as primary analysis	1
Secondary		
To demonstrate QTc assay sensitivity	ΔΔQTcF (placebo-corrected change from baseline QTcF) for moxifloxacin	2
To assess the safety and tolerability of evobrutinib	Nature, occurrence, and severity of TEAEs Absolute values and changes in safety laboratory tests Vital signs assessed from time of first dose to end of study participation Single 12-lead ECGs evaluated by Investigator	3
To assess the effect of evobrutinib on other ECG parameters	QT, QTcB, QTcI, PR, QRS, RR, HR, cardiologist assessment including T-wave morphology, and U-wave.	4
To determine the PK of evobrutinib and its major metabolite at 45 mg and 225 mg oral dose (solution) under fasting conditions and moxifloxacin at 400 mg oral dose	AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, and t_{max} for evobrutinib and major metabolite AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, and t_{max} for moxifloxacin	5

4 Study Design

This is a Phase 1, single-center, randomized, double-blinded, placebo- and positive-(moxifloxacin) controlled, single-dose, 4-period crossover thorough QT study. There will be a at least 7-day washout period between successive doses. CCI [redacted] Eligible participants will be randomized to 1 of 4 treatment sequences in which each of the 4 treatments will be administered sequentially during 4 treatment periods. The 4 treatments are:

- Therapeutic dose, double-blind: single oral dose of evobrutinib (45 mg) solution, administered under fasted conditions;
- Supratherapeutic dose, double-blind: single oral dose of evobrutinib (225 mg) solution, administered under fasted conditions;
- Placebo control, double-blind: single oral dose of placebo solution, administered under fasted conditions;
- Positive control, open-label: single oral dose of 1 moxifloxacin tablet (400 mg), administered under fasted conditions.

4.1 Overall Design

Study Design	Single-dose, 4-way crossover
Control Method	Placebo- and positive-controlled
Single or Multicenter	Single center
Study Population Type	Healthy participants
Level and Method of Blinding	Double-blind for evobrutinib and placebo
Bias Minimalization Method(s)	Randomization, blinding
Study Intervention Assignment Method	Randomization
Data and Safety Monitoring /Other Committee:	No
Total Duration of Study Participation per Participant	Up to 57 days, including the Screening Period (maximum of 28 days), 23 days of intervention period with at least a 7-day washout between each study period, and the Safety Follow-up call on Day 29, 1 week after the last dose of study intervention. A study schema and a detailed Schedule of Assessments are provided in Section 1.2 and Section 1.3, respectively.
Provisions for Study Extension or Entry into Roll-Over Studies	Not applicable
Adaptive Aspects of Study Design	Not applicable

A study design schema and a detailed Schedule of Activities are provided in Section 1.2 and Section 1.3, respectively.

4.2 Scientific Rationale for Study Design

The design of this thorough QT study, a randomized, assessor-blinded, placebo- and positive-(moxifloxacin) controlled, single-dose, 4-period crossover study, is the standard design for this type of QT assessment study.

4.2.1 Use of Moxifloxacin

A positive control is recommended by regulatory authorities to be able to detect a ~ 5 ms change from baseline- and placebo-corrected QTc duration (ΔΔQTc) to confirm the sensitivity of the study. Moxifloxacin is frequently used in thorough QT studies because it induces small and consistent prolongations of QT/QTc but is not considered as having a proarrhythmic activity (as outlined in ICH E14/S7B Q&A 2020). A pooled analysis of 14 crossover thorough QT studies with 400 mg single oral dose of moxifloxacin demonstrated a largest mean ΔΔQTcF effect of 12.3 ms at 3 h postdose (Yan 2010). In this study, a single 400 mg dose of moxifloxacin will be administered orally to the participants (refer to approved product information).

4.2.2 Participant Input into Design

Not applicable.

4.3 Justification for Dose

Evobrutinib

The evobrutinib therapeutic dose to be used in this study CCI is expected to result in C_{max} similar to those in the Phase 3 studies in patients dosed with 45 mg tablets (fed) BID, and the supratherapeutic dose CCI is expected to result in 5-fold higher C_{max}. A CCI higher C_{max} is expected to provide adequate coverage for the clinically relevant high-exposure scenario for evobrutinib $C_{max,}$ if administered with a moderate or strong CYP3A4 inhibitor CCI

Moxifloxacin

Moxifloxacin is frequently used in thorough QT studies because it induces a small and consistent QT/QTc prolongation with a low incidence of inducing proarrhythmic activity. A single oral dose of 400 mg given in a fasted state is the standard dose used for this type of study.

4.4 End of Study Definition

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

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

Study Termination Criteria

The study will be discontinued or terminated if:

- unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment is identified. This might include the occurrence of AEs which character, severity or frequency is new in comparison to the existing risk profile.
- any data derived from other clinical trials or toxicological studies become available which negatively influence the risk/benefit assessment.

General information on study termination is specified in Appendix 2.

5 Study Population

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

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

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

5.1 Inclusion Criteria

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

Category	Criterion
Age	1. Are between 18 and 55 (inclusive) years of age at the time of signing the informed consent.
Type of Participant and Disease Characteristics	2. Are overtly healthy as determined by medical evaluation, including no clinically significant abnormality identified on physical examination or laboratory evaluation and no active clinically significant disorder, condition, infection, or disease that would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion.
Weight	3. Have a body weight within 50.0 and 100.0 kg (inclusive) and BMI within the range 19.0 and 30.0 kg/m^2 (inclusive).

Category	Criterion
Sex and Contraception/ Barrier Requirements	4. • Male o No contraception and barrier requirements needed. • Female o Is **not** a woman of childbearing potential (Appendix 3). Note: Study to include approx. 30% or more of each sex
Informed Consent	5. Are capable of giving signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the ICF and this protocol.
Smoking	6. Are stable nonsmokers for at least 3 months preceding the first administration of study intervention.

