Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	Phase I, Open-Label, Single-Sequence Study of the Effect of Multiple Doses of Carbamazepine on Single-Dose Evobrutinib Pharmacokinetics in Healthy Participants
Study Number:	MS200527_0108
Protocol Version:	12 October 2021/Version 1.0
Merck Compound:	Evobrutinib (M2951)
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	Phase I
Short Title:	DDI Study of Evobrutinib and Carbamazepine
Principal Investigator:	PPD
Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 64293, Darmstadt, Germany
Regulatory Agency Identifying Numbers:	EudraCT: 2021-003381-13
Keywords	Clinical Pharmacology

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1 Protocol Summary

1.1 Synopsis

Protocol Title: Phase I, Open-Label, Single-Sequence Study of the Effect of Multiple Doses of Carbamazepine on Single-Dose Evobrutinib Pharmacokinetics in Healthy Participants

Short Title: DDI Study of Evobrutinib and Carbamazepine

[redacted]

Objectives and Endpoints:

Objectives	Endpoints	Ref #
Primary		
To investigate the effect of multiple doses of carbamazepine on the PK of a single dose of evobrutinib in healthy participants	• Plasma evobrutinib: $AUC_{0-\infty}$ • Plasma evobrutinib: C_{max}	1
Secondary		
To assess the safety and tolerability of evobrutinib when administered together with carbamazepine in healthy participants	• Nature, occurrence, severity, and seriousness of TEAEs • Absolute values and changes in safety laboratory tests from time of first dose to end of study participation • Single 12-lead ECGs evaluated by Investigator from time of first dose to end of study participation • Vital signs assessed from time of first dose to end of study participation	2
To characterize the effect of carbamazepine on additional evobrutinib PK parameters in healthy participants	• Plasma evobrutinib: CL/F • Plasma evobrutinib: V_Z/F • Plasma evobrutinib: $AUC_{0-tlast}$ • Plasma evobrutinib: t_{max} • Plasma evobrutinib: $t_{½}$	3
To characterize the effect of carbamazepine on evobrutinib metabolite (MSC2729909A) PK in healthy participants	• Plasma MSC2729909A: $AUC_{0-\infty}$ • Plasma MSC2729909A: $AUC_{0-tlast}$ • Plasma MSC2729909A: C_{max} • Plasma MSC2729909A: t_{max} • Plasma MSC2729909A: t_{lag}	4

Objectives	Endpoints	Ref #
	• Plasma MSC2729909A: $t_{1/2}$ • Plasma MSC2729909A: respective metabolic ratios M/P($AUC_{0-\infty}$) and M/P(C_{max})	

AUC=area under the concentration-time curve; C_{max}=maximum observed concentration; CL/F=apparent total body clearance; MR=metabolic ratio; M=metabolite; P=parent; PK=pharmacokinetics; $t_{½}$=apparent terminal half-life; t_{lag}=time prior to the first measurable (nonzero) concentration; t_{max}=time to reach the maximum observed concentration; V_Z/F=apparent volume of distribution.

Overall Design: This will be a nonrandomized, open-label, single-sequence Phase I study in 18 healthy participants.

Brief Summary:

The purpose of this study is to investigate the effect of multiple doses of carbamazepine on single dose evobrutinib PK in healthy participants. Study details include:

- Study Duration: up to 54 days.
- Treatment Duration: 25 days.
- Visit Frequency: Participants will be resident in the Clinical Research Unit from Day -1 to Day 20 and return on Day 26 for a Safety Follow-Up visit.

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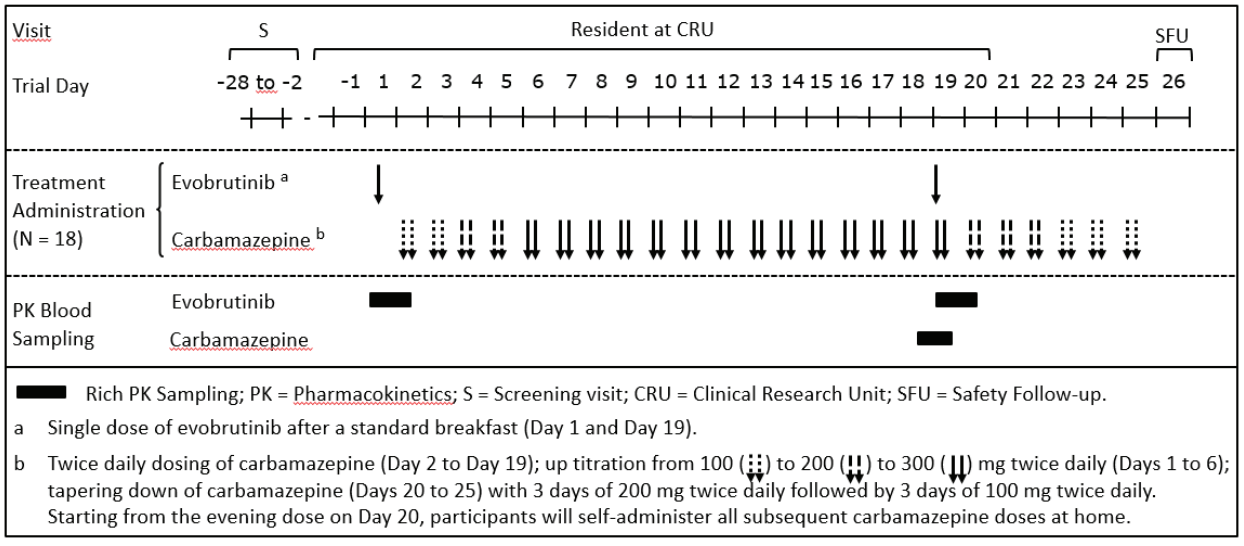
Study Intervention Groups and Duration: Single-sequence study, 25 days

