Clinical Trial Protocol

Clinical Trial Protocol Number	MS200095-0030
Title	Phase 1, Open-label, Single Sequence, Two-Period Crossover Trial to Evaluate the Effect of Tepotinib on Cytochrome P450 (CYP) 3A by Investigating the Pharmacokinetics of the CYP3A Substrate Midazolam in Healthy Subjects
Phase	1
IND Number	Not applicable
EudraCT Number	2017-005055-92
Principal Investigator	PI , PI PI , Germany
Sponsor	Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany Medical Responsible: PI , PI Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany Phone: PI Mobile: PI
Clinical Trial Protocol Version	12 June 2018 / Version 1.0
Replaces Version	Not applicable

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List of Abbreviations

Abbreviation	Definition of Terms
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
Alu	Aluminum
anti-HCV	Hepatitis C virus antibody
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero (= dosing time) extrapolated to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification
AUCextra	The AUC from time t_{last} extrapolated to infinity
AUCextra%	AUCextra / AUC0-∞ in percent
beta-HCG	Beta-human chorionic gonadotropine
BMI	Body mass index
CI	Confidence interval
C_{max}	Maximum plasma concentration observed
c-Met	Mesenchymal-epithelial transition factor
CRO	Contract research organization
CTCAE	Common Terminology Criteria for AEs
CTFG	Clinical Trial Facilitation Group
CV	Coefficient of variation

Abbreviation	Definition of Terms
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GeoCV%	Geometric coefficient of variation in percent
GeoMean	Geometric mean
h	Hour(s)
HBsAg	Hepatitis B surface antigen
HCC	Hepatocellular carcinoma
HGF	Hepatocyte growth factor
HIV1/HIV2	Human immunodeficiency virus 1 and 2
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product

Abbreviation	Definition of Terms
LLOQ	Lower limit of quantification
Min	Minute(s)
MR	Metabolic ratio
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
PD	Pharmacodynamics
PGx	Pharmacogenetics
PK	Pharmacokinetics
QTcF	Corrected QT interval per Fridericia's formula
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard operational procedures
SUSAR	Suspected unexpected serious adverse reactions
T/R ratio	Test/Reference ratios
$t_{1/2}$	Terminal half-life
TEAE	Treatment emergent adverse event
TF2	Tablet formulation 2
t_{last}	The last sampling time at which the concentration is at or above the lower limit of quantification
t_{max}	Time to reach the maximum plasma concentration

Abbreviation	Definition of Terms
TPR	Translocated promoter region
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal range
λ_z	Terminal rate constant

1 Synopsis

Clinical Trial Protocol Number	MS200095-0030
Title	Phase 1, Open-label, Single Sequence, Two-Period Crossover Trial to Evaluate the Effect of Tepotinib on Cytochrome P450 (CYP) 3A by Investigating the Pharmacokinetics of the CYP3A Substrate Midazolam in Healthy Subjects
Trial Phase	1
IND Number	Not applicable
FDA covered Trial	No
EudraCT Number	2017-005055-92
Principal Investigator	PI PI , Germany
Sponsor	Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany
Trial Center	PI , Germany
Planned Trial Period (first subject in - last subject out)	Q3-Q4 2018
Trial Registry	EU Clinical Trials Register, ClinicalTrials.gov

Primary Objective:

- To investigate the effect of multiple doses of tepotinib on AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of the CYP3A substrate midazolam in healthy subjects.

Secondary Objectives:

- To further investigate effects of multiple doses of tepotinib on the PK of midazolam
- To investigate the effect of multiple doses of tepotinib on the PK of the main midazolam metabolite 1-hydroxymidazolam
- To assess the safety and tolerability of tepotinib alone and upon co-administration of midazolam.

Exploratory Objective:

- To explore the effect of pharmacogenetics (PGx) and variations of associated genes on the PK profile of tepotinib and/or midazolam.

Methodology: Phase 1, open-label, 2-period, crossover trial.

The trial will be divided into 2 periods. Period 1 will evaluate the PK of midazolam and 1-hydroxymidazolam after single dose administration of midazolam over a sampling period of 48 h post-dose. In Period 2, tepotinib will be administered alone for 10 days. On Day 11 of Period 2, midazolam and tepotinib will be co-administered and the PK of midazolam and 1-hydroxymidazolam will be evaluated again over 48 h post-dose. Dosing of tepotinib will be performed after completion of breakfast. Midazolam will be administered 4 h after tepotinib administration, when tepotinib systemic exposure is building up, and a quasi-fasted condition is reached to minimize for food effects on midazolam absorption. Day 1 of Period 2 will be 2 days after midazolam administration in Period 1.