5.2 Exclusion Criteria

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

Category	Criterion
Medical Conditions	1. History or presence of clinically relevant respiratory, gastrointestinal, renal, hepatic, hematological, lymphatic, neurological, cardiovascular, musculoskeletal, genitourinary, immunological, dermatological, connective tissue, psychiatric (due to rare risk of hallucinations, agitation and activation of psychosis), and other diseases or disorders, and epilepsy, as determined by medical evaluation.
	2. Individuals with diagnosis of hemochromatosis, Wilson´s disease, alpha 1 antitrypsin deficiency, or any other chronic liver disease including Gilbert's disease will be excluded from the study. Prior history of cholecystectomy or splenectomy, and any clinically relevant surgery within 6 months prior to the first administration of study intervention.
	3. History of any malignancy.
	4. History of seizures.

Category	Criterion
	5. History of pharmacologically treated psychiatric disease.
	6. History of chronic or recurrent acute infection or any bacterial, viral, parasitic or fungal infections within 30 days prior to Screening and at any time between Screening and admission, or hospitalization due to infection within 6 months prior to the first administration of study intervention.
	7. History of shingles within 12 months prior to Screening.
	8. History of drug hypersensitivity (e.g. quinolones and ascertained or presumptive allergy/hypersensitivity to the active drug substance and/or formulation ingredients); history of serious allergic reactions leading to hospitalization or any other hypersensitivity reaction in general including contact hypersensitivity to ECG electrodes, which may affect the safety of the participant and/or outcome of the study per the Investigator's discretion.
	9. History of alcoholism or drug abuse within 2 years prior to the first administration of study intervention, or positive for drugs of abuse, nicotine/cotinine or alcohol by the laboratory assays conducted during Screening and Study Day -1.
	10. History of residential exposure to tuberculosis, or a positive QuantiFERON® test within 4 weeks prior to or at the time of Screening.
	11. Positive for a) hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, or human immunodeficiency virus I and II tests at Screening; b) SARS CoV-2 at Screening or Study Day -1.
	12. Any condition, including findings in the laboratory tests, medical history (e.g. heart failure, hypokalemia, family history of Long QT Syndrome), or other Screening assessments, that in the opinion of the Investigator constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study's objectives, conduct, or evaluation.

Category	Criterion
	13. Administration of live vaccines or live-attenuated virus vaccines within 3 months prior to Screening. Administration of other types of vaccines (e.g. SARS-CoV-2 vaccines) is allowed until 42 days before the first administration of study intervention, thereafter it is prohibited until the end of the study. Note: In case of clinical symptoms, the participant should be symptom-free for at least 1 week prior to the first administration of study intervention.
Prior/Concomitant Therapy	14. Moderate or strong inhibitors or inducers of CYP3A4/5 or P-gp within 4 weeks prior to the first administration of study intervention.
	15. Use of any prescribed medicine or over-the-counter drug or dietary supplement, including herbal remedies, vitamins, and minerals, antacids and dietary supplements such as fish oils within 2 weeks or 5 times the half-life of the respective drug, whichever is longer, prior to the first administration of study intervention. Occasional paracetamol (acetaminophen) up to 2 g per day is permitted.
Prior/Concurrent Clinical Study Experience	16. Use of any investigational drug in any clinical study within 60 days prior to Study Day 1 administration, or have used an experimental monoclonal antibody within the past 1 year prior to Study Day 1, or have participated in a study evaluating a BTK inhibitor within 60 days, or are on extended follow-up in a clinical study, even if last administration of a study intervention was more than 60 days ago, or 5 half-lives of the investigational drug, whichever is longer, prior to the first administration of study intervention.
Diagnostic Assessments	17. Medical history and physical examination results that include any ongoing clinically relevant findings as judged by the Investigator.

Category	Criterion
	18. Clinically relevant findings (excluding minor, not clinically relevant excursions from normal ranges, as judged by the Investigator) at Screening in biochemistry, hematology, coagulation, and urinalysis examinations for the age of the participant, as judged by the Investigator: • Alanine aminotransferase, aspartate aminotransferase: above ULN • Creatinine: above normal limits • Absolute lymphocyte count, absolute neutrophil count: below limit of reference range. • Amylase and lipase above normal ranges, minor deviations are allowed, if not clinically relevant. • Abnormal, low levels of potassium levels
	19. Estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (2009) < 90 mL/min at Screening. In case of a borderline result between ≥ 80 and < 90 mL/min, Cystatin C will be determined in addition, and the participant will only be included if the Cystatin C value is below the upper limit of normal.
	20. Semi-supine systolic blood pressure > 140 mmHg or < 90 mmHg, diastolic blood pressure > 90 mmHg or < 50 mmHg, and pulse rate > 90 or < 50 bpm at Screening. Any abnormal blood pressure results may be repeated once and if the repeat result is within the normal range, it is not considered to have met the exclusion criterion.
	21. 12-Lead ECG showing a QT interval corrected for heart rate according to Fridericia's formula (QTcF) > 450 ms, PR > 215 ms, or QRS > 110 ms at Screening.
	22. Any other abnormal laboratory results that the Investigator believes should preclude the participant's participation in the study.
Other Exclusions	23. Consumption of an average weekly alcohol intake of > 14 units/week for men or > 7 units/week for women. 1 unit (12 g) of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

- Participants will abstain from consuming Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from these fruits from 14 days before the start of study intervention until after the final dose.
- Participants will receive standardized meals on Day -1 of each period at customary times.
- On Day 1 of each period the participants will be fasting (no food, no beverages, only water is allowed) from at least 10 hours before and until 4 hours after drug administration. Ingestion of water between 1 hour predose and until 1 hour postdose will not be allowed. 4 hours after drug

administration, a standardized lunch will be served. An afternoon snack will be provided approximately 8 hours and dinner approximately 12 hours postdose.