Involvement of Special Committee(s): No

1.2 Schema



1.3 Schedule of Activities

Assessments & Procedures	Screening														Safety Follow-Up	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18**	**19**	**20**	**21**	**22**	**23 to 25**	**26**	
Informed consent	X															Prior to any screening activity.
Participants resident at CRU		X	X	X	X	X	X	X	X	X	X				X	
Eligibility criteria	X	X														Recheck of eligibility criteria on Day -1, (Sections 5.1 and 5.2).
Demography, height & weight	X															Demography to include, at minimum age (year of birth), sex, race, and ethnicity.
Medical history	X															
Physical examination	X	X													X	Brief examination on Day -1 Section 8.2.1.
FSH	X															In postmenopausal women.
Viral serology, TSH, QuantiFERON® test	X															
Clinical laboratory tests (blood and urine)	X	X						**X**[a]	X						X	a Safety lab to be collected from Day 10 to Day 14. Appendix 5 and Section 8.2.4.
Cotinine, drug screen, alcohol breath test, SARS-CoV-2	X	X														Appendix 5.
Safety ECG & vital signs	X	X	X	X					X	X	X				X	Predose, 4 and 6 hours postdose on Days 1 and 19. Sections 8.2.2 and 8.2.3.
AE/concomitant medication review	X	X	X	X	X	X	X	**X**	X	X	X	X	X	X	X	Section 6.8.
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Assessments & Procedures	**Screening**														**Safety Follow-Up**	**Notes**
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18**	**19**	**20**	**21**	**22**	**23 to 25**	**26**	
Carbamazepine administration, mg				2× 100	2× 100	2× 200	2× 200	**2× 300**	2× 300	2× 300	2× 200[b]	2× 200[b]	2× 200[b]	2× 100[b]		First dosing on Day 2 after 24-hour PK sampling for evobrutinib. b On Day 20 evening dose, as well as on Days 21 to 25, participants will take carbamazepine at home. Twice daily administration (2×). Section 5.3.1, Section 6.1.
CCI [redacted]									CCI	CCI						CCI [redacted]
Evobrutinib administration			X							X						Section 5.3.1, Section 6.1.
Evobrutinib and metabolite PK blood sampling			X	X						X	X					Sampling Days 1/2 and 19/20: Predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours postdose. Section 8.4.

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

2 Introduction

Evobrutinib is an oral, selective, irreversible inhibitor of BTK 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 carbamazepine. Complete information about the potential side effects of carbamazepine administration is described in the currently approved SmPC for carbamazepine.

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2.2 Background

Evobrutinib

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

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

Evobrutinib will be dosed under fed conditions in this study. Administration of evobrutinib 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). Median (range) t_{max} under fed conditions was 1.5 hours (0.5 to 3 hours).

Carbamazepine

Carbamazepine (5H-dibenzo[b,f]azepine-5-carboxamide) has been in therapeutic use since 1962 (Moshé 2009). It is an essential medicine (WHO model list of essential medicines: 21st list, 2019) for the treatment of epilepsy, paroxysmal pain of trigeminal neuralgia, as well as for the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy (carbamazepine SmPC).

Carbamazepine is classified as a BCS Class II compound according to the FDA BCS guidance. Ingestion of food has no significant influence on the rate and extent of absorption. Carbamazepine is metabolized in the liver to an active epoxy-metabolite, primarily by CYP3A4. It induces CYP3A4 and CYP1A2 and thereby induces its own metabolism during prolonged treatment, which is complete in 3 to 5 weeks with a fixed dosing regimen. Physiologically based PK simulations indicated that 14 days are sufficient to reach the maximal effect on induction at 600 mg/day (Xu 2011). The elimination half-life of carbamazepine averages approximately 36 hours following a single oral dose, whereas after repeated administration it averages 16 hours to 24 hours (due to auto-induction), depending on the duration of the treatment (Carbamazepine SmPC).

2.3 Benefit/Risk Assessment

Evobrutinib

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

Evobrutinib treatment will be administered as a single dose of 45 mg each on Day 1 and Day 19 of this study under fed conditions. This regimen was previously tested in healthy participant studies and does not exceed exposures reached in first-in-human clinical Study EMR200527_001, where single doses of evobrutinib from 25 up to 500 mg and 14 days of dosing with 25, 75, and 200 mg/day were tested and shown to be well tolerated.

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

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

Carbamazepine

Carbamazepine will be dosed twice daily under fed conditions for 18.5 days at the CRU (from Day 2 morning dose to Day 20 morning dose; Section 6.1), followed by 5.5 days of tapering the dose down at home (starting from Day 20 evening dose to Day 25 evening dose). The gradual dose increase will be applied with 600 mg daily dose of carbamazepine administered from Day 6 onwards. Starting on Day 20, the dose will be tapered down over 6 days (Section 6.1). Maximum recommended dose for adults is 1,200 mg per day.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of carbamazepine may be found in the SmPC.