The subjects will be admitted to the trial site on Trial Day -1. They will be resident at the trial site under medical supervision from Day -1 of Period 1 until Day 13 of Period 2 (Trial Day 15). The End of Trial Visit is planned 7 days (± 1 day) after the last drug administration in Period 2 (Trial Day 20 ± 1).

After the first 6 subjects completed administration up to Day 11 of Period 2, safety and PK data will be reviewed by the responsible functional representatives.

Planned number of subjects: Overall, 12 healthy subjects are planned to be included.

Primary endpoint:

- AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of midazolam (at Day 1 of Period 1 and Day 11 of Period 2 from time zero to 48 h post-dose).

Secondary endpoints:

- t_{max} and $t_{1/2}$ of midazolam
- AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max} and $t_{1/2}$ of 1-hydroxymidazolam; metabolic ratio (MR)
- Occurrence of treatment emergent adverse events (TEAEs; incidence, frequency, intensity and causality), occurrence of changes in clinical laboratory assessments, 12-lead electrocardiograms (ECGs) and vital signs in subjects receiving tepotinib alone and together with midazolam assessed from Day 1 of Period 2 until the End of Trial Visit.

Exploratory endpoint:

- Genetic variants and mutations in genes that potentially influence PK of tepotinib and/or midazolam.

Pharmacokinetics:

Blood samples for the determination of plasma concentrations of midazolam and 1-hydroxymidazolam will be taken on Day 1 of Period 1 and Day 11 of Period 2 from time pre-dose to 48 h post midazolam dosing. Blood samples for determination of tepotinib and its metabolites trough levels will be taken before tepotinib administration on Days 9, 10 and 11. PK parameters will be calculated using non-compartmental analysis.

Other assessments: Not applicable.

Diagnosis and key inclusion and exclusion criteria: Healthy males and females (of non-childbearing potential) between 18 and 44 years of age (inclusive) with total body weight between 50 to 100 kg (inclusive) and body mass index (BMI) between 18.5 and 29.9 kg/m^2 (inclusive) at the time of the Screening examination.
Investigational Medicinal Product: dose/mode of administration/ dosing schedule: Tepotinib film-coated tablet (Tablet Formulation 2, TF2) containing 500 mg of drug substance, oral administration. Midazolam: commercially available midazolam, ie Dormicum® 7.5 mg film-coated tablets. Treatment A (Period 1): On Day 1 of Period 1, a single oral dose of 7.5 mg midazolam as tablet will be administered in a quasi-fasted state 4 h after completion of a standardized breakfast together with 240 mL water. Treatment B (Period 2): On Days 1 to 10 of Period 2, 500 mg tepotinib will be administered together with 240 mL of water after a continental breakfast (about 30 min after start of breakfast). Some flexibility of the continental breakfast is allowed, but the breakfast should be not high caloric. On Day 11 of Period 2, the subjects will receive a standardized breakfast, which must be consumed completely within 25 min. The standardized breakfast must match with the breakfast on Period 1, Day 1, with regard to composition and content. 30 min after start of the breakfast, 500 mg tepotinib will be administered together with 240 mL of water. A single oral dose of 7.5 mg midazolam will be administered 4 h after tepotinib administration together with 240 mL water.
Reference therapy: dose/mode of administration/dosing schedule: Not applicable.
Planned trial and treatment duration per subject: About 6 weeks from Screening to End of Trial Visit, treatment on Day 1 of Period 1 (Treatment A) and on Days 1-11 of Period 2 (Treatment B).

Statistical methods:

A general linear model with a fixed effect for TREATMENT and a random effect for SUBJECT will be applied to log-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of midazolam based on the PK analysis set. Treatment differences on the log scale of midazolam with tepotinib vs midazolam alone will be estimated for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ together with their 90% confidence intervals (CIs). Point estimates and CIs will be back-transformed to the original scale. For the statistical analysis of AUC_{0-t} of midazolam data, a-priori ordered hypotheses will be tested The confidence intervals for AUC will be compared to acceptance ranges for moderate effects [0.2 ; 5.0] (to be tested first) and mild effects [0.5 ; 2.0].