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid

- During each dosing period participants will abstain from ingesting caffeine- or xanthine-containing products (e.g. coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until after collection of the final PK sample.
- In this study the consumption of alcohol is not allowed from 48 hours prior to first administration of study intervention (see Section 5.2) until after collection of the final PK sample.
- During the study, participants will abstain from THC or cannabinoid-containing products for 2-weeks before the start of dosing until after collection of the final PK sample.
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted from at least 3 months preceding Screening until after the final follow-up visit.

5.3.3 Activity

Participants will abstain from strenuous exercise for 3 days before each blood collection for clinical laboratory tests and PK samples. Participants may participate in light recreational activities (e.g. watching television or reading).

5.4 Screen Failures

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

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

Rescreening will be limited to 2 rescreenings per participant.

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

5.5 Criteria for Temporarily Delaying Administration of Study Intervention

Not applicable.

6 Study Intervention(s) and Concomitant Therapies

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

6.1 Study Intervention(s) Administration

Study Intervention(s) Administered

Intervention Label	Placebo	Moxifloxacin	Evobrutinib	Evobrutinib
Intervention Name	Placebo	Moxifloxacin	Evobrutinib	Evobrutinib
Intervention Description	Participants will receive an oral solution of placebo	Participants will receive an oral 400 mg dose of moxifloxacin	Participants will receive an oral 45 mg dose of evobrutinib	Participants will receive an oral 225 mg dose of evobrutinib
Type	Drug	Drug	Drug	Drug
Dose Formulation	Solution	Tablet	Solution	Solution
Unit Dose Strength(s)	N/A	400 mg	45 mg	225 mg
Dose	Fasted	400 mg (fasted)	45 mg (fasted)	225 mg (fasted)
Dosage Regimen	Single dose	Single dose	Single dose	Single dose
Route of Administration	Oral	Oral	Oral	Oral
Use	Placebo-experimental	Positive control	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP
Sourcing	Will be provided by Nuvisan GmbH.	Will be provided by Nuvisan GmbH, commercial	-	-

		product from German market.		
Supplier	-	-	Merck Healthcare KGaA; The powder in bottle formulation and the oral solution will be manufactured by Nuvisan.	Merck Healthcare KGaA; The powder in bottle formulation and the oral solution will be manufactured by Nuvisan.
Packaging and Labeling	Study intervention will be provided in bottles. Each bottle will be labeled per country requirement. Additional details of packaging and labeling of study intervention will be defined in a separate IMP Handling Manual.	Study Intervention will be provided in the original, commercial packaging. Commercial blisters and original folding cartons will be labeled as per country requirement.	Study Intervention will be provided in bottles. Each container will be labeled per country requirement. Additional details of packaging and labeling of study intervention will be defined in a separate IMP Handling Manual.	Study Intervention will be provided in bottles. Each container will be labeled per country requirement. Additional details of packaging and labeling of study intervention will be defined in a separate IMP Handling Manual.

Study Arm(s)

Arm Name	Placebo: double-blind period	Moxifloxacin: 400 mg open-label period	Evobrutinib: 45 mg double-blind period	Evobrutinib: 225 mg double-blind period
Arm Type	Placebo-experimental	Active control	Experimental	Experimental
Arm Description	Single dose	Single dose	Single dose	Single dose
Associated Intervention Labels	Placebo	Moxifloxacin	Evobrutinib	Evobrutinib

- Evobrutinib and placebo solution will be administered after reconstituting API (or placebo) in 100 mL buffer. A second bottle of buffer will be used to rinse the bottle with reconstituted API (or placebo) twice (50 mL each time). The participants will then receive 40 mL of water to reach a total volume of 240 mL. Further details are provided in the IMP handling manual.
- All treatments will be administered following an overnight fast (10 h). Subjects will not be allowed any liquid from 1 h predose until 1 h postdose, except for the 240 mL water and buffer required to consume the dose with. Subjects will remain fasting until 4 h postdose.
- To mask the taste of the active compound, both the active compound and placebo will contain orange flavor to allow identical taste. The placebo oral solution will be matched for appearance and volume in order to maintain the blind.
- Moxifloxacin dose will be administered together with a total amount of 240 mL water in a standing position.

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

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

- Upon receipt of the study intervention(s), the Investigator or designee will confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the IMP Handling Manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
    - Confirmation of receipt, in good condition and in the defined temperature range.
    - The inventory provided for the clinical study and prepared at the site.
    - The dose(s) each participant used during the study.
    - The disposition (including return, if applicable) of any unused study intervention(s).
    - Dates, quantities, batch numbers, medication numbers, expiry dates, and the participant numbers.
- The Investigator site will maintain records which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.

- Unused study intervention(s) will not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the IMP Handling Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Study using Pre-Coded Randomization provided to site	On Study Day 1 participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to one of the 4 treatment sequences of the study, per the randomization schedule generated prior to the study by Nuvisan GmbH CTS Department. • Sequence 1: A-B-C-D • Sequence 2: B-D-A-C • Sequence 3: C-A-D-B • Sequence 4: D-C-B-A A, B, C, and D are used to denote placebo (solution, fasted), moxifloxacin 400 mg (tablet, fasted), evobrutinib 45 mg (solution, fasted) and evobrutinib 225 mg (solution, fasted), but not necessarily in that respective order.

Each participant is identified by the study site's unique participant identification code (Nuvisan GmbH identification code). After informed consent procedure, every participant is given a screening number. Only participants who comply with all selection criteria (Sections 5.1 and 5.2) can be included into the study.

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

6.3.2 Blinding

Blinding Method

Randomization codes will be kept strictly confidential, accessible only to authorized staff (i.e. randomization statistician, unblinded reconstitution team, bioanalytical laboratories responsible for analyses of the PK samples and unblinded monitor), until the time of unblinding. All other study-related individuals, ancillary site staff, clinical research associates/monitors, the Investigator, Sponsor, ECG core lab, and clinical research organization staff will remain blinded to study intervention.

