Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase I, Open-Label, Two-Part Study of the Effect of Multiple-Dose Evobrutinib on Transporter Substrates Digoxin, Metformin, Rosuvastatin, and Sumatriptan Pharmacokinetics in Healthy Participants
Study Number:	MS200527_0078
Protocol Version:	24 August 2021/Version 2.0
Merck Compound:	Evobrutinib (M2951)
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	Phase I
Short Title:	Drug-Drug Interaction Study of Evobrutinib on Transporter Substrates
Principal Investigator:	PPD Nuvisan GmbH, PPD PPD Neu-Ulm, Germany
Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 64293, Darmstadt, Germany
Regulatory Agency Identifying Numbers:	EudraCT: 2021-001923-42
Keywords	• Clinical Pharmacology

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	13 Jul 2021

Protocol Version (24-August-2021)

Overall Rationale for the Amendment

This protocol amendment was requested by the German competent authority and involved Ethics Committees.

Section # and Name	Description of Change	Brief Rationale
4.4 End of Study Definition	Editorial change	To correct a typo.
5 Study Population; Appendix 2 Study Governance	Deletion of "or the participant's legal/ his/her(their) legally authorized representative (where allowed by local laws and regulations)".	It is not allowed in Germany that persons with a legally authorized representative participate in the study.
5.2 Exclusion Criteria	Migraine was added to exclusion criterion number 1.	To clarify that participants with a history of diagnosed migraine should not be included in the study.
	In exclusion criterion 17 it was clarified that participants with amylase and lipase values out of the normal range and not as previously greater than 2 × the upper limit of normal would be excluded from the study.	To minimize the additional risk of pancreatitis observed with rosuvastatin.
8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting; Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	It was clarified that serious adverse events and adverse events of special interest have to be reported to the Sponsor or designee immediately.	To meet the requirements of the German competent authority.
8.4 Pharmacokinetics	Table 4 PK Sampling Time Windows: "5" added before "min" under time point > 1 to 12 hours postdose.	To correct a typo.

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase I, Open-Label, Two-Part Study of the Effect of Multiple-Dose Evobrutinib on Transporter Substrates Digoxin, Metformin, Rosuvastatin, and Sumatriptan Pharmacokinetics in Healthy Participants

Short Title: Drug-Drug Interaction Study of Evobrutinib on Transporter Substrates

Rationale: The results of nonclinical studies with evobrutinib have indicated the potential for evobrutinib to be an inhibitor of several drug transporters (e.g., organic cation transporter 1 [OCT1], P-glycoprotein [P-gp], multidrug and toxin extrusion [MATE]1/MATE2-K, breast cancer resistance protein [BCRP]).

The intent of this study is to provide information pertaining to the effect of evobrutinib on transporter activity in humans using drug transporter substrates. The selected drug transporter substrates are well characterized and have been established as selective substrates that are commonly used in clinical drug-drug interaction (DDI) studies and, except for sumatriptan (OCT1), are considered as index substrates in the most recent update of the Food and Drug Administration (FDA) guidance and European Medicines Agency (EMA) guideline.

Results of this study may be used to make future recommendations regarding the concomitant administration of specific transporter substrates with evobrutinib.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To investigate the effect of multiple doses of evobrutinib on single doses of digoxin, metformin, and rosuvastatin (Part 1), and sumatriptan (Part 2) PK in healthy participants	• Plasma transporter substrates $AUC_{0-\infty}$ and C_{max}
Secondary	
To assess the safety and tolerability of evobrutinib when administered together with digoxin, metformin, and rosuvastatin (Part 1), and sumatriptan (Part 2) in healthy participants	• Nature, occurrence, and severity of TEAEs • Absolute values and changes in safety laboratory tests • Single 12-lead ECGs evaluated by Investigator, and • Vital signs assessed from time of first dose to end of study participation
To characterize the effect of evobrutinib on digoxin, metformin, and rosuvastatin (Part 1), and sumatriptan (Part 2) secondary PK parameters in healthy participants	• Plasma PK parameters (Part 1 and Part 2): t_{max}, $t_{½}$, and $AUC_{0-tlast}$, CL/F, and V_Z/F • Urine PK parameters (Part 1, metformin only): Ae_{0-36} and CL_R

CL/F=apparent total body clearance, CL_R=renal clearance, ECG= electrocardiogram, PK=pharmacokinetics, TEAE=treatment-emergent adverse event, V_Z/F= apparent volume of distribution.

Overall Design: This will be a nonrandomized, open-label, single-sequence, two-part Phase I study in 40 healthy participants (20 per part).

Brief Summary:

The purpose of this study is to investigate the effect of multiple doses of evobrutinib on single doses of digoxin, metformin, and rosuvastatin (Part 1), and sumatriptan (Part 2) PK in healthy participants. Study details include:

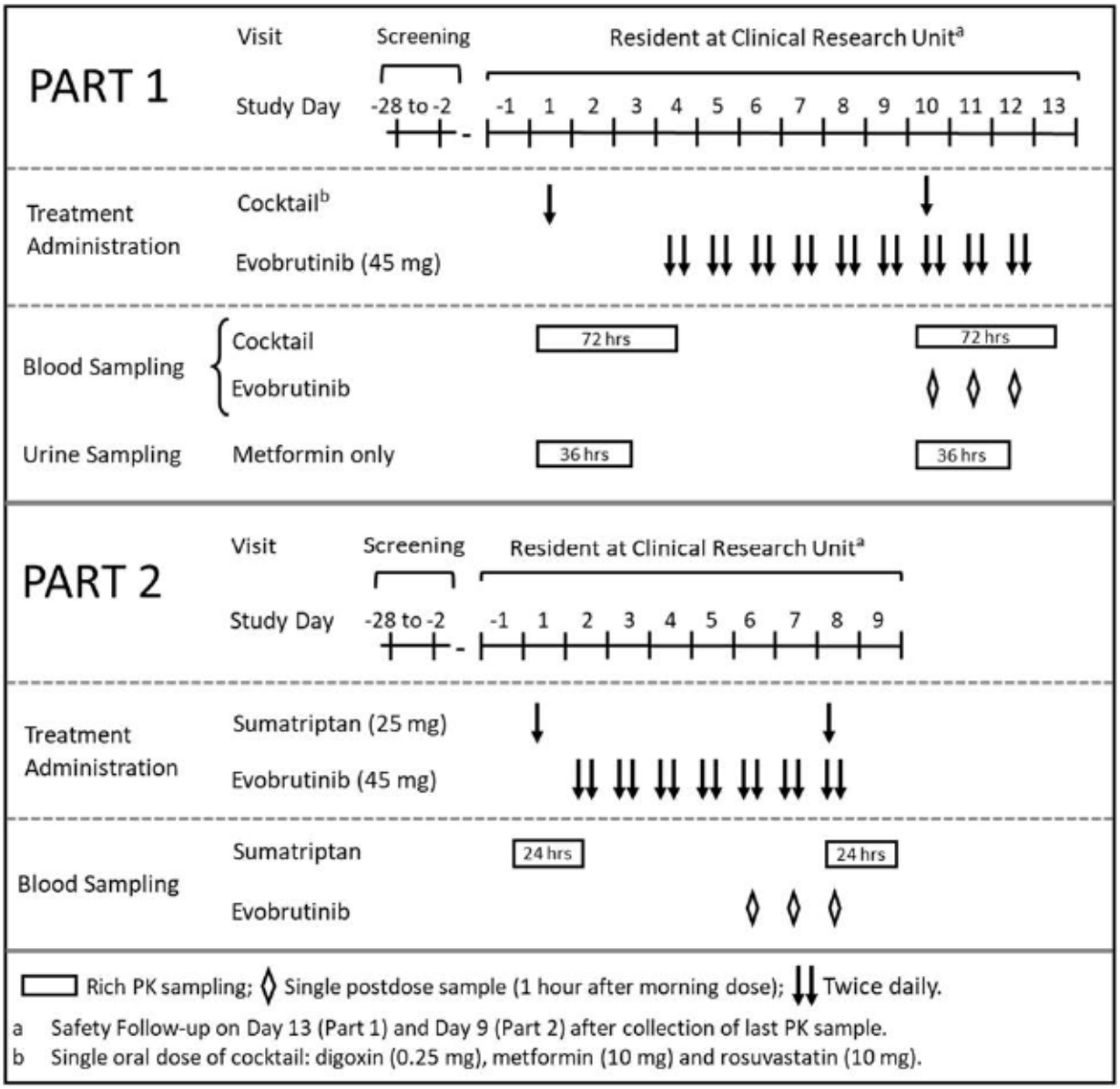
- Study Duration: up to 6 weeks for each part
- Treatment Duration: 12 days (Part 1), 8 days (Part 2)
- Visit Frequency: Part 1: Participants will be resident in the Clinical Research Unit (CRU) from Day -1 to Day 13; Part 2: Participants will be resident in the CRU from Day -1 to Day 9

Number of Participants: Part 1: A maximum of 20 participants will be assigned to study intervention such that approximately 16 evaluable participants complete the study. Part 2: A maximum of 20 participants will be assigned to study intervention such that approximately 16 evaluable participants complete the study.

