Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	Phase I, Open-label, Single-sequence, Cross-over Study of the Effect of Multiple Doses of Itraconazole on Single-dose Tepotinib Pharmacokinetics in Healthy Participants
Study Number:	MS200095_0053
Protocol Version:	15 September 2021 / V1.0
Merck Compound**:**	Tepotinib
Study Phase:	Phase I
Short Title:	Tepotinib Drug-Drug Interaction Study With Itraconazole in Healthy Participants
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: 2021-003513-19
Keywords:	Clinical pharmacology, metabolite, inhibition of metabolism

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1 Protocol Summary

1.1 Synopsis

Protocol Title: Phase I, Open-label, Single-sequence, Cross-over Study of the Effect of Multiple Doses of Itraconazole on Single-dose Tepotinib Pharmacokinetics in Healthy Participants

Short Title: Tepotinib Drug-Drug Interaction Study With Itraconazole in Healthy Participants

[redacted]

Objectives and Endpoints:

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

ECG=electrocardiogram, PK=pharmacokinetics, TEAE=treatment emergent adverse events.

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

Brief Summary:

The purpose of this study is to assess the effect of multiple doses of itraconazole on single-dose tepotinib pharmacokinetics in healthy participants. Study details include:

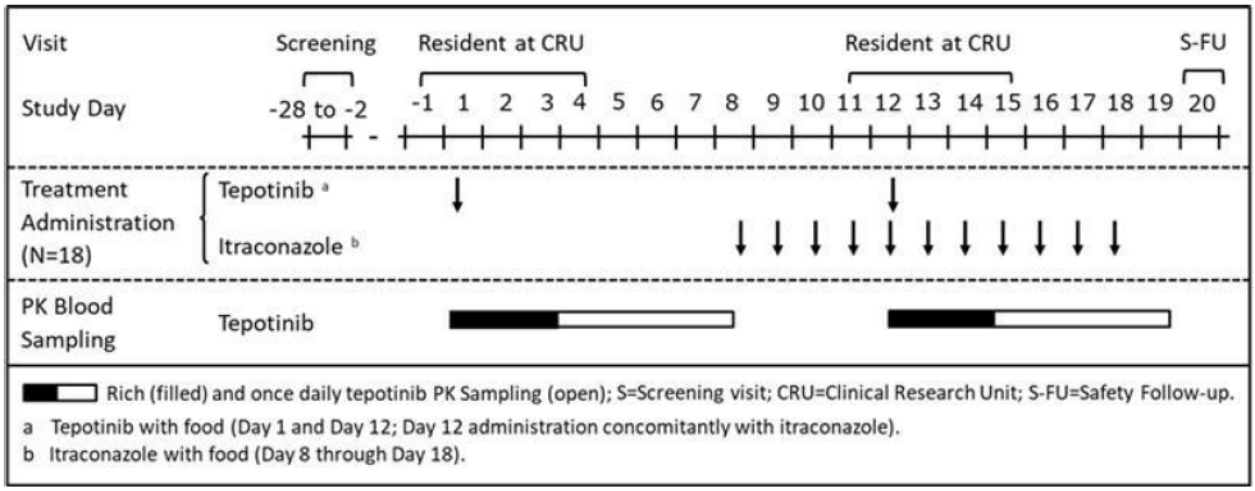
- Study Duration: up to 48 days
- Treatment Duration: single dose of tepotinib on Days 1 and 12, 11 days of treatment with itraconazole (Days 8 to 18)
- Visit Frequency: residence in the Clinical Research Unit from Days -1 to 4 and Days 11 to 15, ambulatory daily visits from Days 5 to 10 and 16 to 20

Number of Participants: A maximum of 18 participants will be assigned to study interventions such that at least 14 evaluable participants complete the study.

Study Intervention Groups and Duration: 21 days of intervention period including Safety Follow Up on Day 20; single dose of tepotinib on Days 1 and 12, 11 days of treatment with itraconazole (Days 8 to 18).

Involvement of Special Committee(s): No

1.2 Schema



1.3 Schedule of Activities

Assessments & Procedures	Screening	Intervention Period (Days)																			Safety Follow Up	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Informed consent	X																						Prior to any Screening activity.
Participants resident at CRU		X	X	X	X	X							X	X	X	X	X						
Ambulatory visits at CRU							X	X	X	X	X	X						X	X	X	X	X	
Elig bility criteria	X	X																					Recheck of elig bility 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									X	Brief examination on Day -1 to check eligibility. Section 8.2.1.
Serum pregnancy test	X	X																				X	Section 8.3.4 and Appendix 5.
FSH	X																						In postmenopausal women, only (Appendix 5).
Viral serology, TSH	X																						Appendix 5.
Clinical laboratory tests (blood and urine)	X	X								X			X		X		X		X			X	Details in Appendix 5.
Cotinine, drug screen, alcohol breath test, SARS-CoV-2	X	X											X										Details in Appendix 5.
Vital signs & safety ECG	X	X	X	X									X	X	X	X	X					X	Predose on dosing days. Sections 8.2.2 and 8.2.3.

Assessments & Procedures	Screening	Intervention Period (Days)																			Safety Follow Up	Notes
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
AE/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.8. Section 8.3.
CCI [redacted]		C																					CCI [redacted]
Itraconazole administration										X	X	X	X	X	X	X	X	X	X	X			Once daily with food (Section 5.3.1 and Section 6.1).
Tepotinib administration			X											X									Section 5.3.1. Section 6.1.
CCI [redacted]			X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X		Detailed PK sampling scheme in Table 1.
Fecal sampling			X	X	X	X								X	X	X	X						All stools during the stay at CRU to be collected (Section 8.4).
Mild laxative					X											X							To be administered in the evenings (Section 8.4).

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

Table 1 Tepotinib and Metabolite PK Sampling Schema

Study Day	1	2	3	4	5	6	7	8	Notes
	12	13	14	15	16	17	18	19	
Timing PK blood sampling	Predose[a] and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours postdose	24, 30, 38 hours	48, 60 hours	72 hours	96 hours	120 hours	144 hours	168 hours	a Within 60 minutes before tepotinib dosing. All other samples to be collected post tepotinib dose. For PK sampling window allowance see Table 2.