Since moxifloxacin will be administered open-label, and evobrutinib and placebo administered double-blinded, the treatment sequences will not be displayed in this protocol. Placeholders ('Treatment A', 'Treatment B', 'Treatment C', and 'Treatment D') will be used to refer to the study interventions. Only authorized staff mentioned above will be aware of the sequences actually used.

The procedures of database lock and unblinding statistical analyses will be documented in the Data Management Plan and Unblinding Plan.

Confirmation of the Indistinguishability of the Study Interventions: evobrutinib and placebo solutions will be identical in volume and appearance.

The analytical laboratories responsible for analysis of the PK samples will be unblinded to study treatment codes to enable sample testing of evobrutinib and moxifloxacin prior to database lock. Masked participant identifiers will be used to support association of PK data with treatment codes while preventing association of treatment codes with any other clinical data, such as safety and clinical response data.

Evobrutinib and moxifloxacin information that would unblind the study participants will not be reported with participant identifiers to investigative sites or blinded personnel until the study has been unblinded.

Assignment Method Retention

Unblinding may be done in the event of an emergency necessary for participant safety or the reporting of SUSARs using code break envelopes provided to the site by the CTS department.

6.3.3 Emergency Unblinding

In an emergency, the Investigator is solely responsible for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety is always the first consideration in this decision. If the Investigator decides that unblinding is warranted, the Investigator makes every effort to contact the Sponsor prior to the unblinding, unless this could delay emergency treatment. The Sponsor will be notified within 24 hours after unblinding. The Investigator will provide the Sponsor the reason for unblinding without revealing the study intervention, except to the designated global patient safety representative via the Emergency

Unblinding Notification Form. The date of and reason for unblinding will be recorded in the source documents and CRF. Contact information for unblinding in an emergency is given on the participant emergency card provided to each participant, as noted in Appendix 2.

6.4 Study Intervention Compliance

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

6.5 Dose Modification

Doses will not be modified.

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

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

6.7 Treatment of Overdose

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

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

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

6.8 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g. medicines or nondrug interventions) used from the signing of the ICF until the end of treatment assessment at the timepoints specified in the SoA, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information. For nondrug interventions, record the name, the indication, and dates administered.

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

Paracetamol/Acetaminophen, at doses of ≤ 2 g/24 hours, is permitted for use any time during the study, at the discretion of the Investigator. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor if required.

6.8.1 Rescue Medicine

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

In case of toxicity during moxifloxacin, refer to the approved product information.

6.8.2 Permitted Medicines

The only permitted medicines are the following:

Acetaminophen (paracetamol) up to 2 g per day, at the discretion of the Investigator.

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

6.8.3 Prohibited Medicines

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

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

Inhibitors or inducers of CYP3A4/5 or P-gp within 4 weeks prior to the first administration of study intervention, and until after the Safety Follow-Up assessment, are prohibited. Also, drugs mainly metabolized by CYP3A4/5 and that have a narrow therapeutic index should be avoided.

6.8.4 Other Interventions

Additional restrictions that study participants should adhere to from Day -1 until the Final assessment are detailed in Section 5.2.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1 Discontinuation of Study Intervention

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

- Participant withdraws consent.
- A participant is enrolled but is subsequently discovered not to have met inclusion/exclusion criteria at Screening.
- AEs, if discontinuation of study intervention is considered necessary by the Investigator and/or desired by the participant. This includes in particular AEs of severe intensity and SAEs regardless of the relationship to study intervention.
- Pregnancy (see Section 8.3.4).
- Protocol noncompliance judged as significant by the Investigator (after discussion with the Sponsor).
- Use of a nonpermitted concomitant drug if clinically relevant as agreed by Sponsor and Investigator, as defined in Section 5.2, where the predefined consequence is withdrawal from study intervention.
- Any events that unacceptably endanger the safety of the participant.

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety assessments: The SoA indicates data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

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

7.1.1 Liver Clinical Safety Laboratory Tests Stopping Criteria

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

All confirmed events of ALT or AST ≥ 5 × ULN triggers stopping criteria.

All confirmed events of ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN triggers stopping criteria.

All liver related events will be reported as AESI according to the risk profile of evobrutinib.

7.1.2 Cardiac Safety Stopping Criteria

If a clinically significant finding is identified (including changes from baseline in QT interval corrected using Fridericia's formula [QTcF > 60 ms and QT/QTcF > 500 ms]) after start of study intervention, the Investigator or qualified designee will determine if the participant can continue

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

7.1.3 Hypersensitivity/Allergic Reactions Stopping Criteria

Hypersensitivity, allergic reactions and Severe Cutaneous Adverse Reactions have been reported for fluoroquinolones, including moxifloxacin, after first administration. In cases of clinical manifestations of severe hypersensitivity reactions or signs and symptoms of severe skin reactions Participant should be discontinued from the study.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may discontinue from the study at any time, at his/her own request or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons (e.g. disruption of operations due to natural disasters, interruption of lab or facility accreditation, participant moving to another country, resignation of key staff").
- At the time of study discontinuation, if possible, a discontinuation visit will be conducted, as listed in the SoA. The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.
- If the participant revokes consent for the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- If a participant requests the destruction of any biological samples still remaining, the Investigator will document this in the site study records and inform the Sponsor. The samples will be destroyed.

7.3 Lost to Follow-Up

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

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

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

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA.
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant will continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g. blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria, were performed within the time frame defined in the SoA, and if reviewed and approved by the Sponsor.
- Any data (including Safety, PK and ECG data) that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- About 450 ml of blood total will be taken throughout the study. Up to 100 ml of blood may be drawn at certain visits. These blood samples will be used for the following purposes: clinical laboratory tests and PK analyses.