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 see current IB Section 6.1). Elevations of liver transaminases (ALT, AST) 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 tests (e.g., ALT, AST) will be adequately monitored during the study.
Important potential risk: Embryo-fetal toxicity	Based on nonclinical findings, embryo-fetal toxicity is considered as an important potential risk in women of childbearing potential exposed to evobrutinib.	Only women of nonchildbearing potential are included in this study.
Carbamazepine (SmPC)		
Hepatitis, hepatic failure, vanishing bile duct syndrome	Hepatitis and vanishing bile duct syndrome (see also the hypersensitivity reactions below) are listed with rare frequency, while hepatic failure is considered very rare. Due to enzyme induction, some liver function tests in patients receiving carbamazepine may be found to be abnormal: particularly GGT and modest elevations in ALP.	The risk from potential overlapping toxicities with regards to liver function tests is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2) and adequate monitoring. Inclusion will be only allowed for participants with adequate hepatic function.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Severe cutaneous adverse reactions including SJS, TEN (also known as Lyell's syndrome), and acute generalized exanthematous pustulosis, urticaria	Serious TEN and SJS have been reported very rarely with carbamazepine. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. Most of the SJS/TEN cases appear in the first few months of treatment with carbamazepine. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. Mild skin reactions e.g., isolated macular or maculopapular exanthema, can also occur and are mostly transient and not hazardous, however, it may be difficult to differentiate the early signs of more serious skin reactions from mild transient reactions, and consideration must be given to immediately withdraw the drug should the reaction worsen with continued use.	The risk is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2) and by close monitoring for skin reactions.
Hypersensitivity reactions including DRESS	DRESS, a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome, which may occur in various combinations. Other organs may also be affected (e.g.; lungs, kidneys, pancreas, myocardium, colon). In general, if signs and symptoms suggestive of hypersensitivity reactions occur, carbamazepine should be withdrawn immediately. Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that 25% to 30% of these patients may experience hypersensitivity reactions with oxcarbazepine (Trileptal). Cross-hypersensitivity can occur between carbamazepine and aromatic antiepileptic drugs (e.g., phenytoin, primidone, and phenobarbital).	The risk is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2) and by close monitoring of skin reactions, fever and lymphadenopathy (physical examination).
Agranulocytosis, aplastic anemia, pancytopenia, leucopenia, thrombocytopenia, eosinophilia	Very rare agranulocytosis and aplastic anemia have been associated with carbamazepine; however, due to the very low incidence of these conditions, meaningful risk estimates for carbamazepine are difficult to obtain. Decreased platelet or white blood cell counts occur rarely to very commonly.	The risk is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2) and by monitoring of hematology parameters and early toxic signs and symptoms such as fever, sore throat, rash, ulcers in the mouth, easy bruising, and petechial or purpuric hemorrhage.
Ataxia, dizziness, somnolence, diplopia, fatigue, accommodation disorders (e.g., blurred vision)	Events may lead to falls and, consequently fractures or other injuries.	The risk is considered as managed by adequate measures such as eligibility criteria (Sections 5.1 and 5.2), confinement during the study, and advising participants to be careful when operating machinery during the outpatient tapering-down period.

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

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DRESS=drug reaction with eosinophilia and systemic symptoms; ECG=electrocardiogram; GGT=Gamma-glutamyl transferase; IB=investigator brochure; SJS=Stevens-Johnson syndrome; SmPC=summary of product characteristics; TEN=toxic epidermal necrolysis.

Safety Risks not Applicable for Healthy Participants

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Carbamazepine (SmPC)		
Renal damage, hyponatremia	In patients with preexisting renal conditions associated with low sodium or in patients treated concomitantly with sodium-lowering medicinal products.	Not expected to constitute the risk for healthy participants. The risk is considered as managed by adequate measures such as exclusion criteria (Section 5.2).
Hypothyroidism	Serum concentrations of thyroid hormones may be reduced due to enzyme induction requiring an increase in dose of thyroid replacement therapy in patients with hypothyroidism.	Not expected to constitute the risk for healthy participants. The risk is considered as managed by adequate measures such as exclusion criteria (Section 5.2).
Suicidal behavior /ideation	Suicidal ideation and behavior have been reported in patients treated with antiepileptic agents in several indications (note the indications for carbamazepine can be considered as the risk). The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for carbamazepine.	Not expected to constitute the risk for healthy participants. The risk is considered as managed by adequate measures such as exclusion criteria (Section 5.2).
Cardiovascular disorders including conduction disorders, arrhythmia and atrioventricular block with syncope	Tachycardia, atrioventricular block, premature ventricular contractions, ventricular tachycardia and junctional escape rhythms have been reported in patients due to carbamazepine toxicity.	The risk is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2) and scheduled monitoring of ECG.

ECG=electrocardiogram; 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 COVID-19 pandemic situation is ongoing.

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

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

In order to minimize the risk coming from a current infection and the risk of getting infected by other participants during the in-house period (covering the whole treatment phase) of the study, the following measures are implemented: Only participants without any symptoms of a respiratory disease and without contact to any known SARS-CoV-2 positive patient or COVID-19 patient 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 and/or carbamazepine 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 (until the carbamazepine tapering-down period) 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 carbamazepine are justified in healthy participants.