PK=pharmacokinetics.

2 Introduction

Tepotinib (Tepmetko®) is a highly selective, reversible ATP-competitive inhibitor of the receptor tyrosine kinase MET in clinical development for the treatment of patients with e.g., advanced NSCLC with METex14 skipping alterations or MET amplification.

Detailed information on the chemistry, pharmacology, efficacy, and safety of tepotinib is in the IB (current version).

There is extensive clinical experience in the use of itraconazole. It was approved in the United States in 1992 (www.accessdata.fda.gov) and is widely used as antifungal agent. Full information about the potential side effects of itraconazole administration is described in its currently approved SmPC and USPI (refer to Itraconazole SmPC and USPI).

CCI [redacted]

[redacted]

[redacted]

[redacted]

2.2 Background

Tepotinib

MET, along with its ligand, the HGF have been implicated in carcinogenesis and metastatic tumor progression, because of their ability to enhance angiogenesis, cancer cell proliferation, migration and invasion, as well as conferring resistance to apoptosis. Pharmacological interference with the HGF/MET axis is considered a promising strategy to inhibit primary tumor growth and metastasis in patients with e.g., NSCLC (refer to current tepotinib IB and USPI).

Tepotinib CCI [redacted] at 500 mg, exhibited substantial and sustained clinical activity in participants with advanced NSCLC harboring METex14 skipping alterations across the endpoints studied in the Phase II VISION study (MS200095_0022). The efficacy analyses provided strong evidence of a clinically meaningful response rate, deep and durable responses, and rapid onset of responses. Progression free survival and overall survival analyses provided additional supportive evidence of tepotinib's clinical activity. Tepotinib was well tolerated in healthy participants and patients.

These data have recently led to marketing authorizations in several geographies including the conditional approval by the US FDA for treatment of patients with advanced NSCLC harboring METex14 skipping alterations (refer to current tepotinib IB and USPI).

Tepotinib is classified as a CCI [redacted]

Itraconazole

Itraconazole is an antifungal drug which is a potent inhibitor of drug-metabolizing enzymes and transporters. Enzymes and transporters reported to be affected by itraconazole include CYP3A4 and P-gp. Several drugs are substrates for CYP3A4 or P-gp, and these pathways are inhibited by itraconazole simultaneously. Therefore, itraconazole may slow down the metabolism and reduce the activity of certain coadministered drugs and has the potential to cause clinically important drug-drug interactions (refer to Itraconazole SmPC and USPI).

Itraconazole is classified as a BCS Class II compound according to the FDA BCS guidance. It is readily absorbed from the gastrointestinal tract. Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following an oral capsule dose. The observed absolute oral bioavailability of itraconazole is about 55%. The oral bioavailability of itraconazole is maximal when itraconazole capsules are taken immediately after a full meal (Barone 1993 and 1998). Most of the itraconazole in plasma is bound to protein (99.8%), with albumin being the main binding component. Only 0.2% of the itraconazole in plasma is present as free drug. Itraconazole is distributed in a large apparent volume in the body (> 700 L), suggesting extensive distribution into tissues. Itraconazole is extensively metabolized by the liver into a large number of metabolites. The main metabolite is hydroxy-itraconazole, which has *in vitro* antifungal activity comparable to itraconazole (refer to Itraconazole SmPC and USPI) and is also known to inhibit CYP3A4 (Isoherranen 2004) and P-gp (Lempers 2016). Elimination half-life of itraconazole in healthy participants is in the range of ~6 ± 5 hours (Lestner and Hope 2013, Heykants 1989). Following multiple-dose administration, a 26% to 60% increase in the elimination half-life of itraconazole and a time-dependent reduction (69% to 80%) in oral clearance (CL/F) has been

observed (Templeton 2008, Haria 1996, Hardin 1988, Heykants 1989). Itraconazole is excreted mainly as inactive metabolites in urine and in feces (refer to Itraconazole SmPC and USPI).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of tepotinib may be found in Section 4.2, the IB, and the USPI.

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

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

2.3.1 Risk Assessment

Based on the currently available nonclinical as well as clinical safety data for tepotinib, and the lack of genotoxicity in nonclinical studies, there is no objection against administration of single doses or short-term multiple administrations to healthy participants. The participants will be under close monitoring for e.g., potential AEs, safety laboratory parameters, ECG, and vital signs in the clinical research unit to reduce the risk for any untoward effects of tepotinib.

Exposure to tepotinib at different dose levels including 500 mg tepotinib HCl hydrate were well tolerated by healthy participants (refer to current tepotinib IB). Cumulatively, 702 patients and 225 healthy participants and participants with hepatic impairment were exposed to tepotinib (500 mg in the majority of studies in healthy participants and 30 mg and 100 mg each in 1 study) in interventional clinical studies sponsored by Merck or any affiliate (DSUR No. 9, reporting period 25 September 2020 to 24 March 2021, data lock point 24 March 2021).

No maximum tolerated dose could be defined in the first-in-man study EMR200095_001, using up to 1,400 mg once daily administered in 21-day cycles (refer to current tepotinib IB).

No single identified metabolic pathway comprises more than 25% of the administered dose (refer to current tepotinib IB). Therefore, the DDI potential with tepotinib as victim to inhibitors of coadministered CYP3A4 inhibitors is considered low.