Where allowed by local law/regulations, samples collected during this clinical study may be transferred to a biobank and used for future research outside the clinical protocol when additional consent for this purpose is given. Transfer to the biobank will be documented and any testing of coded biobank samples will **not** be reported in the CSR.

8.1 Efficacy Assessments and Procedures

Not applicable

8.2 Safety Assessments and Procedures

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

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

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the 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.

8.2.2 Vital Signs

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

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

8.2.3 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA and will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones).

Together with the ECG recorders also laptops, a server laptop and printer will be provided by the ECG core lab. With the aid of this setup, site personnel will be able to trigger and print 12-lead safety ECGs directly from the Holter devices using the laptops. A detailed manual for this process will be supplied by the ECG core lab. An on-site training will be done prior to study start.

Detailed information on Holter ECGs is given in Section 8.4.3.

8.2.4 Clinical Safety Laboratory Tests

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 6 at the timepoints listed in the SoA. All samples will be clearly identified.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by Nuvisan GmbH laboratory; the QuantiFERON® Test will be performed by Synlab, Augsburg, Germany.
- The Investigator will review each laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE, unless it does **not** meet the AE definition, as specified in Appendix 4. The laboratory reports will be filed with the source documents.

- Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded (see Section 6.3.2 and 6.3.3).

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

- The definitions of an AE and SAE are in Appendix 4.
- The Investigator and any qualified designees (e.g. Subinvestigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study, as specified in Section 8.3.2.
- Requests for follow-up will usually be made via the Sponsor or CRO-designated study team member, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.
- All AEs and SAEs will be collected from the signing of the ICF until the safety follow-up call at the timepoints specified in the SoA (Section 1.3). Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.
- Investigators are not obligated to actively solicit information on Aes or SAEs after the end of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.1 Method of Detecting Adverse Events and Serious Adverse Events

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

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

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

8.3.2 Follow-up of Adverse Events and Serious Adverse Events

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

8.3.3 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- Individual Case Safety Reports will be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators within 15 days.
- An Investigator or Subinvestigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g. Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will read it and confirm completion of this activity. This information will be filed in the Investigator's Site File, and the IRB/IEC will be notified, if appropriate, according to applicable local laws/regulations and site SOPs.

8.3.4 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the Safety Follow-up. Note: In this study, only women of nonchildbearing potential will be included.
- If a pregnancy is reported, the Investigator will record the pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of female participant pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Adverse pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered and reported as SAEs. A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to

8 weeks beyond the estimated delivery date for a healthy newborn. In case of a congenital anomaly or other illness of the newborn, follow-up will continue until the illness has resolved or there is a definite outcome of the event.

- Any post study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.3. While the Investigator is not obligated to actively seek this information in former study participants he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.5 Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.7 Adverse Events of Special Interest

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

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

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

- Seizures

  Seizures are more common in patients with MS than in the general population, occurring in 2% to 3% of patients with MS (Poser 2003). Convulsions were observed in early studies of evobrutinib in dogs, however the plasma concentration of evobrutinib was approximately 140-fold greater than it is predicted for the dose used in this study. 1 participant with RMS with significant brain lesion load reported seizure of unclear clinical picture. The PK data for this participant did not exceed the expected values and was similar to other participants in the study. Anticonvulsant therapy was started, and the participant continued treatment with evobrutinib with no reoccurrence. The Investigator did not consider the event to be related to evobrutinib.

No event of convulsion/seizure was reported in other indications. Evobrutinib has been administered to approximately 800 patients with MS, rheumatoid arthritis and systemic lupus erythematosus. Moreover, an electroencephalogram study in healthy volunteers did not show an epileptogenic potential for evobrutinib. Any type of seizures/epilepsy of any grade or its consequences are classified as AESIs.

- Elevated lipase, elevated amylase, pancreatitis

  Asymptomatic elevations in amylase or lipase or both in participants treated with evobrutinib have been observed at a variety of time points and reported as TEAEs or noted as laboratory abnormalities. In RMS Study MS200527_0086, the incidence of TEAEs of lipase increased was slightly higher in evobrutinib 75 mg once daily and 75 mg twice daily arms (5 [9.4%] and 5 [9.3%], respectively) when compared to other arms (approximately between 4% to 6%). However, shifts from Baseline to highest grade on treatment were similar across all treatment arms for both amylase and lipase. In evobrutinib studies in other indications and in healthy participants, the incidence of TEAEs of increased amylase or lipase, or both was infrequent and no clinically meaningful differences were observed across treatment arms. Any elevation of > 2 × ULN of lipase or amylase and any type of pancreatitis are classified as AESIs.

- Liver related events

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

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

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

8.4 Pharmacokinetics

8.4.1 Blood Sampling and Bioanalysis

- Samples are collected only where allowed by local law/regulations.
- The actual date and time (24-hour clock time) of:
  - Each sample collection
  - Study intervention administration prior to sample collection

  will be recorded in the eCRF to determine the elapsed time of sampling in relation to the administration of study intervention.
- Blood samples for measurements of plasma evobrutinib CCI [redacted] and moxifloxacin concentrations will be collected. Collection times are specified in the SoA.
- The actual date and time (24-hour clock time) of:
  - start and end of each blood collection interval

- study intervention administration prior to sample collection
- the volume of each blood collection fraction

will be recorded in the eCRF, in order to determine the elapsed time of sampling in relation to the administration of study drug. The accepted time deviations from planned PK sampling times that will not be considered a protocol violation are listed in Table 1.

- The quantification of evobrutinib and moxifloxacin in plasma will be performed using a validated assay method. CCI [redacted]

[redacted]. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

- Details on processes for collection and handling of these samples are in the Laboratory Manual.