3 Objectives and Endpoints

Objectives	Endpoints	Ref #
Primary		
To investigate the effect of multiple doses of carbamazepine on the PK of a single dose of evobrutinib in healthy participants	• Plasma evobrutinib: $AUC_{0-\infty}$ • Plasma evobrutinib: C_{max}	1
Secondary		
To assess the safety and tolerability of evobrutinib when administered together with carbamazepine in healthy participants	• Nature, occurrence, severity, and seriousness of TEAEs • Absolute values and changes in safety laboratory tests from time of first dose to end of study participation • Single 12-lead ECGs evaluated by Investigator from time of first dose to end of study participation • Vital signs assessed from time of first dose to end of study participation	2
To characterize the effect of carbamazepine on additional evobrutinib PK parameters in healthy participants	• Plasma evobrutinib: CL/F • Plasma evobrutinib: V_Z/F • Plasma evobrutinib: $AUC_{0-tlast}$ • Plasma evobrutinib: t_{max} • Plasma evobrutinib: $t_{½}$	3
To characterize the effect of carbamazepine on evobrutinib metabolite (MSC2729909A) PK in healthy participants	• Plasma MSC2729909A: $AUC_{0-\infty}$ • Plasma MSC2729909A: $AUC_{0-tlast}$ • Plasma MSC2729909A: C_{max} • Plasma MSC2729909A: t_{max} • Plasma MSC2729909A: t_{lag} • Plasma MSC2729909A: metabolite to parent ratios M/P($AUC_{0-\infty}$) and M/P(C_{max})	4

Objectives	Endpoints	Ref #
CCI [redacted]		
[redacted]	[redacted]	[redacted]

AUC=area under the concentration-time curve; C_{max}=maximum observed concentration; C_{min}= minimum observed concentration; CL/F=apparent total body clearance; ECG=electrocardiogram; M=metabolite; P=parent; PK=pharmacokinetics; TEAE=treatment emergent adverse event; $t_{½}$=apparent terminal half-life; t_{lag}=time prior to the first measurable (nonzero) concentration; t_{max}=time to reach the maximum observed concentration; V_Z/F=apparent volume of distribution.

4 Study Design

4.1 Overall Design

Study Design	Nonrandomized, open-label, single-sequence
Control Method	None
Single or Multicenter	Single center
Control Group	Not applicable
Study Population Type	Healthy participants
Level and Method of Blinding	Open-label
Bias Minimalization Method(s)	Not applicable
Study Intervention Assignment Method	Not applicable
Involvement of Special Committee(s)	No
Total Duration of Study Participation per Participant	Up to 54 days (4-week Screening period, 25 days of intervention period, including the Safety Follow-Up 1 day after the last dose of carbamazepine on Day 25); a study schema and a detailed Schedule of Assessments are provided in Section 1.2 and Section 1.3, respectively.
Provisions for Study Extension or Entry into Roll-Over Studies	Not applicable
Adaptive Aspects of Study Design	Not applicable

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

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[redacted]

[redacted]

[redacted]

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 following a standardized meal, is the same as for Phase III studies evaluating evobrutinib in participants with RMS; however, in this study evobrutinib will be given as single doses for the purpose of assessing the effect of CYP3A4 induction instead of following a twice daily dosing regimen as in the Phase III studies. This design is supported by the dose-linear and time-independent PK of evobrutinib. This dose is anticipated to be well tolerated based on prior clinical experience and is considered to be adequate for characterizing 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. 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 30% to 35% when administered approximately 2 hours after a low-fat meal (Study MS200527_0072). 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.

Carbamazepine

The carbamazepine dose to be used in this study, 300 mg twice daily, is a common dosing regimen used to assess the effect of CYP3A4 induction on the PK of CYP3A4 substrates in DDI studies of this type (website: https://clinicaltrials.gov, search criterion: carbamazepine).

The carbamazepine dose will be titrated up from an initial dose of 100 mg twice daily in 100 mg twice daily increments to a final maintenance dose of 300 mg twice daily. This gradually increasing dosing regimen is expected to improve tolerability and reduce drop-out rate. It is in line with label recommendations (carbamazepine SmPC). Similar dosing regimens were used in other DDI studies (website: https://clinicaltrials.gov, search criterion: carbamazepine; Lutz 2018, Song 2016, Ucar 2004) and were considered sufficient for achieving the respective near maximal CYP3A4 induction (Xu 2011).

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 discontinued or terminated if:

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

- any data derived from other clinical trials or toxicological studies become available which negatively influence the risk/benefit assessment.

General information on study termination are 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 BMI within the range 19.0 and 30.0 kg/m^2 (inclusive).
Sex and Contraception/Barrier Requirements	4. • Male o No contraception and barrier requirements needed. • Female o Is **not** a woman of childbearing potential (Appendix 3).
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 nonsmokers for at least 3 months preceding Screening.

5.2 Exclusion Criteria

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

Category	Criterion
Medical Conditions	1. History or presence of clinically relevant respiratory, gastrointestinal, renal, hepatic, hematological, lymphatic, neurological, cardiovascular, musculoskeletal, genitourinary, immunological, dermatological, connective tissue, psychiatric (due to rare risk of hallucinations, agitation and activation of psychosis), and other diseases or disorders, and epilepsy, as determined by medical evaluation.

Category	Criterion
Medical Conditions	2. Individuals with diagnosis of hemochromatosis, Wilson´s disease, alpha 1 antitrypsin deficiency, or any other chronic liver disease including Gilbert's disease will be excluded from the study. Prior history of cholecystectomy or splenectomy, and any clinically relevant surgery within 6 months prior to Screening.
	3. History of any malignancy.
	4. History of chronic or recurrent acute infection or any bacterial, viral, parasitic or fungal infections within 30 days prior to Screening and at any time between Screening and admission, or hospitalization due to infection within 6 months prior to Screening.
	5. History of shingles within 12 months prior to Screening.
	6. History of drug hypersensitivity ascertained or presumptive allergy/hypersensitivity to the active drug substance and/or formulation ingredients; history of serious allergic reactions leading to hospitalization or any other hypersensitivity reaction in general 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. **Note:** Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that 25% to 30% of these patients may experience hypersensitivity reactions with oxcarbazepine (Trileptal). Cross-hypersensitivity can occur between carbamazepine and aromatic antiepileptic drugs (e.g., phenytoin, primidone, and phenobarbital).
	7. 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.
	8. History of residential exposure to tuberculosis, or a positive QuantiFERON® test within 4 weeks prior to or at the time of Screening.
	9. 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.
	10. 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.