Study Intervention Groups and Duration: 12 days (Part 1), 8 days (Part 2), single-sequence study (each part)

Involvement of Special Committee(s): No

1.2 Schema



PK=pharmacokinetic.

1.3 Schedule of Activities

Part 1: Schedule of Assessments

Assessments & Procedures	Screening	Intervention Period (Days)													Safety Follow-up	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Informed consent	X															Prior to any Screening activity.
Participants resident at CRU		< ----------													>	
Eligibility criteria	X	X														For re-check of eligibility criteria on Day -1, Sections 5.1 and 5.2).
Demography, height & weight, medical history	X															Demography to include, at minimum, age, sex, race, and ethnicity.
Physical examination	X	X													X	Brief examination on Day -1 to check eligibility.
Serum pregnancy test	X	X													X	
Viral serology, TSH and QuantiFERON® test	X															
Clinical laboratory tests	X	X										X			X	Details in Appendix 5.
Cotinine, drug screen, alcohol breath test, SARS-CoV-2 and FSH	X	X														FSH in postmenopausal women at Screening only.
ECG & vital signs	X	X	X									X			X	Predose, 4 and 6 hours after cocktail administration on Days 1 and 10.
CCI																
Digoxin, metformin, rosuvastatin administration			X									X				Single dose, fed conditions (Sections 5.3.1 and 6.1).
Blood collection digoxin, metformin, rosuvastatin			X	X	X	X						X	X	X	X	Table 1 and Section 8.4.
Urine collection for metformin analysis			X	X								X	X			Table 1 and Section 8.4.

Assessments & Procedures	Screening	Intervention Period (Days)													Safety Follow-up	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Evobrutinib administration						X	X	X	X	X	X	X	X	X		Twice daily, fed conditions (Sections 5.3.1 and 6.1).
PK blood sample evobrutinib												X	X	X		Table 1 and Section 8.4.
AE/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

AE=adverse events, CRU=clinical research unit, ECG=electrocardiogram, FSH=follicle stimulating hormone, PK=pharmacokinetics, SARS-CoV-2=severe acute respiratory syndrome coronavirus type 2, TSH=thyroid stimulating hormone.

Table 1 Part 1: PK Sampling Schedule

Sample type	Day 1	Day 2	Day 3	Day 4	Day 10	Day 11	Day 12	Day 13
Blood sampling times (transporter cocktail)	Predose, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 hours postdose	24, 36 hours postdose	48, 60 hours postdose	72 hours postdose	Predose 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 hours postdose	24, 36 hours postdose	48, 60 hours postdose	72 hours postdose
Urine sampling intervals (metformin)	Predose, 0 to 4, 4 to 8, 8 to 12 hours postdose	12 to 24, 24 to 36 hours postdose			Predose, 0 to 4, 4 to 8, 8 to 12 hours postdose	12 to 24, 24 to 36 hours postdose		
Blood sampling times (evobrutinib)					1 hour[a]	1 hour[a]	1 hour[a]	

Note: for associated sampling time windows see Section 8.4 (Table 4).

a Post morning evobrutinib dose.

Part 2: Schedule of Assessments

Assessments & Procedures	Screening	Intervention Period (Days)									Safety Follow-up	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Informed consent	X											Prior to any Screening activity.
Participants resident in the CRU		< ---------- >										
Eligibility criteria	X	X										For re-check of eligibility criteria on Day -1, Sections 5.1 and 5.2.
Demography, height & weight, medical history	X											Demography to include, at minimum, age, sex, race, and ethnicity.
Physical examination	X	X									X	Brief examination on Day -1 to check eligibility.
Serum pregnancy test	X	X									X	
Viral serology, TSH and QuantiFERON® test	X											
Clinical laboratory tests	X	X								X	X	Details in Appendix 5.
Cotinine, drug screen, alcohol breath test, SARS-CoV-2 and FSH	X	X										FSH in postmenopausal women at Screening only.
ECG & vital signs	X	X	X							X	X	Predose
CCI												
Sumatriptan administration			X							X		Single dose, fed conditions (Sections 5.3.1 and 6.1).
PK samples sumatriptan			X	X						X	X	Table 2 and Section 8.4.
Evobrutinib administration				X	X	X	X	X	X	X		Twice daily, fed conditions (Sections 5.3.1 and 6.1).
PK blood sample evobrutinib								X	X	X		Table 2 and Section 8.4.
AE/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	

AE=adverse events, CRU=clinical research unit, ECG=electrocardiogram, FSH=follicle stimulating hormone, PK=pharmacokinetics, SARS-CoV-2=severe acute respiratory syndrome coronavirus type 2, TSH=thyroid stimulating hormone.

Table 2 Part 2: PK Sampling Schedule

Sample type	Day 1	Day 2	Day 6	Day 7	Day 8	Day 9
Blood sampling time (sumatriptan)	Predose 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 hours postdose	24 hours postdose			Predose 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 hours postdose	24 hours postdose
Blood sampling time (evobrutinib)			1 hour[a]	1 hour[a]	1 hour[a]	

Note: for associated sampling time windows see Section 8.4 (Table 4).

a Post morning evobrutinib dose.

2 Introduction

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

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

There is extensive clinical experience in the use of the transporter substrates digoxin, metformin, rosuvastatin, and sumatriptan selected for this study (Shibata 2020, Stopfer 2018). Full information about the potential side effects of these transporter substrates administration is described in the SmPCs for the respective compounds.

2.1 Study Rationale

The results of nonclinical studies with evobrutinib have indicated the potential for evobrutinib to be an inhibitor of several drug transporters (e.g., OCT1, P-gp, MATE2-K, BCRP).

The intent of this study is to provide information pertaining to the effect of evobrutinib on transporter activity in humans using drug transporter substrates. The selected drug transporter substrates are well characterized (Stopfer 2018, Shibata 2020) and have been established as selective substrates that are commonly used in clinical DDI studies and, except for sumatriptan (OCT1) are considered as index substrates in the most recent update of the FDA guidance and EMA guideline.

Results of this study may be used to make future recommendations regarding the concomitant administration of specific transporter substrates with evobrutinib.

2.2 Background

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

Evobrutinib (also known as M2951 and MSC2364447C) is an oral, selective, irreversible inhibitor of BTK. Evobrutinib inhibits primary B cell responses (BCR), 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 (FcR) activation. All three 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).

Evobrutinib will be dosed under fed conditions in this study. Administration of evobrutinib to healthy participants 30 minutes after the start of a high-fat or low- to moderate-fat meal resulted in a 50% to 75% increase in exposure (studies CCI [redacted], and administration with a light meal (toast and coffee) resulted in a 38% increase in exposure (study MS200527_0072). Preliminary data from a recent study utilizing the current TF2 formulation demonstrated that administration of evobrutinib TF2 30 minutes after the start of a high-fat breakfast resulted in a 61% and 12% increase in AUC and C_{max}, respectively, relative to fasted conditions (study MS200527_0077). Median (range) t_{max} under fed conditions was 1.5 hours (0.5 to 3 hours).