Table 1 Time Deviations from PK sampling times

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

8.4.2 PK Parameters

- The following PK parameters for evobrutinib, its major metabolite, and moxifloxacin will be calculated, when appropriate:

Symbol	Definition
AUC_{0-24}	The partial AUC from time zero (= dosing time) to 24 hours.
$AUC_{0-tlast}$	The AUC from time zero (= dosing time) to the time of the last quantifiable concentration (t_{last}).
$AUC_{0-\infty}$	The AUC from time zero (= dosing time) up to infinity with extrapolation of the terminal phase.
AUCextra%	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$.
C_{max}	Maximum observed concentration.
CL/F	The apparent total body clearance following extravascular administration (parent only).
λz	Terminal first order (elimination) rate constant.
T_{max}	The time to reach the C_{max} in a dosing interval.
$T_{1/2}$	The terminal half-life.
V_z/F	The apparent volume of distribution during the terminal phase following extravascular administration (parent only).

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

- Concentration data may be used for integrated data analyses across studies, such as population PK and exposure-response analyses of PD biomarker, QTc, efficacy and/or safety analyses and reported separately from the main CSR.

8.4.3 Electrocardiograms

In this study, ECGs will be recorded using standard 12-lead ECG devices and 12-lead Holter recorders for the following purposes:

- Check of eligibility of a participant for the study during screening using standard 12-lead ECG machines (single ECGs).
- Immediate safety assessment at the site using safety single 12-lead ECGs that are being printed from the Holter recordings.
- Extraction of triplicate 10 s ECGs from continuous Holter recordings for central evaluation and statistical analyses of possible drug effects on cardiac safety parameters.

The standard ten seconds 12-lead ECGs will be recorded by devices (CardioPerfect, Hillroom, Chicago, USA) supplied by the site at times indicated in the Flow Chart. These ECGs will be acquired using Goldberger/Einthoven and Wilson leads in supine position (small pillow under head allowed) and after a rest for at least 15 min. The devices will print the ECGs for immediate evaluation by the investigator or his/her designee. The following automatically calculated parameters will be used: Ventricular rate, PR interval, QRS duration, QT interval (uncorrected) and QTcB and QTcF.

The evaluation by the Investigator includes an overall assessment (normal, description of abnormality including clinical relevance) which will be entered into the eCRF system.

The 12-lead Holter ECGs will be recorded using devices (CM3000 or Seer 12, getemed AG, Berlin, Germany), supplied by the ECG core lab (nabios GmbH, Munich, Germany). All devices will be tested prior to shipment and installed at the site. An on-site training will be performed for the site staff. Details of the ECG recordings and data transfer procedure will be supplied in manuals.

For these continuous recordings modified Goldberger/Einthoven (so-called Mason-Likar) lead positions and Wilson chest leads will be used. The recordings will be started approximately 2 h before the corresponding time point of the planned time of administration on Day -1 and will end shortly after the 24 h time point postdose. At least 15 min prior to the extraction time points the participants have to be in supine position in a quiet environment. This resting period is followed by another 3 min term during which the participant should be at complete rest with no interventions. At the end of this period, the study staff will press the marker button on the recorder to flag this electronically on the ECG signal. Immediately afterwards, further planned measurements and blood samplings will be performed. After the recordings are done, the data will be transferred to the core lab using one of the laptops and a pre-installed and tested data transfer program. At the core lab, triplicate 10 s ECGs with approximately 1-minute time difference between 2 successive ECGs will be extracted from the 12-lead Holter recordings guided by the electronic markers. The timing of the markers will be tested by the core lab staff by checking the markers with the respective nominal times of the individual medication times. In case inconsistencies are detected, the core lab will query the site.

After the ECG have been extracted at the core lab, they will be measured for cardiac intervals RR, PR(Q), QRS, and QT from 4 preferably consecutive heart beats in lead II. If lead II is not evaluable in an ECG lead V or lead I will be used. All ECGs of a particular participant will be measured in the same lead. The measurement will be done using the core labs validated semi-automated programs and procedures. The end of the T wave will be determined using the so-called slope (or tangent) method. This method approximates the downslope of the T wave by a linear function. The end of the T wave is then defined as the crossing point between this straight and the isoelectric line. All fiducial point markings will be reviewed by trained technicians.

Within the ECG laboratory, the staff involved with ECG interval measurements and morphological analyses will be blinded with regard to treatment, date and time as well as time points of the ECG measurements. No more than 2 blinded readers will evaluate all ECGs of the study. The interval measurements for a given participant will be performed in random and blinded sequence by a single reader. For quality assurance and control of the measurements, all ECGs of an individual participant will be subsequently reviewed by the ECG technician supervisor or his/her designee to assess the overall variance of the measured intervals and to detect accidental switching of leads and/or false participant assignments of the ECGs.

In addition to the measurements of the intervals, one randomly selected ECG at each time point will be evaluated by a board-certified cardiologist. This evaluation will include an overall assessment as well as specific findings regarding rhythm, conduction, ST-T segment and T/U-wave, morphology, and myocardial infarction. Standard CDISC terms will be used for this interpretation of the ECG. The cardiologist will review the ECGs one by one and in random order. Thus, she/he is practically blinded to the sequence of the ECG within a participant. After

evaluation of the ECGs, the results will be submitted to the data management company using a predefined data transfer method and specification The transfer will include for any ECG recording classified as “abnormal” the description of the abnormality in addition to the clinical relevance (yes/no).

8.5 Pharmacogenetics

Not applicable.

8.6 Biomarkers

Not applicable.

8.7 Immunogenicity Assessments

Not applicable.

8.8 Medical Resource Utilization and Health Economics

Healthcare resource utilization data are not collected in this study.

[redacted]

There will be no other formal statistical hypotheses testing.

CCI [redacted]

[redacted]

[redacted]

9.3 Analysis Sets

The analysis sets are specified below.