Tepotinib is substrate to P-gp dependent transport. Assuming a worst case in which P-gp mediated biliary secretion accounts for 30% of the total clearance of tepotinib, the maximum AUC increase through complete inhibition of P-gp is 43% (refer to current tepotinib IB). The effect of combined inhibition of CYP3A4 and P-gp is unknown.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) – Tepotinib		
Nonclinical Risks: Teratogenicity	CCI [redacted]	CCI [redacted]
Clinical identified risk: increased creatinine	Increase of creatinine is commonly reported in clinical studies. The observed increases in creatinine are thought to occur due to competition of renal tubular secretion. The levels decrease after discontinuation from tepotinib.	Increases in serum creatinine were transient after single administrations. The residual risk in this single-dose study is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2) and monitoring of blood creatinine by routine laboratory testing (Section 8.2.4 and Appendix 5).
Clinical identified risk: hypoalbuminemia	Hypoalbuminemia is commonly reported in tepotinib studies. For more information refer to IB (current version) Section 5.3, 6.1.2 and 6.1.3.2.	Clinically relevant hypoalbuminemia was not observed after single administrations. The residual risk is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2) and monitoring of albumin by routine laboratory testing (Section 8.2.4 and Appendix 5).
Clinical identified risk: amylase and lipase	Increases were generally asymptomatic and not associated with pancreatitis. For more information refer to IB (current version) Section 5.3, 6.1.2 and 6.1.3.2.	The risk is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2) and monitoring of amylase and lipase by routine laboratory testing (Section 8.2.4 and Appendix 5).
Clinical identified risk: ALT and AST increased Potential clinical risk: severe hepatotoxicity	The hepatobiliary system was identified as target organ of toxicity in toxicology studies. For more information refer to IB (current version) Section 4.3, 5.3, 6.1.2 and 6.1.3.2.	The risk is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2) and monitoring of ALT and AST by routine labs (Section 8.2.4 and Appendix 5).
Clinical identified risks of gastrointestinal toxicity	The gastrointestinal tract was identified as target organ of toxicity in toxicology studies. Diarrhea, nausea, and vomiting is commonly reported in tepotinib studies. For more information refer to IB (current version) Section 4.3, 5.3, 6.1.2 and 6.1.3.2.	The risk is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2) and monitoring of gastrointestinal-related AEs.
Potential clinical risk: QTc prolongation	In an exposure-QTc analysis across multiple studies, tepotinib did not prolong the	The risk is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2) and ECG monitoring.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	QTcF interval in cancer patients to a clinically relevant extent. For more information refer to IB (current version) Section 5.2.12.3 and 6.1.3.2.	
Clinical identified risk: blood ALP increased	The hepatobiliary system was identified as target organ of toxicity in toxicology studies. The increases were asymptomatic, nonserious and low grade.	The risk is considered as managed by adequate measurements such as eligibility criteria and monitoring of ALP by routine laboratory testing (Section 8.2.4 and Appendix 5).
Study Intervention(s) – Itraconazole		
Identified Risks: Hepatotoxicity	Refer to itraconazole SmPC and USPI.	The risk from potential overlapping toxicities with regards to LFT is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2) and close monitoring. Inclusion will be only allowed for participants with adequate hepatic function.
Identified Risks: cardiac dysrhythmias, congestive heart failure (frequency unknown).	Refer to itraconazole SmPC and USPI.	The risk is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2), ECG monitoring and monitoring for symptoms of congestive heart failure (Section 8.2.3).
AEs with a frequency of common: abdominal pain, nausea, constipation, headache, pruritus, rash , rhinitis, and edema.	Refer to itraconazole SmPC and USPI.	The risk is considered as managed by adequate measurements such as eligibility criteria (Sections 5.1 and 5.2) and by routine pharmacovigilance.
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.		

AEs=adverse events, ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, c-Met=tyrosine-protein kinase Met or hepatocyte growth factor receptor, ECG=electrocardiogram, IB=investigator's brochure, LFT=liver function test, SmPC=summary of product characteristics, USPI=United States prescribing information.

2.3.1.1 Potential Risks associated with the COVID-19 Pandemic Situation

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

During the entire study, all recommendations issued by the Robert Koch Institute as well as local guidelines will be followed with respect to the minimization of the risk of disease spreading, e.g., social distancing, disinfection, hygiene, and wearing of appropriate mouth-nose masks. 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 periods of the study, the following measures are to be 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. The continuation of the study in the case of a SARS-CoV-2 infection in a study participant or in an identified contact to a SARS-CoV-2 positive participant or COVID-19 patient will be decided at the Investigator's discretion and in agreement with the medical monitoring team. The Sponsor will monitor the events related to any SARS-CoV-2 infection reported following tepotinib regularly and update the recommendations, if necessary.

2.3.2 Benefit Assessment

Healthy participants may not expect a benefit from participating in a clinical study with tepotinib. The inclusion of healthy participants minimizes variability compared to a study in patients. This study significantly contributes to the process of developing new therapies to areas of unmet need.

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), close biochemical and hematology laboratory monitoring (Section 8.2.4), stringent contraception requirements (e.g., WOCBP excluded; Section 5.2), adverse events and the observation of vital signs and ECGs (Sections 8.2.2 and 8.2.3). Tepotinib and/or itraconazole will be discontinued in case of events that unacceptably endanger the safety of the participant (Section 8.3). Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with tepotinib and itraconazole are considered justified in healthy participants.

3 Objectives and Endpoints

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

ECG=electrocardiogram, CCI [redacted], PK=pharmacokinetics, TEAE=treatment emergent adverse events.

4 Study Design

4.1 Overall Design

Study Design	Single-sequence
Control Method	Cross-over design
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 7 weeks, including the Screening period (Day -28 to Day -2) and 21 days of intervention period (last dose of tepotinib on Day 12, last PK sample collected on Day 19), and a Safety Follow Up on Day 20 (Sections 1.2 and 1.3).
Provisions for Study Extension or Entry into Roll-Over Studies	Not applicable
Adaptive Aspects of Study Design	Not applicable

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.3 Justification for Dose

Tepotinib

The tepotinib dose to be used in this study is 500 mg tepotinib HCl hydrate (equivalent to 450 mg free base) as tablet formulation. This is the clinical dose which was extensively studied during clinical development and which was recently approved by the US FDA (refer to tepotinib USPI). 2 single doses of 500 mg of tepotinib HCl hydrate, consisting of 2 tablets (250 mg) each will be administered in this study.