Drug transporters

During development of NMEs, characterization of potential DDI liabilities with involvement of drug transporters is required (König 2013, Giacomini 2010, Zolk 2011). In particular, regulatory authorities request a thorough assessment of the propensity of an NME to cause DDIs by inhibition of those drug transporters with compelling clinical evidence for relevance (Hillgren 2013), including P-gp (ATP-ABCB1), OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, and BCRP (ABCG2). Recently, interest in the use of the probe drug cocktail approach in transporter DDI clinical trials has increased considerably (Stopfer 2016, Stopfer 2018, Prueksaritanont 2017, Zhang 2017). Such cocktails allow simultaneous investigation of the effect of an NME on the PK of several probe drugs with different transporter specificities in a single trial, thus reducing the number of clinical DDI studies in the development program (Stopfer 2018).

Table 3 Summary of Drug Transporters and Their Index Substrates

Drug Transporter	Clinical Substrate
P-gp	Digoxin
MATE1, MATE2-K	Metformin
BCRP	Rosuvastatin
OCT1	Sumatriptan

Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-1 (for digoxin, metformin and rosuvastatin); Chu 2018 (sumatriptan).

BCRP=Breast Cancer Resistance Protein, MATE1/2= Multidrug and Toxin Extrusion 1/2, OCT1= Organic Cation Transporter 1, P-gp=P-glycoprotein.

2.3 Benefit/Risk Assessment

Evobrutinib

As of 31 July 2020, approximately 1,318 adult participants in 14 completed and 4 ongoing clinical studies have been exposed to evobrutinib, including healthy participants (227),

participants with RMS (261), systemic lupus erythematosus (451), or rheumatoid arthritis (363), and participants with renal impairment (31). Evobrutinib was generally safe and well tolerated in all participants. The TEAEs have been primarily mild to moderate in severity.

The evobrutinib treatment duration in this study will be 9 days (Part 1) or 7 days (Part 2), with 45 mg twice daily dosing of evobrutinib under fed conditions. This regimen was previously tested in healthy participant studies and does not exceed exposures reached in first-in-human clinical study CCI where single doses of evobrutinib from 25 up to 500 mg and 14 days of dosing with 25, 75, and 200 mg/day were tested and shown to be well tolerated.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of evobrutinib may be found in Section 4.2 and the IB.

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

Transporter Substrates

Transporter substrates are to be administered at relatively low doses and are unlikely to cause any listed adverse event, which are provided for completeness (Section 2.3.1).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of on the transporter substrates (digoxin, metformin, rosuvastatin, and sumatriptan) may be found in the respective SmPCs.

2.3.1 Risk Assessment

Safety Risks Applicable to Healthy Participants

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Evobrutinib		
Important identified risk: Elevated liver transaminases	Elevated liver transaminases have been observed in participants 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, asymptomatic, and reversible, and occurred within 6 months of treatment. This has not been observed in healthy participants after a single dose nor in participants receiving short treatment with evobrutinib.	Participants with known history of hepatic disorder will not be included in the study. Study participants will be confined, and liver transaminases will be adequately monitored during the study.
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.	Female participants of childbearing potential must not be pregnant, must have a negative pregnancy test at the time of enrollment and use highly effective contraception (Section 5.1) during the study period and for 120 days after the last dose and agree not to donate eggs for reproduction during this period.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Digoxin (SmPC)		
Important identified risk: Arrhythmias Digoxin Toxicity and Overdosage	Digoxin increases the ability of heart muscle to contract by complex mechanisms involving sodium, potassium and calcium ions. Any changes in the calcium ion mobility can therefore impact on heartbeat regulation. Compared to a therapeutic use of digoxin with a loading dose of 0.5 to 0.75 mg given as 2 doses 6 hours apart, only a single dose of 0.25 mg is given in this study. The symptoms and signs of toxicity are generally nonspecific: fatigue, blurred vision, change in color vision (e.g. "yellow vision"), weight loss, nausea (feeling sick), vomiting, diarrhea, abdominal pain, headache, dizziness, confusion, and delirium. It is also associated with irregular heartbeats.	Appropriate ECG monitoring after digoxin administration, Sections 1.3 and 8.2.3
Rosuvastatin (SmPC)		
Important Identified Risk: Rhabdomyolysis	As with other cholesterol-lowering medicines, a very small number of people have experienced unpleasant muscle effects and rarely these have gone on to become a potentially life-threatening muscle damage known as rhabdomyolysis. This has been reported in rosuvastatin-treated participants with all doses, and in particular with doses more than 20 mg rosuvastatin.	Rosuvastatin should be stopped and medical support should be sought immediately if any unusual aches or pains in muscles occur.
Increased transaminases; Hepatitis; Jaundice	Increase in liver enzymes in the blood has been observed in 1 to 10 users in 10,000. The liver problems following rosuvastatin are reported more with the highest dose that is 40 mg. Jaundice and hepatitis has been observed in less than 1 user in 10,000.	Blood test for liver function test should be carried out before and after treatment with rosuvastatin.
Increased transaminases; Pancreatitis	Severe stomach pain (caused by inflamed pancreas) has been observed in 1 to 10 users in 10,000.	Report to treating physician any diagnosis or symptoms of pancreatitis
Increased transaminases; Memory Loss	Memory loss has been observed in less than 1 user in 10,000.	Memory loss is not expected in this study and participants should be permanently discontinued in case of occurrence.
Increased transaminases; Proteinuria	Participants treated with higher doses of rosuvastatin (in particular rosuvastatin 40 mg) are likely to develop increase in the amount of protein in the urine. This usually returns to normal on its own without having to stop taking rosuvastatin tablets.	Routine urine test to detect proteinuria during the follow-up of participants on highest dose of rosuvastatin is recommended.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Sumatriptan (SmPC)		
Ischaemic heart disease	Following administration, sumatriptan can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat. Where such symptoms are thought to indicate ischemic heart disease, no further doses of sumatriptan should be given and appropriate evaluation should be carried out. Special consideration should be given to postmenopausal women and males over 40 with these risk factors. These evaluations, however, may not identify every patient who has cardiac disease, and in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.	Study conducted with healthy participants under in-house monitoring of clinical status at the CRU.
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 to ECG electrodes will not be included in the study.
Other		
Not applicable		

AE=adverse event, CRU=clinical research unit, IB=Investigator's Brochure, ECG=electrocardiogram, SmPC=summary of product characteristics.

Safety Risks not Applicable for Healthy Participants

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Metformin (SmPC)		
Important Identified Risk: Lactic acidosis	Lactic acidosis is a rare, but serious (high death rate in the absence of prompt treatment), condition that can occur due to metformin build up. Reported cases of lactic acidosis in participants on metformin have occurred primarily in diabetic participants with significant kidney failure and in participants with other associated risk factors.	All participants under metformin treatment should discuss with their doctors if they are having muscle cramps with digestive disorders, such as abdominal pain, and severe asthenia (weakness / loss of strength), as these symptoms are characteristic of lactic acidosis
Important Identified Risk: Liver Insufficiency	It is not indicated to use metformin in participants with liver insufficiency.	Participants with liver insufficiency should avoid use of metformin
Important Identified Risk: Hypoglycemia	Caution is advised when metformin is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides) in order to avoid hypoglycemia	When using metformin in combination with insulin or other oral antidiabetics participant should always take the exact dose specified by their physicians. Monitoring of blood glucose is necessary frequently.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Use in participants with kidney impairment	Decreased kidney function in elderly subjects is frequent and symptom free. Elderly participants should adjust the metformin dosage due to the potential for decreased kidney function. It is not indicated to use metformin in participants with kidney failure or kidney dysfunction (creatinine clearance < 60 ml/min).	Regular assessment of kidney function is necessary. Creatinine clearance (amount of creatinine in urine in comparison to the blood) should be determined before initiating treatment and regularly thereafter
Sumatriptan (SmPC)		
Seizures	Sumatriptan should be used with caution in patients with a history of seizures or other risk factors which lower the seizure threshold, as seizures have been reported in association with sumatriptan.	Study conducted with healthy participants under in-house monitoring of clinical status at the CRU.