Analysis Set	Description
SCR	All participants, who provided informed consent, regardless of the participant's enrollment and study intervention status in the study.
SAF	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
PK	The PK Analysis Set is a subset of the SAF, and the PK population will include all participants: Who have completed the study without any relevant protocol deviations and factors likely to affect the comparability of PK results. With adequate study intervention compliance. With evaluable PK data, i.e. nonmissing values for primary endpoints. If participants received prohibited concomitant therapy or medicines, as specified in Section 6.8, they will be excluded from the PK population. All PK analyses will be based on this analysis set.
ECG	The ECG Analysis Set will be the basis of the C-QTc analysis and will be a subset of the SAF. Only participants who had a baseline Holter ECG in triplicate and at least one post-baseline Holter ECG in triplicate with a time-matched concentration will be retained for C-QTc analysis. Participants with protocol deviations likely to affect the comparability of ECG measurements or PK concentrations will not be considered in the C-QTc analysis.

9.4 Statistical Analyses

CCI [redacted]

[redacted]

CCI [redacted]

[redacted] handling of concentration values below the limit of quantification will be described in the IAP.

9.4.1 Safety Analyses

All safety analyses will be performed on the Safety Analysis set.

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

9.4.2 Other Analyses (QTc and PK analyses)

Reference #	Endpoint	Statistical Analysis Methods
Primary		
1	ΔΔQTcF (evobrutinib)	A mixed-effects model with repeated measures will be used to analyze the relationship between evobrutinib concentrations and ΔΔQTcF. Based on this model, the predicted ΔΔQTcF at clinically relevant concentrations will be calculated, with two-sided 90% confidence intervals. Model selection, including consideration of linear and nonlinear function to describe the C-QTc relationship, will be based on graphical exploration, along with standard goodness-of-fit plots., Additionally, the effects of evobrutinib on ΔΔQTcF will be descriptively summarized at each postdose timepoint (by timepoint analysis). Number and frequency of QTcF values within specified ranges will be summarized. Further details will be described in the IAP.
Secondary		
2	ΔΔQTcF (moxifloxacin)	Assay sensitivity will be demonstrated by showing that the lower bound of the 90% CI of the predicted ΔΔQTcF (from C-QTc model) for moxifloxacin at the observed geometric mean C_{max} at 400 mg dose exceeds 5 ms. Further details will be described in the IAP.
4	ΔΔHR, ΔΔPR, ΔΔRR, ΔΔQRS, T-wave morphology and U-wave	The effects of evobrutinib on these endpoints will be evaluated at each postdose timepoint (by timepoint analysis). Further details will be described in the IAP.
5	PK parameters (in Section 8.4)	Summary statistics of PK parameters will be provided. All PK analyses will be performed on the PKAS.

9.4.3 Sequence of Analyses

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

10 References

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11 Appendices

Appendix 1 Abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
API	Active Pharmaceutical Ingredient
AxMP	Auxiliary Medicinal Product
BMI	Body Mass Index
BTK	Bruton's Tyrosine Kinase
CDISC	Clinical Data Interchange Standards Consortium
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Clinical Research Organization
CRU	Clinical Research Unit
CSR	Clinical Study Report
CYP3A4/5	Cytochrome P450 3A4/5
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EudraCT	European Clinical Trials Database
FIH	First In Human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HRT	Hormone Replacement Therapy
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
MS	Multiple Sclerosis
NIMP	Noninvestigational Medicinal Product
PD	Pharmacodynamic

PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
QTc	Corrected QT interval
QTcB	Corrected QT interval by Bazett's formula
QTcF	Corrected QT interval by Fridericia' formula
QTcI	Individual corrected QT interval
QTL	Quality Tolerance Limit
RMS	Relapsing Multiple Sclerosis
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCR	Screening
SoA	Schedule of Activities
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Event
TdP	Torsade de Pointes
THC	Tetrahydrocannabinol
TQT	Thorough QT
ULN	Upper Limit of Normal

Appendix 2 Study Governance

Financial Disclosure

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

Informed Consent Process

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

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable) who will be required to give consent for their data to be used, as specified in the informed consent.
- The participant will be informed that 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 Principal Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Principal Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

- The study will be conducted at a single center, the Clinical Pharmacology Unit of Nuvisan GmbH, Neu-Ulm, Germany. Nuvisan GmbH will be responsible for the following activities:
  - Clinical conduct and laboratory services
  - Data management
  - Statistical programming and analysis
  - PK analysis
  - Medical writing
  - Independent monitoring
  - Medical monitoring
  - Project management
  - Regulatory services

  Clinical trial supplies will be provided by Thermo Fisher.

  The12-lead Holter recorders, accessories and laptops will be supplied by the ECG core lab nabios GmbH, Munich, Germany.

  Primary and secondary hypothesis evaluation with regard to ECG will be conducted by Certara.

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

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

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

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g. unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the Phase 1 facility will provide the appropriate means to contact a physician. This includes the provision of a 24-hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

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

Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Principal Investigator and any other relevant study-appointed experts of the Sponsor and Nuvisan GmbH.

Publication

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

Dissemination of Clinical Study Data

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

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g. laboratory data). The Investigator is responsible for

verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Data Management Plan.

- The Investigator will maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- QTLs will not be predefined in this study because study duration is too short and number of study participants is too small to allow for meaningful QTL data collection.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.
- 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 25 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

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

Study and Site Start and Closure

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

Study and Site Closure

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further development of the Sponsor’s compound.
- Sponsor discontinuation of the study due to an unacceptable risk, any relevant toxicity, or negative change in the risk/benefit assessment.

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any third-party service providers of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Contraception and Barrier Requirements

Note:
This study includes women of nonchildbearing potential only (Section 5.1). However, please see the definition for a woman of childbearing potential below for information on criteria to be used.

Definitions:

Woman of childbearing potential:

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

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

Postmenopause:

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

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

Permanent sterilization:

For this study, permanent sterilization includes:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

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

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

AE Definition

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

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

SAE Definition

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

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

a. Results in death.