Individual estimates of relative bioavailability and MR of midazolam will be calculated for each subject and summarized. Summary statistics will be provided for all parameters.

Table 1 Schedule of Assessments - Period 1 (Administration of Midazolam Alone)

Assessment / Activity	**Screening**	**Period 1**		
Day of Period 1	**Day -21 to -2**	**-1**	**1**	**2**
Trial Day		**-1**	**1**	**2**
Written informed consent [a]				
Hospitalization		X ←----------→ X		
Ambulatory visit	X			
In-/exclusion criteria	X	X		
Demographic data (incl. height, weight, BMI)	X			
Medical history	X			
Physical examination	X	X		
Vital signs (blood pressure, pulse rate, body temperature)	X	X	X [b]	X [b]
Pulse oximetry			X [c]	
12-lead ECG	X	X	X [b]	X [b]
Clinical laboratory (hematology, biochemistry, urinalysis)	X	X		
Serology (HIV/hepatitis)	X			
Pregnancy test	X [d]	X [d]		
Drugs of abuse, Alcohol breath test	X	X		
Administration of midazolam			X	
PK blood sampling midazolam and 1-hydroxymidazolam			X [e]	X [e]
PGx blood sampling (mandatory)			X [f]	
Adverse event monitoring	X ←----------→ X [g]			
Prior and concomitant medication	X ←----------→ X [g]			

BMI = Body Mass Index; ECG = electrocardiogram, FSH: Follicle-stimulating hormone, HIV = human immunodeficiency virus, PGx = pharmacogenetics, PK = pharmacokinetics.

a Written informed consent must be obtained prior to any Screening activities

b Vital signs and ECG will be measured after at least 5 min rest at pre-dose (within 60 min prior to dosing) as well as 4, 8, 24 and 48 h post-dose (48 h post-dose midazolam administration = pre-dose tepotinib administration in Period 2)

c Pulse oximetry will be performed from about 30 min before until 6 h after midazolam administration

d Women of non-childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Day -1 of Period 1; **Females are considered postmenopausal if they have age-related amenorrhea ≥ 12 consecutive months and increased FSH > 40 mIU/mL), or if they have undergone hysterectomy, bilateral oophorectomy or bilateral salpingectomy**

e PK blood samples for determination of midazolam and 1-hydroxymidazolam will be collected at pre-dose (within 60 min prior to administration of midazolam) and 15, 30, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose after administration of midazolam (48 h post-dose = pre-dose tepotinib administration in Period 2)

f PGx blood samples of 2 x 2 mL to be drawn at pre-dose on Day 1 of Period 1

g Adverse events and concomitant medication will be assessed from signing of the informed consent form (ICF) throughout the whole trial until the End of Trial Visit.

Table 2 Schedule of Assessments - Period 2 (Administration of Tepotinib and Midazolam)

Assessment / Activity	**Period 2**					**End of Trial Visit**
Day of Period 2	**1**	**2 - 10**	**11**	**12**	**13**	**Day 18 (± 1)**
Trial Day	**3**	**4 - 12**	**13**	**14**	**15**	**Day 20 (± 1)**
Hospitalization	X	X	X	X	X	
Ambulatory visit						X
Physical examination					X	X
Vital signs (blood pressure, pulse rate, body temperature)	X [a]	X [a]	X [b]	X [b]	X [b]	X
Pulse oximetry			X [c]			
12-lead ECG	X [d]	X [d]	X [d]	X [d]	X [d]	X
Clinical laboratory (hematology, biochemistry, urinalysis)	X [e]	X [e]	X [e]	X [e]		X
Pregnancy test (serum)						X
Administration of tepotinib	X	X	X			
Administration of midazolam			X			
PK blood sampling for tepotinib and its metabolites		X [f]	X [f]			
PK blood sampling for midazolam and 1-hydroxymidazolam	X [g]		X [h]	X [h]	X [h]	
Adverse event monitoring	X [i]	X [i]	X [i]	X [i]	X [i]	X
Concomitant medication	X [i]	X [i]	X [i]	X [i]	X [i]	X