CRU=clinical research unit, SmPC=summary of product characteristics.

2.3.1.1 Potential Risks associated with the COVID-19 Pandemic Situation

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

Evobrutinib is a BTK inhibitor and, as such, works as an immunomodulator. There was some decrease in immunoglobulin M, an increase in immunoglobulin A, and some modest changes in immunoglobulin G following long-term treatment with evobrutinib; these changes were not clinically significant. In addition, duration of the evobrutinib treatment in this study will be limited to 9 days (Part 1) and 7 days (Part 2). Although BTK is not required to clear viral infections, apart from enteroviruses, no information is available regarding BTK inhibitors as a class or evobrutinib- specifically regarding the risk for either contracting SARS-CoV-2 or severity of COVID-19 at this point. The published data on approved BTK inhibitors (e.g., ibrutinib and acalabrutinib) used in oncology suggest a protective effect of BTK inhibitors for severity and mortality of COVID-19 (Scarfò 2020; Thibaud 2020; Treon 2020).

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

In order to minimize the risk coming from a current infection and the risk of getting infected by other participants during the in-house phase (covering the whole treatment phase) of the study, the following measures are implemented: Only participants without any symptoms of a respiratory disease and without contact to any known SARS-CoV-2 positive patient or

COVID-19 patient will be included into the study. Furthermore, as a part of the clinical study procedures, participants will be closely monitored (including for signs of COVID-19) during the entire study duration. Continuation of the study in case of a SARS-CoV-2 infection in the study participant or an identified contact to a SARS-CoV-2 positive participant or COVID-19 patient will be done at the Investigator's discretion and agreement with the medical monitoring team. The Sponsor will monitor the events related to any SARS-CoV-2 infection reported following evobrutinib regularly and update the recommendations, if necessary.

2.3.2 Benefit Assessment

The healthy 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 (Section 5.2), adequate biochemical and hematology laboratory monitoring (Section 8.2.4), and observation of vital signs and ECGs (Sections 8.2.2 and 8.2.3). Evobrutinib will be discontinued in case of events that unacceptably endanger the safety of the participant (Section 8.3). Participants will be admitted to the study site for the duration of the study to allow continuous safety monitoring.

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with evobrutinib and the transporter substrates digoxin, metformin, rosuvastatin, and sumatriptan are justified in healthy participants.

3 Objectives and Endpoints

Objectives	Endpoints
Primary	
To investigate the effect of multiple doses of evobrutinib on single doses of digoxin, metformin, and rosuvastatin (Part 1), and sumatriptan (Part 2) PK in healthy participants	• Plasma transporter substrates $AUC_{0-\infty}$ and C_{max}
Secondary	
To assess the safety and tolerability of evobrutinib when administered together with digoxin, metformin, and rosuvastatin (Part 1), and sumatriptan (Part 2) in healthy participants	• Nature, occurrence, and severity of TEAEs • Absolute values and changes in safety laboratory tests • Single 12-lead ECGs evaluated by Investigator, and • Vital signs assessed from time of first dose to end of study participation
To characterize the effect of evobrutinib on digoxin, metformin, and rosuvastatin (Part 1), and sumatriptan (Part 2) on secondary PK parameters in healthy participants	• Plasma PK parameters (Part 1 and Part 2): t_{max}, $t_{½}$, and $AUC_{0-tlast}$, CL/F, and V_Z/F • Urine PK parameters (Part 1, metformin only): Ae_{0-36} and CL_R
CCI	

CL/F=apparent total body clearance, CLR=renal clearance, ECG=electrocardiogram, PK=pharmacokinetics, TEAE=treatment-emergent adverse event, V_Z/F= apparent volume of distribution.

See Section 9.4 for the statistical aspects of the endpoints.

4 Study Design

4.1 Overall Design

Study Design	Nonrandomized, open-label, single-sequence (for each part; Sections 1.2 and 1.3)
Control Method	Not applicable
Single or Multicenter	Single center
Control Group	Not applicable
Study Population Type	Healthy participants (Section 5.1)
Level and Method of Blinding	Not applicable
Bias Minimalization Method(s)	Not applicable
Study Intervention Assignment Method	Not applicable
Involvement of Special Committee(s):	No
Total Duration of Study Participation per Participant	Up to 6 weeks, including the Screening period (maximum 4 weeks) and a maximum of 2 weeks of intervention period, including the Safety Follow-up on the day after the last dose of study intervention, Day 13 for Part 1 and Day 9 for Part 2 (Sections 1.2 and 1.3).
Provisions for Study Extension or Entry into Roll-Over Studies	Not applicable
Adaptive Aspects of Study Design	Not applicable

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

4.2 Scientific Rationale for Study Design

The study design and endpoints are typical for a DDI study of this type. The effect of evobrutinib on transporter activities will be investigated by measurement of the PK of the transporter substrates digoxin, metformin, rosuvastatin, and sumatriptan. Oral administration of the probe drug transporter substrates is expected to be a sensitive test for potential interactions with drug transporters such as P-gp, MATE1/MATE2-K, BCRP, and OCT1 since they reflect effects on both presystemic and systemic clearance. The transporter substrate cocktail (digoxin, metformin, and rosuvastatin) will be administered during Part 1 of the study as a reference treatment on Day 1 followed on Day 4 through Day 12 by multiple doses of evobrutinib twice daily, with a second dose of substrate cocktail given with the morning dose of evobrutinib on Day 10. During

Part 2, sumatriptan will be administered on Day 1 as reference and on Day 8, and evobrutinib will be administered twice daily on Days 2 through 8.

A single-sequence design for Part 1 and Part 2 was chosen because the exact mechanism of inhibition of the transporters by evobrutinib and therefore the time course of on- / offset of these effects are not known. Therefore, evobrutinib will be administered twice daily for 6 days before the second administration of transporter substrates in each study part.

The transporter substrate cocktail to be used in Part 1 of this study (digoxin [0.25 mg], metformin [10 mg] and rosuvastatin [10 mg]) has been optimized as a screening tool for transporter mediated DDIs (Wiebe 2020, Stopfer 2018) based on PK analyses of the substrates both separately and in combination. The safety profiles of the individual substrates of the cocktail are well established since these drugs are routinely used in clinical practice. Stopfer reported mild or moderate adverse events in 15 of 30 participants (Stopfer 2018). Similarly, for Part 2, sumatriptan (25 mg) has been recommended and used as a substrate for determining PK effects of potential OCT1 effectors (Chu 2018). The safety profile of sumatriptan is well established since it is routinely used in clinical practice (Sumatriptan SmPC).

Because some of the transporters to be investigated in this study might exist as polymorphic variants, which could affect the interpretation of the study results, samples for CCI [redacted] will be collected and analyzed.

4.2.1 Participant Input into Design

Not applicable.

4.3 Justification for Dose

Evobrutinib

The evobrutinib dose to be used in this study, 45 mg twice daily, with each dose to follow a standardized meal, is the same as for Phase III studies evaluating evobrutinib in participants with RMS. This dose is anticipated to be well tolerated based on prior clinical experience and is adequate to characterize evobrutinib PK.

Evobrutinib will be dosed under fed conditions in this study. Evobrutinib exposure increased when given with either a high-fat or low-fat meal. Following administration of the TF1 tablet formulation, mean $AUC_{0-\infty}$ and C_{max} increased by 70% and 27%, respectively, following a high-fat meal, and by 50% and 25%, respectively, following a low-fat meal. Data from a recent study utilizing the current TF2 formulation demonstrated that administration of evobrutinib TF2 30 minutes after the start of a high-fat breakfast resulted in 61% and 12% increases in AUC and C_{max}, respectively, relative to fasted conditions (Study MS200527_0077). Additionally, evobrutinib exposure was increased by approximately 32% to 36% when administered approximately 2 hours after a meal. The exposure in this study is therefore expected to not exceed that of other studies in healthy participants, in which a single dose up to 500 mg and multiple doses up to 200 mg evobrutinib for 14 days were administered and well tolerated.