Category	Criterion
Medical Conditions	11. Administration of live vaccines or live-attenuated virus vaccines within 3 months prior to Screening. Administration of other types of vaccines (e.g., SARS-CoV-2 vaccines) is allowed until 2 weeks before admission to CRU, thereafter it is prohibited until the end of the study. **Note:** In case of clinical symptoms, the participant should be symptom-free for at least 1 week prior to admission to CRU.
Prior/Concomitant Therapy	12. Moderate or strong inhibitors or inducers of CYP3A4/5 (Appendix 7) or P-gp within 4 weeks prior to the first administration of study intervention.
	13. Use of any prescribed medicine or over-the-counter drug or dietary supplement, including herbal remedies, vitamins, and minerals, antacids and dietary supplements such as fish oils within 2 weeks or 5 times the half-life of the respective drug, whichever is longer, prior to the first administration of study intervention. Occasional ibuprofen up to 1.2 g per day is permitted.
Prior/Concurrent Clinical Study Experience	14. Use of any investigational drug in any clinical study within 60 days prior to Study Day 1 administration, or have used an experimental monoclonal antibody within the past 1 year prior to Study Day 1, or have participated in a study evaluating a BTK inhibitor within 60 days, or are on extended follow-up in a clinical study, even if last administration of a study intervention was more than 60 days ago, or 5 half-lives of the investigational drug, whichever is longer, prior to Screening.
Diagnostic Assessments	15. Medical history and physical examination results that include any ongoing clinically relevant findings as judged by the Investigator.
	16. Clinically relevant findings (excluding minor, not clinically relevant excursions from normal ranges, as judged by the Investigator) at Screening in biochemistry, hematology, coagulation, and urinalysis examinations for the age of the participant, as judged by the Investigator: • Alanine aminotransferase, aspartate aminotransferase: above ULN • Creatinine: above normal limits • Absolute lymphocyte count, absolute neutrophil count: below limit of reference range • Amylase and lipase above normal ranges, minor deviations are allowed, if not clinically relevant.

Category	Criterion
Diagnostic Assessments	17. Estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (2009) < 90 mL/min at Screening. In case of a borderline result between ≥ 80 and < 90 mL/min, Cystatin C will be determined in addition, and the participant will only be included if the Cystatin C value is below the upper limit of normal.
	18. Semi-supine systolic blood pressure > 140 mmHg or < 90 mmHg, diastolic blood pressure > 90 mmHg or < 50 mmHg, and pulse rate > 90 or < 50 bpm at Screening. Any abnormal blood pressure results may be repeated once and if the repeat result is within the normal range, it is not considered to have met the exclusion criterion.
	19. 12-Lead ECG showing a QT interval corrected for heart rate according to Fridericia's formula (QTcF) > 450 ms, PR > 215 ms, or QRS > 120 ms.
	20. Any other abnormal laboratory results that the Investigator believes should preclude the participant's participation in the study.
Other Exclusions	21. 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.
	22. Carriers of HLA-B*1502, Han Chinese, Thai and other Asians, (e.g., Philippines, Malayans, South Asian Indians) or carriers of HLA-A*3101 (carbamazepine SmPC).
	23. Contraindication to carbamazepine (carbamazepine SmPC).
	24. Excessive consumption of xanthine-containing food or beverages (> 5 cups of coffee a day or equivalent) or inability to stop consuming caffeine, from 48 hours prior to study intervention administration until after collection of the final PK sample.
	25. Consumption of alcohol from 48 hours prior to first administration of study intervention.
	26. Herbal supplements including, but not limited to, St. John's wort (hypericum perforatum), grapefruit, Seville oranges, cranberries, or juices of these fruits within 14 days prior to the first administration of study intervention.
	27. Donation or loss of more than 450 mL of blood in the 60 days prior to Screening, donation of plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.

Category	Criterion
Other Exclusions	28. Travel to a country with a high prevalence of tropical diseases within 3 months prior to Screening.
	29. Inability to communicate reliably with the Investigator or considered by the Investigator to be unable to or unlikely to co-operate with the requirements of the study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

On Day 1 and Day 19, participants will receive a single dose of 45 mg evobrutinib (tablets) after overnight fasting for at least 10 hours in the morning 0.5 hours after the start of a standard moderate-fat/moderate-calorie breakfast at the CRU. The breakfast should be consumed within 25 to 30 minutes. The start date and time and stop time of the breakfast will be recorded in the participant's eCRFs as well as whether the entire breakfast was consumed. If the entire meal is not consumed, the percentage of meal consumed (in quartiles) should be recorded.

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

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

On Days 2 to 19, each participant will receive 100, 200 or 300 mg carbamazepine (tablets) twice daily (at least 10 hours apart) during, after, or between meals at the CRU at approximately the same time each day. On Day 19, in the morning, carbamazepine will be co-administered with evobrutinib. The morning carbamazepine dose on Day 20 will be administered at the CRU prior to participants' release from the CRU. Once in the evening of Day 20 and twice daily on Days 21 to 25, participants will take carbamazepine at home.

Study interventions will be administered with 240 mL of water in a standing position at the CRU. On all dosing days (Schedule of Assessments in Section 1.3), participants may consume water ad libitum and should drink at least 1.5 L/day.