ECG = electrocardiogram, PK = pharmacokinetics

a Vital signs (blood pressure and pulse rate) will be measured after at least 5 min rest before each (within 60 min prior to dosing) and 6 h after each tepotinib administration at Days 1, 2, 5, 8 and 10 of Period 2

b Vital signs will be measured after at least 5 min rest before (within 60 min prior to dosing) as well as 4, 8, 24 and 48 h after midazolam administration at Day 11 of Period 2

c Pulse oximetry will be performed from about 30 min before until 6 h after midazolam administration

d 12-lead ECGs will be recorded and printed out after at least 5 min rest before each time point
On Days 1, 2, 5, 8 and 10 of Period 2: within 60 min prior to dosing and 6 h after each tepotinib administration;
On Day 11 of Period 2: within 60 min prior to dosing, as well as 4, 8, 24, and 48 h after midazolam administration

e Laboratory assessments will be performed prior to tepotinib administration on Days 1, 2, 5, 8 and 11 of Period 2, on Day 12 of Period 2 and at the End of Trial visit (on Day 2 of Period 2 biochemistry only)

f PK blood samples for determination of trough levels of tepotinib and its metabolites will be collected pre-dose (within 60 min prior to tepotinib administration) on Days 9, 10 and 11

g 48 h PK blood sampling for determination of midazolam and 1-hydroxymidazolam of Period 1

h PK blood samples for determination of midazolam and 1-hydroxymidazolam will be collected at pre-dose (within 60 min prior to administration of midazolam) and 15, 30, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose after administration of midazolam

i Adverse events and concomitant medication will be assessed from signing of the ICF throughout the whole trial until the End of Trial Visit.

2 Sponsor, Investigators and Trial Administrative Structure

This clinical trial will be sponsored by:

Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany.

The trial will be conducted at one site in Germany.

The Principal Investigator (PI , PI) will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report consistent with the International Council for Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP) [14].

Signature pages for the Protocol Leads and the Principal Investigator as well as a list of Sponsor responsible persons for the trial are in Appendix I.

Nuvisan GmbH, Wegenerstrasse 13, 89231 Neu-Ulm, Germany, a contract research organization (CRO), will conduct the clinical part of the trial including trial set-up, coordination, safety and analytical lab, monitoring, data capture, data management, statistical analysis, and clinical trial reporting. Nuvisan GmbH will also submit the necessary applications to the applicable Independent Ethics Committee (IEC) and regulatory bodies on behalf of and in close alignment with the Sponsor.

Laboratory sample processing, handling, and storage instructions will be presented in a separate Lab Manual which will be prepared by Nuvisan GmbH in cooperation with the Sponsor. Monitoring and data management procedures will be defined in separate Monitoring and Data Management Plans which will be prepared by Nuvisan GmbH.

The Sponsor will provide the Investigational Medicinal Products (IMPs) tepotinib and midazolam. Packaging, labeling and distribution of all IMPs to the trial site will be conducted by a designated contract manufacturing organization (Nuvisan GmbH, Wegenerstrasse 13, 89231 Neu-Ulm, Germany). The Sponsor will supervise all outsourced activities.

3 Background Information

The mesenchymal-epithelial transition factor (c-Met), along with its ligand, the hepatocyte growth factor (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/c-Met axis is considered as a promising strategy to inhibit primary tumor growth and metastasis.

In primary pharmacodynamic (Pd) studies, tepotinib (MSC2156119J) potently inhibited c-Met kinase activity in a dose-dependent manner. This inhibitory effect was confirmed both in tumor cells expressing full-length c-Met upon stimulation with HGF, and in tumor cells in which c-Met was activated in a ligand independent manner, ie in cells harboring c-Met gene amplification or expressing the oncogenic fusion protein translocated promoter region (TPR) Met.

Until 30 September 2017, 452 subjects have been exposed to tepotinib. 60 subjects of these have been exposed to a tepotinib + gefitinib combination. Five studies have been completed; 3 of these were conducted as single dose studies in healthy subjects (EMR200095-002, EMR200095-007, and MS200095-0012; n = 79 subjects), and 2 as multiple dose studies in subjects with different solid tumors (EMR200095-001 and EMR200095-003; n = 161). In addition, 4 studies in subjects with hepatocellular carcinoma (HCC; EMR200095-004, EMR200095-005) or epidermal growth factor receptor (EGFR) mutated or c-Met mutated non-small cell lung cancer (NSCLC; EMR200095-006, and MS200095-0022) are ongoing. In the ongoing studies, subjects with HCC received tepotinib as multidose monotherapy, and subjects with NSCLC received either multidose tepotinib monotherapy or a multidose combination with gefitinib in Phase 1 or Phase 1b/2 studies. Doses of tepotinib of up to 1400 mg daily in subjects with solid tumors (EMR200095-001) and up to 1000 mg daily in subjects with HCC (EMR200095-004) have been explored. The recommended Phase 2 dose (RP2D) is 500 mg tepotinib once daily.