Drug transporter substrates

The doses for the cocktail of transporter substrates digoxin (0.25 mg tablet), metformin (10 mg oral solution) and rosuvastatin (10 mg tablet) in Part 1 have been chosen based on the extensive experience with these drugs in routine clinical practice; i.e., digoxin in treatment of congestive cardiac failure, metformin in the treatment of type 2 diabetes mellitus, and rosuvastatin in the treatment of hypercholesterolemia. Furthermore, consideration was given to publications supporting the optimizing of transporter substrate cocktails for DDI studies (Stopfer 2018, Shibata 2020). A subtherapeutic metformin dose is to be used because of potential interaction with rosuvastatin (the typical clinical dose of metformin starts at 500 mg, Stopfer 2018).

The dose for the OCT1 transporter substrate sumatriptan (routinely used to treat migraine) in Part 2 has been used previously in similar studies (e.g. ClinicalTrials.gov identifier: NCT04355845) and is considered adequate to assess any potential PK effects on OCT1 activity due to evobrutinib administration.

4.4 End of Study Definition

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

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

Study Termination Criteria

The study will be terminated if:

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

General information on study termination is specified in Appendix 2.

5 Study Population

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

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

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

5.1 Inclusion Criteria

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

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 body mass index within the range 19.0 and 30.0 kg/m^2 (inclusive).

Category	Criterion
Sex and Contraception/Barrier Requirements	4. Male or Female The Investigator confirms that each participant agrees to use appropriate contraception and barriers, if applicable. The contraception, barrier, and pregnancy testing requirements are below. Contraceptive use will be consistent with local regulations on contraception methods for those participating in clinical studies. • Is **not** breastfeeding • Is **not** pregnant (i.e., has a negative serum pregnancy test, as required by local regulations, within 24 hours before the first dose of study intervention). • Is **not** a WOCBP. • If a WOCBP, uses a highly effective contraceptive method (i.e., with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods: 1. Before the first dose of the study intervention(s), if using hormonal contraception: • Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses; **OR**, • Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay. 2. During the study intervention period 3. After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 120 days after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period. The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention. The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

Category	Criterion
Informed Consent	5. Capable of giving signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the ICF and this protocol.
Smoking	6. Are stable non-smokers for at least 3 months preceding Screening.

5.2 Exclusion Criteria

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

Category	Criterion
Medical Conditions	1. History or presence of clinically relevant respiratory, gastrointestinal, renal, hepatic, hematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, dermatological, connective tissue, metabolic diseases or disorders, migraine, or 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.
	3. Prior history of cholecystectomy or splenectomy, and any clinically relevant surgery within 6 months prior to Screening.
	4. History of any malignancy.
	5. History of chronic or recurrent acute infection or any bacterial, viral, parasitic or fungal infections within 30 days prior to Screening and at any time between Screening and admission, or hospitalization due to infection within 6 months prior to Screening.
	6. History of shingles within 12 months prior to Screening.

Category	Criterion
	7. History of drug hypersensitivity, ascertained or presumptive allergy/hypersensitivity to the active drug substance and/or formulation ingredients; history of serious allergic reactions leading to hospitalization or any other hypersensitivity reaction in general 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.
	8. History of alcoholism or drug abuse within 2 years prior to Screening, or positive for drugs of abuse, nicotine/cotinine or alcohol by the laboratory assays conducted during Screening and Day -1.
	9. History of residential exposure to tuberculosis, or a positive QuantiFERON® test within 4 weeks prior to or at the time of Screening.
	10. Positive for a) hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, or human immunodeficiency virus I and II tests at Screening; b) SARS-CoV-2 at Screening or Day -1.
	11. Any condition, including findings in the laboratory tests, medical history, or other Screening assessments, that in the opinion of the Investigator constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study's objectives, conduct, or evaluation.
	12. 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, final boost) is allowed until 1 week before admission to CRU. Note: In case of clinical symptoms, the participant should be symptom-free for at least 1 week prior to admission to CRU.
Prior/Concomitant Therapy	13. Moderate or strong inhibitors or inducers of CYP3A4/5 within 4 weeks prior to the first administration of study intervention.

Category	Criterion
	14. Use of any prescribed medicine or over-the-counter drug or dietary supplement, including herbal remedies, vitamins, and minerals, antacids and dietary supplements such as fish oils within 2 weeks or 5 times the half-life of the respective drug, whichever is longer, prior to the first administration of study intervention. Occasional paracetamol (acetaminophen) up to 2 g per day or hormonal contraceptives/HRT) is permitted.
Prior/Concurrent Clinical Study Experience	15. 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 Screening.
	16. Medical history and physical examination results that include any ongoing clinically relevant findings as judged by the Investigator.
Diagnostic Assessments	17. Clinically relevant findings (excluding minor excursions from normal ranges) 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 out of normal range and/or signs/symptoms of pancreatitis.
	18. 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 subject will only be included if the Cystatin C value is below the ULN.

Category	Criterion
	19. 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.
	20. 12-Lead ECG showing a QTcF > 450 ms, PR > 215 ms, or QRS > 120 ms.
	21. Any other abnormal laboratory results that the Investigator believes should preclude the participant's participation in the study.
Other Exclusions	22. Consumption of an average weekly alcohol intake of > 14 units/week for men or > 7 units/week for women. One unit (12 g) of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
	23. 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.
	24. Consumption of alcohol from 48 hours prior to first administration of study intervention.
	25. 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.
	26. Donation or loss of more than 450 mL of blood in the 60 days prior to Screening, donation of plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
	27. Travel to a country with a high prevalence of tropical diseases within 3 months prior to Screening.
	28. Inability to communicate reliably with the Investigator or considered by the Investigator to be unable to or unlikely to co-operate with the requirements of the study.
	29. Site staff, study staff members and family members of the Principal Investigator.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

The following general instructions on meals and dietary restrictions including composition and timing of meals apply to both study parts:

- During the in-house period at the CRU for both parts, participants should start the moderate-fat/-calorie breakfast 30 minutes prior to administration of transporter substrates, following an overnight fast of at least 10 hours. The breakfast should be consumed within 25 to 30 minutes. Lunch will be provided approximately 4 hours and dinner at about 11 hours after the morning doses of study interventions (evobrutinib and/or transporter substrates).

- Start date and time and stop time of the breakfast on transporter substrate dosing days, Days 1 and 10 in Part 1 and Days 1 and 8 in Part 2, will be recorded in the participants' eCRFs as well as whether the entire breakfast was consumed. If the entire meal was not consumed, the percentage of meal consumed (in quartiles) should be recorded. Start date and time and stop time of dinner on Days 4 to 12 will also be recorded in the participants' eCRF. All other meals during the inpatient stay at the study center, will be standardized and no documentation of time and complete consumption is needed.

- Standard moderate-fat, moderate-calorie breakfasts on transporter substrate dosing days in this study are defined as follows: approximately 490 calories composed of approximately 77 g of carbohydrates, 28 g of protein, and 13 g of fat (Naderer 2015).

- All transporter substrates and evobrutinib doses will be administered with 240 mL water in a standing position. Thereafter, the participants will stay in a semi-recumbent position for at least 1 hour postdose on transporter substrates dosing days (Day 1 [Part 1 and 2], Day 8 [Part 2] and Day 10 [Part 1]).

- On dosing days (see Schedule of Assessments in Section 1.3), participants may consume water ad libitum and should drink at least 1.5 L/day.

During **Part 1,** study interventions will be administered under fed conditions as follows:

Day 1: Single dose cocktail of digoxin tablet (0.25 mg), metformin oral solution (10 mg), and rosuvastatin (10 mg) tablet, 0.5 hours after the start of a standard moderate-fat, moderate-calorie breakfast. Metformin will be administered first following the procedure described by Stopfer 2018.

Days 4 to 12: Evobrutinib (45 mg) twice daily 0.5 hours after the start of a standardized breakfast and within 1.5 hours of the start of a standardized dinner.