The 500 mg tepotinib HCl hydrate single oral dose with food has been evaluated in previous studies in healthy participants and was found to be safe and well tolerated (refer to Tepotinib IB). The dose of 500 mg tepotinib HCl hydrate is the RP2D for the treatment of human malignant tumors (refer to Tepotinib IB). This is also the recommended dosage taken orally once daily with food (refer to Tepotinib USPI).

For more detailed information on dose selection refer to current tepotinib IB.

Itraconazole

The itraconazole dose to be used in this study, 200 mg once daily for 4 days before CYP3A4 substrate administration, is a common dosing regimen used to assess the effect of CYP3A4 inhibition on the PK of CYP3A4 substrates in drug-drug interaction studies of this type (Chen 2019, Liu 2016, Ke 2014, Gibbons 2015, Oda 2003, Backman 1998, Kivisto 1998). Itraconazole does not inhibit adrenal steroidogenesis at doses of 200 mg once daily; reversible adrenal insufficiency has, however, been reported at a dose of 600 mg once daily (Liu 2016, Queiroz-Telles 1997, Sharkey 1991). In addition, the risk of QTc prolongation is considered low and manageable at the itraconazole dose of 200 mg once daily (Liu 2016, Sung 2012, Honig 1993). Cardiac risks increased with doses greater than 400 mg once daily (Paul 2017,

Okamoto 2007, Teaford 2020). Administration of 400 mg had a limited additional CYP3A inhibitory effect over that observed with 200 mg (Templeton 2010) and is higher than the daily dose of 100 or 200 mg recommended for most indications (refer to Itraconazole SmPC). Although 4 days is not sufficient for attainment of steady state, the 4-day lead-in allows for some accumulation, with higher itraconazole and metabolite exposure and therefore a potentially greater degree of CYP3A4 inhibition, with consideration for potential logistical and safety concerns associated with a longer itraconazole dosing period (Liu 2016, Chen 2019).

Itraconazole is available as hard-gelatin capsule and solution; both formulations have been used in DDI studies (Barone 1998, Templeton 2010, Liu 2016). Although the solution provides higher systemic exposure, with less variability, the capsule provides adequate exposure of itraconazole and metabolites to ensure strong CYP3A4 inhibition when dosed with food (Barone 1993, Liu 2016, refer to Itraconazole USPI and SmPC). Simple medication intake is guaranteed when using capsules. Another advantage of itraconazole hard-gelatin capsules is the fact, that this formulation does not contain hydroxypropyl-β-cyclodextrin, which is used as an excipient to increase the solubility of itraconazole in the solution formulation (refer to Itraconazole USPI and SmPC). Cyclodextrins act by forming inclusion complexes which might affect the PK of tepotinib as published for fenebrutinib (Chen 2020, Durk 2020).

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 shown in Section 1.3).

A participant has completed the study if he/she has completed all study parts, including Safety Follow Up assessments on Day 20 (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 whose character, severity or frequency is new in comparison to the existing risk profile.
- Any data derived from other clinical studies or toxicological studies become available which negatively influence the risk/benefit assessment.

General information on study termination is specified in Appendix 2.

5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only 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 by medical history, cardiac monitoring, 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 at Screening and Day -1.
Weight	3. Have a body weight within 50 and 100 kg inclusive and BMI within the range $\geq$ 18.5 and $\leq$ 29.9 kg/m^2 (inclusive) at Screening.

Category	Criterion
Sex and Contraception/Barrier Requirements	4. Are male or female (not a WOCBP) The Investigator confirms that each participant agrees to use appropriate contraception and barriers, if applicable. The contraception, barrier, and pregnancy testing requirements are below. Contraceptive use will be consistent with local regulations on contraception methods for those participating in clinical studies. a. Male Participants: Agree to the following during the study intervention period and for at least 1 week after the last dose of study intervention: • Refrain from donating fresh and unwashed sperm PLUS, either: • Abstain from intercourse with a WOCBP. OR • Use a male condom: • When having sexual intercourse with a WOCBP, who is **not** currently pregnant, **and** instruct her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 3, since a condom may break or leak. b. Not a WOCBP, confirmed at Screening, by fulfilling at least 1 of the following criteria: • Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased FSH > 40 mIU/mL). • Documentation of irreversible surgical sterilization by hysterectomy, or bilateral oophorectomy, or bilateral salpingectomy.
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.
Laboratory Parameters	6. All values for hematology, coagulation, and biochemistry tests of blood and urinalysis within the normal range (at Screening and Day -1). Minor (solitary) nonclinically relevant excursion(s) are allowed as judged by the Investigator, however amylase and lipase should not exceed the ULN; ALT, AST and total bilirubin should not exceed the ULN × 1.1.

ALT=alanine aminotransferase, AST=aspartate aminotransferase, BMI=body mass index, FSH=follicle stimulating hormone, ICF=informed consent form, ULN=upper limit of normal, WOCBP=woman of child-bearing potential.

5.2 Exclusion Criteria

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

Category	Criterion
Medical Conditions	1. History or presence of clinically relevant respiratory, gastrointestinal, renal, hepatic, hematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, dermatological, connective tissue diseases or disorders, as determined by medical evaluation.
	2. Participants with gall bladder removal or other relevant surgery of gastrointestinal tract (appendectomy is not considered as relevant).
	3. History of any malignancy except for adequately treated superficial basal cell carcinoma.
	4. History of epilepsy.
	5. Ascertained or presumptive allergy/hypersensitivity to the active drug substance and/or excipients; history of anaphylaxis to drugs or serious allergic reactions leading to hospitalization or any other allergy reaction in general, which the Investigator considers may affect the safety of the participant and/or outcome of the study.
	6. 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.
Prior/Concomitant Therapy	7. Moderate or strong inhibitors or inducers of CYP3A4 and P-gp within 4 weeks prior to the first administration of study intervention.
	8. 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.