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

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	Carbamazepine
Type	Drug	Drug
Dose Formulation	Film-coated tablet (TF2)	Tablet with break-line
Unit Dose Strength(s)	45 mg	200 mg (0.5, 1.0 and 1.5 tablet[s])
Dose Amount	45 mg, fed	100 mg (Days 2 and 3), 200 mg (Days 4 and 5), 300 mg (Days 6 to 19), 200 mg (Days 20 to 22) and 100 mg (Days 23 to 25) per administration, fed
Frequency	Single dose on Day 1 and Day 19	Twice daily at the same time each day in the morning and evening (at least 10 hours apart, ± 1 hour) from Days 2 to 25

Route of Administration	Oral	Oral
Use	Experimental	Experimental
Investigational Medicinal Product	Evobrutinib	Carbamazepine
Supplier	Merck Healthcare KGaA	Merck Healthcare KGaA
Packaging and Labeling	Study intervention will be provided in containers. Each container will be labeled per country requirement. Additional details of packaging and labeling of study intervention will be defined in a separate IMP Handling Manual.	Study intervention will be provided in containers. Each container will be labeled per country requirement. Additional details of packaging and labeling of study intervention will be defined in a separate IMP Handling Manual.

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

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

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

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

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Not applicable as this is a nonrandomized study.

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

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

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by a participant diary during the site visits and documented in the source documents and CRF. Any deviation(s) from the prescribed dosage regimen are recorded in the CRF. Note: In this study, compliance with carbamazepine intake at home will be assessed at the Safety Follow-Up Visit only.

A record of the number of carbamazepine tablets dispensed to and taken by each participant will be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

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/her clinical judgment to manage any overdose, considering the symptoms and any site procedures or standards.

Recommendation for treatment of an overdose of carbamazepine is described in the SmPC for carbamazepine.

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

6.8 Concomitant Therapy

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

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

6.8.1 Rescue Medicine

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

In case of toxicity during carbamazepine, refer to the carbamazepine SmPC.

6.8.2 Permitted Medicines

The only permitted medicines are the following:

1. Ibuprofen up to 1.2 g per day, at the discretion of the Investigator.

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

6.8.3 Prohibited Medicines

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

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

Inhibitors or inducers of CYP3A4/5 (Appendix 7) or P-gp within 4 weeks prior to the first administration of study intervention, and until after the Safety Follow-Up assessment are prohibited. Also, drugs mainly metabolized by CYP3A4/5 and that have a narrow therapeutic index should be avoided.

6.8.4 Other Interventions

Additional restrictions that study participants should adhere to from Day -1 until the 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.
- 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. Note: If study intervention is discontinued the Safety Follow-Up visit should be performed.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may discontinue from the study at any time, at 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. The Schedule of Assessments specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.

  Note: If the study is discontinued the Safety Follow-Up visit should be performed.

- If the participant revokes consent for the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- 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 100 mL of blood may be drawn in a 24-hour period, and no more than 400 mL of blood in a 4-week period.
- Where allowed by local law/regulations, samples collected during this clinical study may be transferred to a biobank and used for future research outside the clinical protocol when additional consent for this purpose is given. Transfer to the biobank will be documented and any testing of coded biobank samples will **not** be reported in the CSR.
- The long-term storage of samples after study completion for future research may be performed will all sample types collected in the study (e.g., PK, CCI [redacted]) if the participant consents to optional future medical research.

8.1 Efficacy Assessments and Procedures

Not applicable.

8.2 Safety Assessments and Procedures

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

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

8.2.1 Physical Examinations

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

8.2.2 Vital Signs

- Blood pressure and participant's position; pulse; respiratory rate; 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 or Fridericia's formula. Documentation of the corrected QT interval by Fridericia's formula is mandatory.

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.
- The Investigator will review each laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE, unless it does **not** meet the AE definition, as specified in Appendix 4. The laboratory reports will be filed with the source documents.

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

- The definitions of an AE and a SAE are in Appendix 4.
- The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study, as specified in Section 8.3.2.
- Requests for follow-up will usually be made via the Sponsor or 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 and under no circumstance will this exceed 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.
- Investigators are not obligated to actively solicit information on AEs or SAEs after the end of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.1 Method of Detecting Adverse Events and Serious Adverse Events

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading 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

Note: In this study, only women of nonchildbearing potential will be included.

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

8.3.5 Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.7 Adverse Events of Special Interest

For this study, AESIs 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

- The following PK parameters will be calculated, when appropriate for evobrutinib and its metabolite MSC2729909A on Day 1 and Day 19:

Symbol	Definition
$AUC_{0-\infty}$	The AUC from time zero (= dosing time) up to infinity with extrapolation of the terminal phase.
$AUC_{0-tlast}$	The AUC from time zero (= dosing time) to the time of the last quantifiable concentration (t_{last}).
C_{max}	Maximum observed concentration.
t_{max}	The time to reach the C_{max} in a dosing interval.
$t_{1/2}$	The terminal half-life.
t_{lag}	The time prior to the first concentration at or above LOQ
CL/F	The apparent total body clearance following extravascular administration.
V_Z/F	The apparent volume of distribution during the terminal phase following extravascular administration.
M/P($AUC_{0-\infty}$)	Molecular weight-corrected ratio of metabolite $AUC_{0-\infty}$ to parent $AUC_{0-\infty}$.
M/P(C_{max})	Molecular weight-corrected ratio of metabolite C_{max} to parent C_{max}.