Day 10: Single doses of 0.25 mg digoxin tablet, 10 mg metformin oral solution, and 10 mg rosuvastatin tablet with the scheduled evobrutinib dose 0.5 hours after the start of a standard breakfast.

During **Part 2**, study interventions will be administered under fed conditions as follows:

- **Day 1**: Single dose of sumatriptan (25 mg) 0.5 hours after the start of a moderate-fat, moderate-calorie standard breakfast.
- **Days 2 to 8**: Evobrutinib (45 mg) twice daily 0.5 hours after the start of a standardized breakfast and within 1.5 hours of the start of a standardized dinner.
- **Day 8**: Single dose sumatriptan (25 mg) with the evobrutinib (45 mg) morning dose 0.5 hours after the start of a moderate-fat, moderate-calorie standard breakfast.

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid

- During each dosing period, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
- During each dosing period, participants will abstain from alcohol and cannabinoid-containing products for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
- Use of tobacco products will not be allowed from Screening until after the final follow-up visit.

5.3.3 Activity

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

5.4 Screen Failures

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

5.5 Criteria for Temporarily Delaying the Administration of Study Intervention Administration

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

Intervention Name	Evobrutinib	Digoxin	Metformin	Rosuvastatin	Sumatriptan
Type	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Film-coated tablet (TF2)	Tablet	Oral solution	Tablet	Tablet
Unit Dose Strength	45 mg	0.25 mg	10 mg	10 mg	50 mg
Dose Amount	45 mg, twice daily, fed	0.25 mg, fed	10 mg, fed	10 mg, fed	25 mg, fed
Frequency	Two daily tablets (12 hours apart each), Days 4 to 12 (Part 1) and Days 2 to 8 (Part 2)	Single doses on Day 1 and Day 10 (Part 1)	Single doses on Day 1 and Day 10 (Part 1)	Single doses on Day 1 and Day 10 (Part 1)	Single doses on Day 1 and Day 8 (Part 2)
Route of Administration	Oral	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental	Experimental	Experimental
Investigational Medicinal Product (IMP)	IMP: evobrutinib	IMP: Transporter substrate	IMP: Transporter substrate	IMP: Transporter substrate	IMP: Transporter substrate
Supplier	Merck Healthcare KGaA	Merck Healthcare KGaA	Merck Healthcare KGaA	Merck Healthcare KGaA	Merck Healthcare KGaA
Packaging and Labeling	Study intervention will be provided in containers. Each container will be labeled per country requirement. Additional details of packaging and labeling of study intervention will be defined in a separate IMP Handling Manual.	Study intervention will be provided in containers. Each container will be labeled per country requirement. Additional details of packaging and labeling of study intervention will be defined in a separate IMP Handling Manual.	Study intervention will be provided in containers. Each container will be labeled per country requirement. Additional details of packaging and labeling of study intervention will be defined in a separate IMP Handling Manual.	Study intervention will be provided in containers. Each container will be labeled per country requirement. Additional details of packaging and labeling of study intervention will be defined in a separate IMP Handling Manual.	Study intervention will be provided in containers. Each container will be labeled per country requirement. Additional details of packaging and labeling of study intervention will be defined in a separate IMP Handling Manual.

Timing of transporter substrates and/or evobrutinib administration with regards to food intake and study day is detailed in Section 5.3.1.

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

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

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Not applicable as this is a nonrandomized study.

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

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

6.3.2 Blinding

Not applicable as this is an open-label study.

6.3.3 Emergency Unblinding

Not applicable as this is an open-label study.

6.4 Study Intervention Compliance

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

6.5 Dose Modification

Doses will not be modified.

6.5.1 Retreatment Criteria

Not applicable.

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

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

6.7 Treatment of Overdose

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

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

Recommendation for treatment of an overdose of digoxin, metformin, rosuvastatin, or sumatriptan is described in the respective SmPC.

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

6.8 Concomitant Therapy

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

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

6.8.1 Rescue Medicine

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

Any kind of toxicity occurring during the study will be treated symptomatically.

For further information see the SmPCs and prescribing information for digoxin, metformin, rosuvastatin, and sumatriptan.

6.8.2 Permitted Medicines

The only permitted medicines are the following:

1. Paracetamol up to 2 g per day, at the discretion of the Investigator
2. Hormonal contraceptives and HRT (see Appendix 3).

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

6.8.3 Prohibited Medicines

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

The participants are prohibited from using prescription or over-the-counter medications (apart from those described above) within 2 weeks or 5 terminal half-lives, whichever is longer, prior to the first administration of study intervention, during the study, and until the Safety Follow-up

assessment (this includes herbal remedies, vitamins, minerals, antacids and dietary supplements such as fish oils).

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

6.8.4 Other Interventions

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

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

A participant 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. The Schedule of Assessments 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.

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.

- The participant may be withdrawn by the Investigator due to participation in another clinical study.
- A participant must be withdrawn if any of the following occurs during the study:
  - Pregnancy.
  - AEs, if study discontinuation is considered necessary by the Investigator and/or desired by the participant. This includes in particular AEs of severe intensity and SAEs regardless of the relationship to study treatment.
  - Use of nonpermitted concomitant medications, as defined in Section 6.8. However, any medications that are considered necessary for the participant's wellbeing (e.g., paracetamol up to 2 g per day) may be given at the discretion of the Investigator.
  - Protocol noncompliance judged as significant by the Investigator, including noncompliance to the required study considerations (e.g., food/diet requirements), as defined in Sections 5.1, 5.2, 5.3, 6.1, and 8.
- If a participant has failed to attend scheduled study assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.
- If a participant must be withdrawn from the study, the Medical Monitor and clinical study leader for the Sponsor will be informed immediately.
- If there is a medical reason for the withdrawal, appropriate medical care will be provided.
- At the time of study discontinuation, if possible, a discontinuation visit will be conducted, as listed in the Schedule of Assessments (Section 1.3). The Schedule of Assessments 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.
- A participant has the right at any time to request destruction of any biological samples taken. The Investigator will document this in the site study records and the CRF and inform the Sponsor. The samples will be destroyed.

The Investigator will secure the safety of the study participants and make every attempt to collect the data.

7.3 Lost to Follow-Up

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

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

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner or caretaker (where allowed by local regulations) for information. These contact attempts will be documented in the participant's medical record.
- If the participant continues to be unreachable, 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 Schedule of Assessments.
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.
- All screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Assessments.
- No more than 150 mL of blood may be drawn in a 24-hour period, and no more than 300 mL of blood in a 4-week period.
- Where allowed by local law/regulations, samples collected during this clinical study may be transferred to a biobank and used for future research outside the clinical protocol when additional consent for this purpose is given. Transfer to the biobank will be documented and any testing of coded biobank samples will not be reported in the CSR.
- The long-term storage of samples after study completion for future research may be performed with all sample types collected in the study (e.g., PK, CCI , biomarkers, or immunogenetics) if the participant consents to optional future medical research.

- Demographic data collected at Screening will include, at minimum, age, sex, race (collected only where allowed by local law/regulations), and ethnicity.

8.1 Efficacy Assessments and Procedures

Not applicable.

8.2 Safety Assessments and Procedures

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

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

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the 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; pulse; respiratory rate; tympanic temperature and location of measurement, weight, and height (at Baseline only) will be measured and recorded.
- Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and measured with an automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the Schedule of Assessments using an ECG machine that automatically measures heart rate, PR, RR, QRS, QT, and corrected QT interval by Bazett's formula or QTcF. Documentation of the QTcF is mandatory.
- 12-Lead ECGs will be recorded in a supine position following 5 minutes of rest.

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5 at the time points listed in the Schedule of Assessments. All samples will be clearly identified.

- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by Nuvisan GmbH laboratory; the QuantiFERON® Test will be performed by Synlab, Augsburg, Germany.
- SARS-CoV-2 tests at Screening and Day -1 will be performed as per local regulations.
- The Investigator will review each laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE, unless it does **not** meet the AE definition, as specified in Appendix 4. The laboratory reports will be filed with the source documents.
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at monthly intervals during study intervention administration.
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the end of relevant systemic exposure of the study intervention and correspond with the time frame for female participant contraception in Section 5.1.
- Additional serum or urine pregnancy testing may be conducted at any time during the study to establish the absence of pregnancy, at the Investigator's discretion or if local regulations require them.