Category	Criterion
	9. Administration of live vaccines or live-attenuated virus vaccines within 3 months prior to Screening. Administration of other types of vaccines (e.g., SARS-CoV-2 vaccines, final boost) is allowed until 1 week before admission to CRU. Note: In case of clinical symptoms, the participant should be symptom-free for at least 1 week prior to admission to CRU.
Prior/Concurrent Clinical Study Experience	10. Participation in the treatment phase of a clinical study within 60 days or 5 half-lives after last dosing of the previous study drug, whatever is longer, before administration of study drug.
Diagnostic Assessments	11. Supine systolic blood pressure > 140 or < 90 mmHg, diastolic blood pressure > 90 or < 50 mmHg, and pulse rate > 90 or < 50 beats per minute at Screening and at admission on Day -1 (any abnormal blood pressure results may be repeated once and if the repeat result is within the normal range, it is not considered to have met the exclusion criterion). (Section 8.2.2)
	12. 12-Lead ECG showing a QTcF > 450 ms, PR > 215 ms, or QRS > 120 ms at Screening and at admission on Day -1.
	13. Creatinine clearance estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (2009) < 90 mL/min at Screening.
	14. 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 on admission on Day -1.
	15. 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 (by rapid antigen test) or at admission on Day -1 (by PCR test).

Category	Criterion
	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: should not exceed the ULN × 1.1 • Creatinine: above normal limits • Absolute lymphocyte count, absolute neutrophil count, absolute platelet count: below limit of reference range • Amylase and lipase above the upper limit of normal and/or signs/symptoms of pancreatitis.
Other Exclusions	17. Contraindication to itraconazole (refer to Itraconazole USPI and SmPC): ventricular dysfunction such as congestive heart failure or a history of congestive heart failure, drug interactions (e.g., coadministration of a number of CYP3A4 substrates), pregnancy, hypersensitivity to itraconazole.
	18. 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.
	19. Excessive consumption of xanthine-containing food or beverages (> 5 cups of coffee or equivalent a day) or inability to stop consuming caffeine at Screening and at admission on Day -1.
	20. Consumption of an average weekly alcohol intake of > 14 units/week for men or > 7 units/week for women. 1 unit (12 g) of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
	21. Consumption of alcohol from 48 hours prior to first administration of study intervention.
	22. Smoker (cigarettes, pipes, cigars, or others) or former smoker who stopped smoking for less than 6 months before the time of the Screening visit.
	23. Intake of grapefruit, Seville orange, pomelo, grapefruit hybrids, exotic citrus fruit, cranberries or juices of these fruits, or St John's Wort, from 14 days prior to admission on Day -1.
	24. Products containing poppy seeds (cake, rolls) may not be consumed within 48 hours before Screening and each admission until discharge.

Category	Criterion
	25. Inability to communicate or cooperate with the Investigator (e.g., language problem, illiteracy, poor mental status) or to comply with the requirements of the entire study, including dietary restrictions.
	26. Other factors, which in the opinion of the Investigator may interfere with study conduct.
	27. Legal incapacity or limited legal capacity.
	28. Participant is in custody by order of an authority or a court of law.

CRU=clinical research unit, CYP=cytochrome P450, PCR=polymerase chain reaction, P-gp=P-glycoprotein, ECG=electrocardiogram, SARS-CoV-2= severe acute respiratory syndrome coronavirus 2, SmPC=summary of product characteristics, ULN=upper limit of normal, USPI=United States prescribing information.

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, cranberries, fruit juices or St John's Wort.

Products containing poppy seeds (cake, rolls) may not be consumed within 48 hours before Screening and each admission until discharge.

On Day 1 and Day 12, participants will receive a single dose of 500 mg tepotinib HCl hydrate (tablets) in the morning at the start of a standard moderate-fat/moderate-calorie breakfast. Following an overnight fast of at least 10 hours, participants should receive a standard moderate-fat/moderate-calorie breakfast which should be consumed within 30 to 60 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.

On Days 8 to 11 and Days 13 to 18, participants will receive once-daily a single dose of 200 mg itraconazole (capsules) taken immediately after the standard moderate-fat/moderate-calorie breakfast. On Day 12, participants will receive a single dose of 200 mg itraconazole (capsules) simultaneously with a single dose of 500 mg tepotinib HCl hydrate (tablets) in the morning at the start of a standard moderate-fat/moderate-calorie breakfast.

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

Standard moderate-fat, moderate-calorie breakfasts 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 CRU will be standardized and no documentation of time and complete consumption is needed. The participants are only permitted to eat meals provided by the CRU. These meals will be provided at usual meal times of the CRU.

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 PD sample.
- During each dosing period, participants will abstain from alcohol and cannabinoid-containing products for 48 hours before the start of dosing until after collection of the final PK and/or PD sample.
- Use of tobacco products will not be allowed from 6 months before the time of the Screening visit 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	Tepotinib (HCl hydrate)	Itraconazole
Type	Drug	Drug
Dose Formulation	Film-coated tablet	Hard-gelatin capsule
Unit Dose Strength(s)	250 mg	100 mg
Dose Amount	500 mg (2 tablets) with food	200 mg (2 capsules) with food
Frequency	Day 1 and 12 in the morning	Once daily at the same time in the morning (every 24 hours ± 1 hour) from Day 8 to Day 18; on Day 12 itraconazole is administered concomitantly with tepotinib (Section 5.3.1).
Route of Administration	Oral	Oral
Use	Experimental	Experimental
Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP)	IMP: tepotinib	IMP: itraconazole
Sourcing	Sponsor (Merck Healthcare KGaA)	Sponsor (Merck Healthcare KGaA)
Packaging and Labeling	Study intervention will be provided as blisters in screw-cap bottles that are packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines. Details on packaging design and administration of tepotinib will be defined in the IMP Handling Manual.	Study intervention will be sourced as commercial packs and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines. Details on packaging design and administration of itraconazole will be defined in the IMP Handling Manual.

IMP=investigational medicinal product.

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

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

- Upon receipt of the study intervention(s), the Investigator or designee will confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the IMP handling manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.

- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, container numbers, expiry dates, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) will not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be redispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the IMP handling manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Not applicable as this is a nonrandomized study.

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

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

6.3.2 Blinding

Not applicable. This is an open-label study.

6.3.3 Emergency Unblinding

Not applicable. This is an open-label study.