CCI [redacted]

[redacted]

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

CCI [redacted]

- Whole blood samples of approximately 2 mL for measurement of plasma concentrations of evobrutinib and its metabolite MSC2729909A will be collected. 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.
- The quantification of evobrutinib and its metabolite MSC2729909A in plasma samples will be performed using fully validated assay methods. Evobrutinib and metabolite concentrations will be used to evaluate the PK parameters of evobrutinib and its major metabolite.

CCI [redacted]

- Remaining samples collected for analyses of evobrutinib and carbamazepine concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Additionally, remaining plasma samples may be used for investigation of other evobrutinib metabolites, if deemed necessary.
- 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).

The exact date and time of sample collection and study intervention administration prior to sample collection (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 evobrutinib and carbamazepine PK times that will not be considered a protocol violation are listed below:

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

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

CCI [redacted]

CCI [redacted]

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 clinical study report.

9.1 Statistical Hypotheses

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

CCI [redacted]

9.3 Analyses Sets

The analysis sets are specified below.

Analysis Set	Description
SCR	All participants, who provided informed consent, regardless of the participant's enrollment and study intervention status in the study.
SAF	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
PK	The PK Analysis Set is a subset of the SAF, and the PK population will include all participants: Who have completed the study without any relevant protocol deviations and factors likely to affect the comparability of PK results. With adequate study intervention compliance. With evaluable PK data, i.e., nonmissing values for primary endpoints. If participants received prohibited concomitant therapy or medicines, as specified in Section 6.8, they will be excluded from the PK population. All PK analyses will be based on this analysis set.

PK=pharmacokinetics; SAF=safety; SCR=Screening.

9.4 Statistical Analyses

Statistical analysis will be performed using the computer program package SAS®. More details on the statistical analysis will be presented in the IAP prior to database lock.

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

Medical history and AE terms will be coded with the latest version of MedDRA (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, sex, race, etc.), baseline and safety assessments, continuous measurements will be summarized by means of descriptive statistics (i.e., number and percentage of observations, number and percentage of missing observations, mean, SD, median, the Q1 and Q3, Min, and Max) and categorical data will be summarized by means of frequency tables (i.e., count and percentages), if not stated otherwise.

All data will be evaluated as observed, 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 Set.

Reference #	Endpoint	Statistical Analysis
Primary		Not applicable
Secondary		
2 - Safety	Nature, occurrence, severity, and seriousness of TEAEs	AE counts and participants with AEs will be summarized for each treatment by SOC and PT. In addition, AEs will be tabulated and listed per participant and analyzed by severity and relationship to study intervention.
	Absolute values and changes in safety laboratory tests from time of first dose to end of study participation	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.
	Single 12-lead ECGs evaluated by Investigator from time of first dose to end of study participation	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	Vital signs by participant, including changes from Baseline, will be listed and summarized by treatment and time point using descriptive statistics.
CCI [redacted]		[redacted]

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

9.4.3 Pharmacokinetic Analyses

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

Reference #	Endpoint	Statistical Analysis
Primary		
1 – Evobrutinib PK	$AUC_{0-\infty}$ and C_{max}	The effect of co-administration of carbamazepine on evobrutinib exposure will be assessed. A general linear model with a fixed effect for TREATMENT and a random effect for SUBJECT will be applied to the log-transformed PK parameters C_{max} and $AUC_{0-\infty}$ based on the PK analysis set. Treatment differences on the log scale of evobrutinib with carbamazepine versus evobrutinib alone (Day 19 versus Day 1) will be estimated for the C_{max} and $AUC_{0-\infty}$ together with their 90% CIs. Point estimates and CIs will be back transformed to the original scale for presentation. Summary statistics will be provided for $AUC_{0-\infty}$ and C_{max}.
Secondary		
3 – Additional evobrutinib PK parameters	CL/F, V_Z/F, $AUC_{0\text{-tlast}}$, t_{max}, $t_{½}$	The same analysis model as described for the primary endpoints will be provided for the secondary endpoint $AUC_{0\text{-tlast}}$ of evobrutinib in plasma. Summary statistics will be provided for all PK parameters.

4 – Evobrutinib metabolite (MSC2729909A) PK	$AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, t_{max} t_{lag} and the respective metabolic ratios MR($AUC_{0-\infty}$) and MR(C_{max})	The same analysis model as described for the primary endpoints will be provided for the secondary endpoints C_{max}, $AUC_{0-tlast}$ and $AUC_{0-\infty}$ of the evobrutinib metabolite MSC2729909A in plasma. Summary statistics will be provided for all PK parameters.
CCI [redacted]		
CCI [redacted]	[redacted]	[redacted]

AUC=area under the concentration-time curve; C_{max}=maximum observed concentration; C_{min}=minimum observed concentration; CL/F=apparent total body clearance; MR=metabolic ratio; PK=pharmacokinetics; $t_{½}$=apparent terminal half-life; t_{lag}=time prior to the first measurable (nonzero) concentration; t_{max}=time to reach the maximum observed concentration; V_Z/F=apparent volume of distribution.