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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 and AESIs.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

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

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

  Do not confuse an AE that is assessed as severe with an SAE. Severe is a category used to rate the intensity of an event; both AEs and SAEs can be assessed as severe. An event is

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

Assessment of Causality

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

Follow-up of AEs and SAEs

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

Reporting of SAEs

SAE Reporting by a Paper Form

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

Reporting of AESIs

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

Reporting of Pregnancies

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

Appendix 5 Liver Safety: Suggested Actions and Follow-up Assessments

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

All confirmed events of ALT or AST ≥ 5 × ULN triggers stopping criteria.

All confirmed events of ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN triggers stopping criteria.

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

Appendix 6 Clinical Laboratory Tests

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

Laboratory Assessment	Parameter	Notes
Biochemistry	Albumin	
	Alanine Aminotransferase	
	Alkaline Phosphatase	
	Amylase	
	Aspartate Aminotransferase	
	Bicarbonate	
	Total Bilirubin	
	Blood Urea Nitrogen	
	Calcium	
	Chloride	
	Cholesterol	
	Creatinine	
	Creatine Phosphatase	
	Glomerular Filtration Rate, Estimated	Refer to SoA
	Gamma Glutamyl Transferase	
	Glucose	
	Inorganic Phosphate	
	Lactate Dehydrogenase	
	Lipase	
	Magnesium	
	Potassium	
	Sodium	
	Triglycerides	
	Urate	
Coagulation	• Prothrombin Intl. Normalized Ratio • Activated partial thromboplastin time	
Hematology	Hematocrit	
	Hemoglobin	
	Leukocytes with Differential: Neutrophils (absolute/%) Lymphocytes (absolute/%) Monocytes (absolute/%) Eosinophils (absolute/%) Basophils(absolute/%)	
	Mean Corpuscular Hemoglobin (MCH)	
	Mean Corpuscular Volume (MCV)	
	Platelets Erythrocytes	

Laboratory Assessment	Parameter	Notes
Hormonal	Thyroid stimulating Hormone	
Routine Urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick.	
	Microscopic examination (if blood or protein is abnormal with positive dipstick).	
	In case of a positive result for hemoglobin, leukocyte esterase, protein or nitrite, a flow cytometry count and classification will be performed.	
Pregnancy Testing	Serum human Choriogonadotropin Beta pregnancy test	At all timepoints listed in the SoA (see Section 1.3).
Other Screening Tests	• Follicle stimulating hormone	All study-required laboratory assessments will be performed by a central laboratory (Nuvisan's clinical laboratory)
	• Urine drug screen (to include at minimum: amphetamine, methamphetamine, barbiturates, 3,4-methylenedioxymethamphetamine [ecstasy], cocaine, opiate, cannabinoids, benzodiazepine, methadone, phencyclidine, oxycodone, and tricyclic antidepressants,)	At Screening and Day -1 of each period.
	• Serology (HIV-1/2 Antibody, hepatitis B virus surface antigen, hepatitis B virus core antibody, hepatitis C virus antibody, QuantiFERON test)	
	• SARS-CoV-2 antigen	At Screening and Day -1 of each period. According to local regulations at the time of study conduct.
	• Thyrotropin (thyroid stimulating hormone)	
	• Cotinine	At Screening and Day -1 of each period.
	• Ethanol (Alcohol breath test)	At Screening and Day -1 of each period.
	• Estimated Glomerular Filtration Rate based on Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (2009)	

MCH= Mean corpuscular hemoglobin; MCV=Mean corpuscular volume, SARS-CoV-2=severe acute respiratory syndrome coronavirus type 2.

Appendix 7 Protocol Amendment History

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

Protocol Version 2.0 (24 October 2022)

Overall Rationale for the Amendment

This non-substantial amendment was prepared to correct a typographical error in the schedule of activities. The PK sampling at 16 h postdose is not included in the schedule of activities, although the corresponding ECG measurement is included in the schedule of activities. The 16 h postdose blood sampling is present in Table 1 (Time Deviations from PK sampling times, Section 8.4.1) and is also consistently displayed in the ICF.

Additionally, in Section 7.1 there was a harmonization with the preexisting next sentence. It was clarified, that if study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety assessments.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	The PK sampling at 16 h postdose was included.	To correct a typographical error, the PK sampling at 16 h postdose was included.
7.1 Discontinuation of Study Intervention	It was clarified, that if study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety assessments.	No content change – just harmonization with the preexisting next sentence.

Appendix 8 Sponsor Signature Page

Study Title:	A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of Evobrutinib on the QTc (Corrected QT) Interval in Healthy Adult Participants
Regulatory Agency Identifying Numbers:	EudraCT: 2022-002664-78
Clinical Study Protocol Version:	01 December 2022/Version 3.0

I approve the design of the clinical study:

PPD

Electronically signed by: PPD

Date: Dec 1, 2022 14:59 GMT+1

Dec 1, 2022

Signature Date of Signature

Name, Academic Degree:	PPD MD
Function/Title:	PPD
Institution:	Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany
Address:	Frankfurter Str. 250, 64293 Darmstadt, Germany
General Merck Phone Number:	Office: +49 6151 72 3564
General Merck Fax Number:	Not applicable

Appendix 8 Principal Investigator Signature Page

Study Title:	A Single-Dose, Randomized, Double-Blind, Placebo- and Positive-Controlled, 4-Way Crossover Study to Evaluate the Effect of Evobrutinib on the QTc (Corrected QT) Interval in Healthy Adult Participants
Regulatory Agency Identifying Numbers:	EudraCT: 2022-002664-78
Clinical Study Protocol Version:	01 December 2022/Version 3.0
Site Number:	Not applicable

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

PPD

Signature

01 DEC 2022

Date of Signature

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