6.4 Study Intervention Compliance

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

6.5 Dose Modification

Doses will not be modified.

6.6 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 tepotinib. The Investigator will use his clinical judgment to manage any overdose, considering the symptoms and any site procedures or standards.

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

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

6.8 Concomitant Therapy

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

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

6.8.1 Rescue Medicine

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

In case of toxicity during itraconazole treatment refer to the itraconazole SmPC and USPI.

6.8.2 Permitted Medicines

The only permitted medications are the following:

- Paracetamol/acetaminophen up to 2 g per day, at the discretion of the Investigator.

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

Medications may be given at the Investigator's discretion if deemed necessary for the participant's immediate wellbeing. Medications may be administered to address adverse reactions or anticipated emergency situations.

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

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).

6.8.4 Other Interventions

Additional restrictions that study participants should adhere to from Day -1 until 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 its 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 (Section 1.3) 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.

If a clinically significant finding is identified (including changes from Baseline in QT interval corrected using QTcF) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection will be documented. Any new clinically relevant finding is reported as an AE.

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 their relationship to study intervention.
  - 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/acetaminophen 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 e.g., Sections 5.1, 5.2, 5.3.1, and 8.
  - Positive for SARS-CoV-2 on admission on Day 11.
- If a participant has failed to attend scheduled study assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.
- If a participant must be withdrawn from the study, the Medical Monitor and clinical study leader for the Sponsor will be informed immediately.
- If there is a medical reason for the withdrawal, appropriate medical care will be provided.

- At the time of study discontinuation, if possible, a discontinuation visit will be conducted, as listed in the Schedule of Assessments (Section 1.3). The Schedule of Assessments specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.
- If the participant revokes consent for the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- A participant has the right at any time to request destruction of any biological samples taken. The Investigator will document this in the site study records and the CRF and inform the Sponsor. The samples will be destroyed.

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 (Section 1.3).
- No protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the 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.
- Demographic data collected at Screening will include, at minimum, age, sex, race (collected only where allowed by local law/regulations), and ethnicity.
- No more than 50 mL of blood may be drawn in a 24-hour period, and no more than 150 mL of blood in a 4-week period.
- Where allowed by local law/regulations, samples collected during this clinical study may be transferred to a biobank and used for future research outside the clinical protocol when additional consent for this purpose is given. Transfer to the biobank will be documented and any testing of coded biobank samples will **not** be reported in the CSR.
- The long-term storage of samples after study completion for future research may be performed with all sample types collected in the study (e.g., PK, CCI CCI or CCI 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, electrocardiograms, and laboratory tests.

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

8.2.1 Physical Examinations

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

8.2.2 Vital Signs

- Blood pressure and participant's position; pulse; respiratory rate; 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.
- Vital signs will be measured in supine position.

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the Schedule of Assessments (Section 1.3) using an ECG machine that automatically measures heart rate, PR, RR, QRS, QT, and QTcB or QTcF. Documentation of the QTcF is mandatory.
- 12-Lead ECGs will be recorded in a supine position following 5 minutes of rest.

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5 at the time points listed in the Schedule of Assessments (Section 1.3). 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 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.

8.2.5 Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

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 CRO-designated study team member, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.
- All AEs and SAEs will be collected from the signing of the ICF until the Safety Follow Up 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

- Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until at least 3 months after the last dose of study intervention.
- 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 partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Adverse pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered and reported as SAEs. A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- The participant /pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant /pregnant female partner and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date for a healthy newborn. In case of a congenital anomaly or other illness of the newborn, follow-up will continue until the illness has resolved or there is a definite outcome of the event.
- Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.3. While the Investigator is not obligated to actively seek this information in former study participants /pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.5 Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.7 Adverse Events of Special Interest

For this study, AESIs include only the following:

- AEs suggestive of drug-induced liver injury including hepatic/liver failure and hepatitis (noninfectious) are considered AESIs.

AESIs will be reported to the Sponsor (or delegate) immediately manner as described in Appendix 4.

8.4 Pharmacokinetics

Collection of Plasma for Pharmacokinetic Analysis

For details on PK sampling timepoints, see the Schedule of Assessments in Section 1.3, and Table 1 and Table 2.

The following PK parameters will be calculated, when appropriate, for tepotinib and [redacted]:

Symbol	Definition
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at tlast, as estimated using the linear regression from λ_z determination. $AUC_{0-\infty} = AUC_{0-tlast} + C_{last\ pred}/\lambda_z$
$AUC_{0-tlast}$	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the time of the last quantifiable concentration (t_{last}), calculated using the mixed log-linear trapezoidal rule (linear up, log down).
AUC_{0-24h}	The AUC from time zero (= dosing time) to timepoint 24 hours. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0-tlast}$ /Dose	The dose normalized AUC from time zero to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Normalized using the actual dose, using the formula $AUC_{0-tlast}$/Dose.
AUC_{0-24h} /Dose	The dose normalized AUC from time zero to timepoint 24 hours. Normalized using the actual dose, using the formula $AUC_{0-24\ t}$/Dose.
C_{max}	Maximum observed concentration.
C_{max} /Dose	The dose normalized maximum concentration. Normalized using the actual dose, and the formula C_{max}/Dose.
T_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)
$t_{1/2}$	Apparent terminal half-life. $T_{1/2} = \ln(2)/\lambda_z$
λ_z	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve.
CL/F (parent drug only)	The apparent total body clearance of study intervention following extravascular administration. $CL/F = Dose_{po}/AUC_{0-\infty}$. Parent drug, only.
V_z/F (parent drug only)	The apparent volume of distribution during the terminal phase following extravascular administration $V_z/F = Dose/(AUC_{0-\infty} \times \lambda_z)$ following single dose. Parent drug, only.
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0-\infty}$)×100.
[redacted]	[redacted]
[redacted]	[redacted]

- Whole blood samples of approximately 2 mL per collection for measurement of plasma concentrations of tepotinib and its CCI CCI will be collected. Collection times are specified in the Schedule of Assessments (Section 1.3) and Table 1. 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 tepotinib and its CCI CCI in plasma will be performed using a validated assay method. Concentrations will be used to evaluate the PK of tepotinib and its metabolites.
- Remaining samples collected for analyses of tepotinib concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- 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.