9.4.4 Sequence of Analyses

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

10 References

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11 Appendices

Appendix 1 Abbreviations

(e)CRF	(Electronic) Case Report Form
AE	Adverse Event
AESI	Adverse Events of Special Interest
BCS	Biopharmaceutics Classification System
BMI	Body Mass Index
BTK	Bruton's Tyrosine Kinase
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
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
EDC	Electronic Data Capture
EudraCT	European Clinical Trials Database
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte Antigen
HRT	Hormone Replacement Therapy
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgA/G/M	Immunoglobulin A/G/M
IMP	Investigational Medicinal Product
IRB	Institutional Review Board

MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MS	Multiple Sclerosis
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
SAF	Safety
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Event
TEB	Toxic Epidermal Necrolysis
ULN	Upper Limit of Normal

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; HIPAA requirements, where applicable; and the IRB/IEC or study center.
- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent will also sign the ICF.
- If the ICF is updated during their participation in the study, participants will be re-consented to the most current, approved version.

Data Protection

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

Study Administrative

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

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

  Clinical trial supplies will be provided by Thermo Fisher.
- 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 CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) will be submitted to an IRB/IEC for review and approved before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

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

Clinical Study Insurance and Compensation to Participants

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

Clinical Study Report

- After study completion, the Sponsor will write a clinical study report in consultation with the Principal Investigator or 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 clinical study report.

  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 require 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 Informed Consent Form.

Study and Site Closure

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

Appendix 3 Contraception and Barrier Requirements

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

Definitions:

Woman of childbearing potential:

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

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

Postmenopause:

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

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

Permanent sterilization:

For this study, permanent sterilization includes:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

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

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

AE Definition

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

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

SAE Definition

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent disability/incapacity

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

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually considered as serious.

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

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

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

Follow-Up of AEs and SAEs

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

Reporting of SAEs

SAE Reporting by a Paper Form

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

Reporting of AESIs

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

Reporting of Pregnancies

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

Appendix 5 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			
Biochemistry	Blood Urea Nitrogen	Potassium	Aspartate aminotransferase	Total Bilirubin
	Creatinine	Sodium	Alanine aminotransferase	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
	Uric acid	Chloride	Gamma-glutamyl transferase	Cholesterol
		Inorganic phosphate	Lactate dehydrogenase	Triglycerides
		Magnesium	Creatinine phosphatase	Amylase
				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	• International normalized ratio • Activated partial thromboplastin time			
Other Screening Tests	• Follicle stimulating hormone (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) • SARS-CoV-2 test (Screening and Day -1) Note: According local regulations at the time of study conduct. • Thyroid stimulating hormone (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) • Presence of HLA-B* 1502 or HLA-A* 3101 (Screening) All study-required laboratory assessments will be performed by a central laboratory (Nuvisan's clinical laboratory) apart from analysis of HLA-B* 1502 or HLA-A* 3101 which will be performed by another vendor with these assessment capabilities.			

HLA-A=human leucocyte antigen A, HLA-B= human leucocyte antigen B, SARS-CoV-2=severe acute respiratory syndrome coronavirus type 2.

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Appendix 7 Examples of Inhibitors or Inducers of CYP3A Enzymes or Substrates with Narrow Therapeutic Range

Inhibitors		
Strong[a]	**Moderate[b]**	**Weak[c]**
Boceprevir, clarithromycin, conivaptan, grapefruit juicedd ,indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,a imatinib, and verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, and zileuton
Inducers		
Strong[a]	**Moderate[b]**	**Weak[c]**
Avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort	Bosentan, efavirenz, etravirine, modafinil, and nafcillin	Amprenavir, aprepitant, armodafinil, echinacea, pioglitazone, prednisone, and rufinamide
Substrates With a Narrow Therapeutic Range		
Alfentanil, astemizole[e] ,cisapride[e,] cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[e]		

CYP=cytochrome P450.

Sources: This is not an exhaustive list. For an updated list, see the following links:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-2.

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-3.

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2.

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3.

Note: CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de pointes).

a: A strong inhibitor is defined as an inhibitor that increases the AUC of a substrate sensitive for that CYP ≥ 5-fold or decreases clearance by > 80%, and a strong inducer decreases AUC of a substrate by ≥ 80%.

b: A moderate inhibitor is defined as an inhibitor that increases the AUC of a substrate sensitive for that CYP ≥ 2-fold but < 5-fold or decreases clearance by 50% to 80%, and a strong inducer decreases AUC by 50% to 80%.

c: A weak inhibitor is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP < 2-fold or decreases clearance 20% to 50%, and a weak inducer decreases AUC by 20% to 50%.

d The effect of grapefruit juice varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation is used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation is used (e.g., low dose, single strength).

e Withdrawn from the US and certain other markets because of safety reasons.

Appendix 8 Sponsor Signature Page

Study Title:	Phase I, Open-Label, Single-Sequence Study of the Effect of Multiple Doses of Carbamazepine on Single-Dose Evobrutinib Pharmacokinetics in Healthy Participants
Regulatory Agency Identifying Numbers:	EudraCT: 2021-003381-13
Clinical Study Protocol Version:	12 October 2021/Version 1.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	Medical Responsible and Protocol Lead
Institution:	Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany
Address:	Frankfurter Str. 250, 64293 Darmstadt, Germany
General Merck Phone Number:	PPD
General Merck Fax Number:	Not Applicable

Appendix 9 Principal Investigator Signature Page

Study Title:	Phase I, Open-Label, Single-Sequence Study of the Effect of Multiple Doses of Carbamazepine on Single-Dose Evobrutinib Pharmacokinetics in Healthy Participants
Regulatory Agency Identifying Numbers:	EudraCT: 2021-003381-13
Clinical Study Protocol Version:	12 October 2021/Version 1.0
Site Number:	Not applicable

I approve the design of the clinical study, am responsible for the conduct of the study at this PPD per the clinical study protocol, any approved protocol nd all applicable Health Authority requirements and

PPD

Date of Signature

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

CCI