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

- The definitions of an AE and a SAE are in Appendix 4.
- The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study, as specified in Section 8.3.2.
- Requests for follow-up will usually be made via the Sponsor or clinical research organization-designated study team member, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.
- All AEs and SAEs will be collected from the signing of the ICF until the Safety Follow-up Visit at the time points specified in the Schedule of Assessments (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, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.

- Investigators are not obligated to actively solicit information on AEs or SAEs after the end of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.1 Method of Detecting Adverse Events and Serious Adverse Events

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

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

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

8.3.2 Follow-up of Adverse Events and Serious Adverse Events

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

8.3.3 Regulatory Reporting Requirements for Serious Adverse Events

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

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

Individual Case Safety Reports will be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

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

8.3.4 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until Safety Follow-Up.
- 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/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.5 Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.7 Adverse Events of Special Interest

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

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

  As per its mechanism of action, evobrutinib may impair B cell function which might lead to a decreased humoral immunity and consequently an increased risk of infection. Overall, in completed studies in participants the Medical Dictionary for Regulatory Activities SOC infection was one of the most reported SOCs (e.g., in the MS200527_0086 RMS study

approximately 18% to 32% of participants treated with evobrutinib reported infection; a similar rate was reported in the placebo group in the 0 to 24 week period), the individual events were of low grade, mainly Grade 1, nonserious and did not lead to study intervention discontinuation. Treatment of infections must be prompt and done in accordance with local standard of care depending on considerations such as the nature and severity of the infection and participant's overall health status. Any Common Terminology Criteria for Adverse Events Grade ≥ 3 or SAEs of infection and opportunistic infection are considered as an AESI.

- Seizures

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

- Elevated lipase, elevated amylase, pancreatitis

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

- Liver related events

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

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

AESIs have to reported immediately. For reporting of AESIs, see Appendix 4.

8.4 Pharmacokinetics

For details on PK sampling refer to the Schedule of Assessments in Section 1.3 and Table 1 for PK sampling during Part 1 and Table 2 for PK sampling during Part 2.

- The following PK parameters will be calculated, when appropriate for the transporter substrates (digoxin, metformin, rosuvastatin, and sumatriptan):

Symbol	Definition
$AUC_{0-\infty}$	The area under the concentration-time curve (AUC) from time zero (= dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λ_z determination. $AUC_{0-\infty} = AUC_{0-tlast} + C_{last\ pred}/\lambda_z$
$AUC_{0-tlast}$	The AUC from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
AUC_{0-36}	The AUC from time zero (= dosing time) to 36 hours postdose (metformin only). Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
C_{max}	Maximum observed concentration.
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (the first occurrence in the case of multiple/identical C_{max} values).
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$
CL/F	The apparent total body clearance of study intervention following extravascular administration. $CL/F = Dose_{p.o.}/AUC_{0-\infty}$.
V_z/F	The apparent volume of distribution during the terminal phase following extravascular administration. $V_z/F = Dose/(AUC_{0-\infty}*\lambda_z)$ following single dose.
Ae_{0-36}	The cumulative amount excreted from time zero (= dosing time) to the end of the collection interval after dosing, calculated for metformin only.
CL_R	Renal clearance. $CL_R = Ae_{0-36}/AUC_{0-36}$, calculated for metformin only.

$C_{last\ pred}$= the predicted concentration at the last sampling time, calculated from the log-linear regression line for λ_z determination.

Part 1

- Whole blood samples of approximately 4 mL per timepoint for measurement of plasma concentrations of digoxin, metformin, and rosuvastatin, will be collected on Days 1 to 4 and Days 10 to 13 (Table 1).
- Whole blood samples of approximately 2 mL for measurement of plasma concentrations of evobrutinib will be collected on Days 10, 11, 12 (Table 1).
- Urine will be collected for metformin analysis (as it is 100% eliminated by renal excretion) on Days 1 to 2 and Days 10 to 11 and an aliquot will be taken from each collection interval for concentration measurements (Table 1). The volume of urine from each collection interval will be measured.

Part 2

- Whole blood samples of approximately 2 mL for measurement of plasma concentrations of sumatriptan will be collected on Days 1 to 2 and Days 8 to 9 (Table 2).
- Whole blood samples of approximately 2 mL for measurement of plasma concentrations of evobrutinib will be collected on Days 6, 7, and 8 (Table 2).

Collection times are specified in the Schedule of Assessments (Section 1.3). The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration. For urine samples, the actual start and end date and time (24-hour clock time) of each urine fraction, as well as the volume of each urine collection fraction, will be recorded.

- The quantification of evobrutinib, digoxin, metformin, rosuvastatin, and sumatriptan in plasma samples, and metformin in urine samples, will be performed using fully validated assay methods. Concentrations will be used to evaluate the PK parameters of the transporter substrates, and evobrutinib concentrations will be summarized.
- Remaining samples collected for analyses of evobrutinib and transporter substrate concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Additionally, remaining plasma samples may be used for investigation of evobrutinib or transporter substrate metabolites.
- Details on processes for collection and handling of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the End of Study are specified in the respective ICF.
- PK parameters will be derived using noncompartmental methods with the validated computer program Phoenix® WinNonlin® (version 6.4 or higher; Certara, L.P., Princeton, New Jersey, USA).

The exact date and time of sample collection and study intervention administration (24-hour clock time) must be recorded in the eCRF and will be used in the calculation of PK parameters. The accepted time deviations from planned PK sampling times that will not be considered a protocol violation are listed in Table 4.

Table 4 PK Sampling Time Windows

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

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

8.6 Biomarkers

Not applicable.

8.7 Immunogenicity Assessments

Not applicable.

9 Statistical Considerations

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

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

9.1 Statistical Hypotheses

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

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9.3 Analyses Sets

The analysis populations are specified below in Table 7. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock.

Table 7 Analysis Sets

Analysis Set	Description
Screening	All participants, who provided informed consent, regardless of the participant's enrollment and study intervention status in the study.
Safety (SAF)	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
Pharmacokinetic (PK)	The PK Analysis Set is a subset of the SAF, and the PK population will include all participants: • Who have completed the study without any relevant protocol deviations and factors likely to affect the comparability of PK results. • With adequate study intervention compliance. • With evaluable PK data, i.e., no missing values for primary endpoints at each PK profile/assessment day (Day 1, Day 10 for Part 1; Day 1 and Day 8 for Part 2). If participants received prohibited concomitant therapy or medicines, as specified in Section 6.8.3, they will be excluded from the PK population. All PK analyses will be based on this analysis set.

9.4 Statistical Analyses

Statistical analysis will be performed using the computer program package SAS® System (release 9.2 or later version; SAS Institute, Cary NC, USA). More details on the statistical analysis will be presented in the IAP prior to database lock.

The statistical analysis will not be started until all data have been corrected and checked for plausibility, and until all necessary coding and assessments have been completed.

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

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

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

All data will be evaluated as observed, no imputation method for missing values. The handling of concentration values below the limit of quantification will be described in the IAP.

9.4.1 Efficacy Analyses

Not applicable.

9.4.2 Safety Analyses

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

Reference	Category	Statistical Analysis
Primary	Not applicable.	Not applicable.
Secondary		
Nature, occurrence, and severity of TEAEs	Main	AE counts and participants with AEs will be summarized for each treatment by SOC and PT.
Absolute values and changes in safety laboratory tests from time of first dose to end of study participation	Main	Safety laboratory parameters will be listed for each participant including changes from Baseline and flags for measurements outside the reference ranges, where applicable. Laboratory parameters (hematology and clinical chemistry) will be summarized by time point including both absolute values and changes from Baseline.

Reference	Category	Statistical Analysis
Single 12-lead ECGs evaluated by Investigator from time of first dose to end of study participation	Main	ECG data will be summarized by absolute and changes from Baseline values by treatment using descriptive statistics. Clinical noteworthy ECG findings for individual participants will be listed and summarized as appropriate.
Vital signs assessed from time of first dose to end of study participation	Main	Vital signs by participant, including changes from Baseline, will be listed and summarized by treatment and time point using descriptive statistics.
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AE=adverse event; ECG=electrocardiogram; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.