The exact date and time of sample collection and study intervention (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 tepotinib PK times that will not be considered a protocol violation are listed below (Table 2).

Table 2 PK Sampling Time Windows

Procedure	Time Point (Relative Time)	Window Allowance
Pharmacokinetics	Predose	- 60 min
	1 to 12 hours postdose	- 5 / + 5 min
	> 12 to 24 hours postdose	- 30 / + 30 min
	> 24 to 72 hours postdose	- 60 / + 60 min
	> 72 to 168 hours postdose	- 180 / + 180 min

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

Collection of Feces for Pharmacokinetic Analysis

In both in-house periods of the study, all feces after administration of tepotinib until discharge from the CRU (i.e., from Day 1 to Day 4, and from Day 12 to Day 15) will be collected for exploratory tepotinib pharmacokinetic analysis.

- To ensure defecation, participants will receive a mild laxative on the evenings of Day 3 and Day 14.
- The exact date and time of sample collection and study intervention (24-hour clock time) must be recorded in the eCRF.

- The cumulative amount (% of dose) of tepotinib excreted in the feces during this time will be quantified.
- Details on processes for collection and handling of these samples are in the Laboratory Manual.

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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] objectives and endpoints can be found in Section 3.

9.2 Sample Size Determination

A maximum of 18 participants will be assigned to study interventions such that at least 14 evaluable participants complete the study.

Although no hypothesis tests will be performed, the sample size of the study should be sufficient to estimate the difference between dosing conditions with adequate precision.

Available information on intraparticipant variability of tepotinib PK parameters following administration of TF2 and/or TF3 under different dosing conditions, observed in studies MS200095_0044, MS200095_0038 and MS200095_0039 are presented in Table 3. The intraparticipant CV is approximately between 10.4% and 18.0% for $AUC_{0-\infty}$ and $AUC_{0-tlast}$, and for C_{max} between 12.7% and 16.4%.

Table 3 Overview of Observed Intraparticipant Variability of Tepotinib Pharmacokinetic Parameters

Study	Comparison	N	Mixed Intraparticipant CV		
			$AUC_{0-tlast}$	$AUC_{0-\infty}$	C_{max}
MS200095_0044 Part A	TF3 versus TF2 (fasted)	38	15.77%	15.83%	13.94%
MS200095_0044 Part B	TF2 (fed versus fasted)	14	17.96%	17.95%	12.67%
MS200095_0044 Part C	TF3 (fed versus fasted)	12	14.93%	15.10%	16.79%
MS200095_0038	5 × 100 mg TF3 versus 2 × 250 mg TF3 (fasted)	18	15.26%	15.29%	16.37%
MS200095_0039	Tepotinib Fed + Omeprazole versus Tepotinib Fed	12	10.41%	10.93%	16.22%

CV=Coefficient of Variation, N=number of participants.

Thus, assuming an intraparticipant CV (%) of 10%, 15%, and 20% for AUC and C_{max} of tepotinib, the precision for the estimated ratio (coadministration of tepotinib and itraconazole versus tepotinib alone) to be achieved with a given number of evaluable participants is summarized in Table 4. Assuming a CV of 20%, if 14 evaluable participants are included in the study and the observed ratio is exactly 1.0, then the 90% CI for the ratio will be contained with 80% probability in 0.805 to 1.242. If the observed ratio is exactly 2.0, then the corresponding limits are 1.611 to 2.484.

This precision is considered adequate to characterize the effect of multiple doses of itraconazole on the PK of tepotinib. A further increase in sample size does not substantially improve the precision. On the other hand, even with a slightly smaller number of completed participants, the precision will be markedly decreased.

Table 4 Width of the 90% CI for the Ratio of Pharmacokinetic Parameters, for Different Geometric Mean Ratios, Sample Sizes, and Within-Participant CVs

		90% Confidence Interval with 80% Tolerance Probability		
Observed Treatment Ratio	N (total)	CV = 10%	CV = 15%	CV = 20%
1.000	10	0.871-1.148	0.814-1.229	0.761-1.315
	12	0.886-1.129	0.834-1.198	0.786-1.272
	14	0.897-1.115	0.849-1.177	0.805-1.242
	16	0.905-1.105	0.861-1.161	0.820-1.220
	18	0.911-1.097	0.870-1.149	0.832-1.202
2.000	10	1.743-2.295	1.628-2.457	1.521-2.629
	12	1.772-2.257	1.669-2.397	1.573-2.543
	14	1.793-2.231	1.699-2.354	1.611-2.484
	16	1.810-2.210	1.722-2.323	1.640-2.439
	18	1.823-2.195	1.741-2.298	1.663-2.405
5.000	10	4.357-5.738	4.069-6.144	3.804-6.573
	12	4.430-5.643	4.172-5.992	3.932-6.358
	14	4.483-5.576	4.247-5.886	4.026-6.209
	16	4.524-5.526	4.305-5.807	4.099-6.098
	18	4.557-5.486	4.352-5.745	4.158-6.012

Calculation performed in R version 3.5.1.
CV=coefficient of variation.

9.3 Analyses Sets

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

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's enrollment and study intervention status in the study.
Safety (SAF)	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
Pharmacokinetic (PK)	The PK Analysis Set is a subset of the SAF, and the PK population will include all participants: Who have completed the study without any relevant protocol deviations and factors likely to affect the comparability of PK results. With adequate study intervention compliance. With evaluable PK data, i.e., nonmissing values for primary endpoints. If participants received prohibited concomitant therapy or medicines, as specified in Section 6.8.3, they will be excluded from the PK population. All PK analyses will be based on this analysis set.

9.4 Statistical Analyses

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

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

Medical history and AE terms will be coded with the latest version of 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 first and third quartile [Q1 and Q3], Min, and Max) and categorical data will be summarized by means of frequency tables (i.e., count and percentages), if not stated otherwise.