9.4.3 Other Analyses

Pharmacokinetic Analyses

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

Part 1

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Analysis of Primary Endpoints

A general linear model with a fixed effect for TREATMENT and a random effect for SUBJECT will be applied to log-transformed PK parameters C_{max} and $AUC_{0-\infty}$ based on the PK analysis set to assess the effect of multiple doses of evobrutinib on the PK of the transporter substrates digoxin, metformin, and rosuvastatin. Treatment differences on the log scale of transporter substrates with evobrutinib vs substrates alone (Day 10 versus Day 1) will be estimated for C_{max} and $AUC_{0-\infty}$ together with their 90% CIs.

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

Analysis of Secondary Endpoints

The same analysis model as described for the primary endpoints will be provided for the secondary endpoint $AUC_{0\text{-tlast}}$ of transporter substrates.

The same analysis model as described for the primary endpoints will be provided for the secondary endpoint CL_R of metformin only.

Part 2

Analysis of Primary Endpoints

A general linear model with a fixed effect for TREATMENT and a random effect for SUBJECT will be applied to log-transformed PK parameters C_{max} and $AUC_{0-\infty}$ based on the PK analysis set to assess the effect of multiple doses of evobrutinib on the PK of the transporter substrate sumatriptan. Treatment differences on the log scale of sumatriptan with evobrutinib vs sumatriptan alone (Day 8 versus Day 1) will be estimated for C_{max} and $AUC_{0-\infty}$ together with their 90% CIs.

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

Analysis of Secondary Endpoints

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

9.4.4 Sequence of Analyses

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

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11 Appendices

Appendix 1 Abbreviations

(e)CRF	(Electronic) Case Report Form
AE	Adverse Event
AESI	Adverse Events of Special Interest
aPTT	Activated Partial Thromboplastin Time
BCRP	Breast Cancer Resistance Protein
BTK	Bruton's Tyrosine Kinase
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of Variation
CYP	Cytochrome P450
DDI	Drug-drug Interaction
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EudraCT	European Clinical Trials Database
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
MATE1/2	Multidrug and Toxin Extrusion 1/2
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume

MS	Multiple Sclerosis
NME	New Molecular Entity
OAT(P)	Organic Anion Transporter (Polypeptide)
OCT1	Organic Cation Transporter 1
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
QTcF	Corrected QT Interval by Fridericia's Formula
QTL	Quality Tolerance Limits
RMS	Relapsing Multiple Sclerosis
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WOCBP	Woman of Childbearing Potential

Appendix 2 Study Governance

Financial Disclosure

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

Informed Consent Process

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

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

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) will be submitted to an IRB/IEC for review and approve before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.
- When the Investigator is not available, the Phase I facility will provide the appropriate means to contact a physician. This includes the provision of a 24-hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

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

Clinical Study Report

- After study completion, the Sponsor will write a CSR in consultation with the Principal Investigator and 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 be predefined in the Operational Manual to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

  Note: QTLs will not be defined in this Phase I study as neither the limited number of planned participants nor the short duration of the study support the collection of meaningful QTLs.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.
- The Sponsor or designee is responsible for Data Management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.
- Study Monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being

protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

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

Study and Site Start and Closure

- The study start date is when the first participant signs the ICF.

Study and Site Closure

- The Investigator may initiate site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended closure.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further development of the Sponsor's compound
  - If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any third-party service providers of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Contraception and Barrier Requirements

Definitions:

WOCBP:

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

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

Postmenopause:

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

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

Permanent sterilization:

For this study, permanent sterilization includes:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

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

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- IUD
- IUS
- Bilateral tubal occlusion
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP, and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - Oral
  - Injectable
- Sexual abstinence: a highly effective method **only** if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

[Barrier Methods (to be used in addition to a highly effective method)

- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide]

Notes:

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

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

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

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

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

AE Definition

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

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

SAE Definition

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or 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 or AESIs.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

Follow-up of AEs and SAEs

- The Investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the Sponsor/designee to elucidate the nature and/or causality of the AE or SAE, as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor/designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor/designee immediately after obtaining knowledge (without undue delay).

Reporting of SAEs

SAE Reporting by a Paper Form

- SAE reporting on a paper report form may be used in single center studies in addition to the standard electronic CRF and as a back-up method for an Electronic Data Capture system failure. The form includes completion instructions for the Investigator, names, addresses, and telephone and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done immediately 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 immediately 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, using the same process for reporting SAEs, as specified above.
- For a serious AESI, the site will complete an SAE report form, using the SAE reporting process, specified above.

Reporting of Pregnancies

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

Appendix 5 Clinical Laboratory Tests

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

Laboratory Assessments	Parameters			
Hematology	Platelet count		Mean corpuscular volume (MCV)	White Blood Cell Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Hemoglobin		Mean corpuscular hemoglobin (MCH)	
	Hematocrit			
	White Blood Cell Count			
	Red blood cell count			
Biochemistry	Blood Urea Nitrogen	Potassium	Aspartate aminotransferase	Total Bilirubin
	Creatinine	Sodium	Alanine aminotransferase	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Cholesterol
	Uric acid	Chloride	γ -Glutamyl-transferase	Triglycerides
	C-reactive protein	Inorganic phosphate	Lactate dehydrogenase	Amylase
		Magnesium	Creatine phosphokinase	Lipase
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood (hemoglobin), ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal with positive dipstick). • Note: In case of a positive result for hemoglobin, leukocyte esterase, protein or nitrite, a flow cytometry count and classification will be performed			
Coagulation	• INR • aPTT			
Pregnancy Testing	• Serum human chorionic gonadotropin pregnancy test at all time points listed in the Schedule of Assessments (Section 1.3) (as needed for a WOCBP)			
Other Screening Tests	• FSH (as needed if a postmenopausal woman **only**, at Screening only) • Urine drug screen (to include at minimum: amphetamines, methamphetamines, barbiturates, ecstasy, cocaine, opiates, cannabinoids, benzodiazepines, methadone, phencyclidine, oxycodone, and tricyclic antidepressants) (Screening and Day -1) • Serology (human immunodeficiency virus I and II antibodies, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, QuantiFERON® Test,at Screening only) • SARS-CoV-2 test (Screening and Day -1) • Thyroid stimulating hormone (TSH, at Screening only) • Cotinine test (Screening and Day -1) • Alcohol breath test (Screening and Day -1) • Estimated Glomerular Filtration Rate based on Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (2009, Screening only) • Cystatin C (if applicable), at Screening only) All study-required laboratory assessments will be performed by a central laboratory, (Nuvisan's clinical laboratory).			


CCI

Appendix 7 Sponsor Signature Page

Study Title:	A Phase I, Open-Label, Two-Part Study of the Effect of Multiple-Dose Evobrutinib on Transporter Substrates Digoxin, Metformin, Rosuvastatin, and Sumatriptan Pharmacokinetics in Healthy Participants
Regulatory Agency Identifying Numbers:	EudraCT: 2021-001923-42
Clinical Study Protocol Version:	24 August 2021/Version 2.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	Medical Responsible 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: Mobile: PPD
General Merck Fax Number:	Not Applicable

Appendix 8 Principal Investigator Signature Page

Study Title:	A Phase I, Open-Label, Two-Part Study of the Effect of Multiple-Dose Evobrutinib on Transporter Substrates Digoxin, Metformin, Rosuvastatin, and Sumatriptan Pharmacokinetics in Healthy Participants
Regulatory Agency Identifying Numbers:	EudraCT: 2021-001923-42
Clinical Study Protocol Version:	24 August 2021/Version 2.0
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, [redacted] all applicable Health Authority requirements and national laws.

PPD

PPD

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	Principal Investigator
Institution:	Nuvisan GmbH
Address:	PPD PPD Neu-Ulm, Germany
Telephone number:	PPD
Fax number:	
E-mail address:	