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

9.4.1 Efficacy Analyses

Not applicable.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis 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 Other Analyses

Analysis of Primary Endpoints

The effect of coadministration of itraconazole on tepotinib 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}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$ based on the PK analysis set. Treatment differences on the log scale of tepotinib with itraconazole versus tepotinib alone (Day 12 versus Day 1) will be estimated for the C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$ together with their 90% CIs. Point estimates and CIs will be back transformed to the original scale for presentation.

The analysis will be repeated with both SUBJECT and TREATMENT as fixed effects.

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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.

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11 Appendices

Appendix 1 Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BCS	Biopharmaceutical classification system
BMI	Body mass index
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Clinical research organization
CRU	Clinical research unit
CSR	Clinical Study Report
CTFG	Clinical Trials Facilitation and Coordination Group
CV	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DSUR	Development safety update report
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EudraCT	European Clinical Trials Database
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HGF	Hepatocyte growth factor
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone replacement therapy

IAP	Integrated analysis plan
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
LFT	Liver function test
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal epithelial transition factor
Min	Minimum
MR	Metabolic ratio
NSCLC	Non-small cell lung cancer
PCR	Polymerase chain reaction
CC	[redacted]
P-gp	P-glycoprotein
PK	Pharmacokinetic
QTcB	Corrected QT internal by Bazett's formula
QTcF	Corrected QT interval by Fridericia' formula
QTL	Quality tolerance limits
SAE	Serious adverse event
SAF	Safety
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SmPC	Summary of product characteristics
SoA	Schedule of assessments
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event

TF2/TF3	Tablet formulation 2/Tablet formulation 3
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
USPI	United States prescribing information
WHO	World Health Organization
WOCBP	Woman of child-bearing potential

Appendix 2 Study Governance

Financial Disclosure

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

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; 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 reconsented to the most current, approved version.

Data Protection

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

Study Administrative

- The Principal Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Principal Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.
- The study will be conducted at a single center, the Clinical Pharmacology Unit of Nuvisan GmbH, Neu-Ulm, Germany. Nuvisan GmbH will be responsible for the following activities:

  - Clinical conduct and laboratory services
  - Data management
  - Statistical programming and analysis
  - PK analysis
  - Medical writing
  - Independent monitoring
  - Medical monitoring
  - Project management
  - Regulatory services
- Clinical trial supplies will be provided by the Sponsor.
- Details of structures and associated procedures will be defined in a separate 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 approval before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

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

information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

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

Clinical Study Insurance and Compensation to Participants

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

Clinical Study Report

- After study completion, the Sponsor will write a clinical study report in consultation with the Principal Investigator and other relevant study-appointed experts of the Sponsor and 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 clinical study report 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 requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

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

Study and Site Start and Closure

The study start date is when the first participant signs the 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

Definitions:

Women of Child-Bearing 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 (> 40 mIU/mL) is required.
- A female on HRT and whose menopausal status are in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization:

For this study, permanent sterilization includes:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

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

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

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

Highly Effective Methods That Are User Dependent

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

Notes:

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

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

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

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

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

AE Definition

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline and are judged to be more severe than expected for the participant's condition are considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease, but may be leading to study intervention discontinuation). • Exacerbation of a chronic or intermittent 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 1 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 1 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 postmortem 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	Bilirubin
	Creatinine	Sodium	Alanine aminotransferase	Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
	Uric acid	Chloride	y-Glutamyl transferase	Cholesterol
		Inorganic phosphate	Lactate dehydrogenase	Triglycerides
		Magnesium	Creatinine phosphokinase	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). Note: In case of a positive result for hemoglobin, leukocyte esterase, protein or nitrite, a urinary cell count will be performed			
Coagulation	• INR • aPTT			
Other Screening Tests	• FSH • Serum hCG pregnancy test (as needed for a WOCBP) at all timepoints listed in the Schedule of Assessments (Section 1.3) • 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 / Day 11) • Serology (human immunodeficiency virus I and II antibodies, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody) • SARS-CoV-2 rapid antigen test at Screening, PCR test at admission on Day -1 • Thyroid stimulating hormone • Cotinine test (Screening and Day -1 / Day 11) • Alcohol breath test (Screening and Day -1 / Day 11) • Estimated Glomerular Filtration Rate based on Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (2009) • All study-required laboratory assessments will be performed by a central laboratory (Nuvisan's clinical laboratory)			

aPTT=activated partial thromboplastin time, FSH=follicle stimulating hormone, hCG=human chorionic gonadotropin, INR=International Normalized Ratio, PCR=polymerase chain reaction, SARS-CoV-2=severe acute respiratory syndrome coronavirus 2, WOCBP=woman of child-bearing potential.

CCI [redacted]

[redacted]

Appendix 7 Sponsor Signature Page

Study Title:	Phase I, Open-label, Single-sequence, Cross-over Study of the Effect of Multiple Doses of Itraconazole on Single-dose Tepotinib Pharmacokinetics in Healthy Participants
Regulatory Agency Identifying Numbers:	EudraCT: 2021-003513-19
Clinical Study Protocol Version:	15 September 2021 / V1.0

I approve the design of the clinical study:

_____ _____

Signature Date of Signature

Name, academic degree:	CCI [redacted]
Function/Title:	CCI [redacted]
Institution:	Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany
Address:	Frankfurter Str. 250 64293 Darmstadt, Germany
General Merck Phone Number:	CCI [redacted]
General Merck Fax Number:	Not Applicable

Appendix 8 Principal Investigator Signature Page

Study Title:	Phase I, Open-label, Single-sequence, Cross-over Study of the Effect of Multiple Doses of Itraconazole on Single-dose Tepotinib Pharmacokinetics in Healthy Participants
Regulatory Agency Identifying Numbers:	EudraCT: 2021-003513-19
Clinical Study Protocol Version:	15 September 2021 / V1.0

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

_____ _____

Signature Date of Signature

Name, academic degree:
Function/Title:
Institution:
Address:

Telephone number:
Fax number:
E-mail address:

CCI [redacted]