Single oral doses of 500 mg tepotinib have been administered in previous studies with 36 healthy subjects in total (EMR200095-007: 12 subjects received 1 single dose of 500 mg, MS200095-0012: 24 subjects received 2 single doses of 500 mg tepotinib in crossover) and was found safe and well tolerated. Refer to the Investigator's Brochure for further information about the nonclinical and clinical programs and the implemented Guidance for the Investigator.

During the development of tepotinib, in all 3 studies performed in healthy subjects (n = 79), the subjects have well tolerated single doses of tepotinib at different dose levels up to 500 mg. All treatment emergent adverse events (TEAEs) were mild to moderate, except one Grade 3 asymptomatic lipase elevation in 1 subject. Treatment emergent adverse events did not show a pattern across all 3 trials. No serious adverse events (SAEs) were reported and no subject died. No clinically significant findings regarding laboratory parameters, vital signs and electrocardiogram (ECG) including corrected QT interval per Fridericia's formula (QTcF) values were noted.

Elevations in serum lipase and amylase are considered as the only identified risks for subjects administered tepotinib so far. These elevations were observed in 5 of 79 (6.3%) healthy subjects exposed to tepotinib and were mild to moderate in severity (exception: one Grade 3 lipase elevation), transient and without apparent dose dependency. All increases of serum amylase/lipase were asymptomatic and not associated with pancreatitis.

Following the nonclinical observation that tepotinib and its metabolite MSC2571109A were identified as inducers of cytochrome P450 (CYP) 3A4, and that MSC2571109A was identified as a mechanism-based inhibitor of CYP3A4/5, the need to investigate tepotinib clinically for any potential to cause CYP3A-mediated drug-drug interaction (DDI) was triggered. In this DDI trial multiple doses of the RP2D of 500 mg tepotinib will be administered to healthy subjects to achieve steady-state levels and robustly evaluate its potential as perpetrator toward the CYP3A substrate midazolam.

Short term multi-day administration in this trial of 500 mg tepotinib to healthy subjects is expected to be safe and well tolerated, considering the previous clinical experience with administration of multiple tepotinib doses up to 1400 mg in patients and of single doses of 500 mg in healthy volunteers, the preclinical safety pharmacology and toxicity data, in

conjunction with the predicted exposures at steady state after multiple dosing of 500 mg/day in healthy subjects, and the absence of genotoxicity.

Since loss of c-Met induces teratogenic effects in c-Met knockout mice, and since a pilot embryo-fetal development trial in rabbits revealed maternotoxic effects and a dose-dependent increased number of skeletal malformations (teratogenicity), stringent criteria are applied to ensure exclusion of women of childbearing potential in this trial. Only healthy women that are known to be postmenopausal or surgically sterile (ie due to hysterectomy and bilateral oophorectomy, or bilateral salpingectomy) will be enrolled in this trial (for details see Section 5, Investigational Plan). Male subjects will be required to take precautions with regards to female partners.

Close safety monitoring will be implemented. Subjects will be admitted to the trial site and remain resident there from Day -1 to Day 2 of Period 1 and from Day 1 to Day 13 of Period 2, to allow continuous safety monitoring of the clinical laboratory parameters, ECG vital signs and pharmacokinetic (PK) sampling. After the first six subjects have completed their treatment up to Day 11 of Period 2, safety and PK data will be reviewed by the responsible functional representatives. In addition, frequent monitoring of subjects is ensured by choosing a CRO experienced in the conduct of clinical pharmacology trials.

It is recognized that healthy subjects will not benefit by participating in this trial.

For PK of tepotinib refer to Investigator's Brochure.

Midazolam

Midazolam is a short-acting sedative-hypnotic benzodiazepine, and is metabolized in the liver and gut wall by CYP3A4 and CYP3A5 [1, 2] to form the major active metabolite 1-hydoxymidazolam, which is further glucuronidated and mainly excreted via the kidneys [3]. Midazolam is rapidly absorbed, reaching maximum plasma concentration after about 1 to 2 hours (h) (time to reach the maximum plasma concentration [t_{max}]) and eliminated with a half-life of approx. 2.5 (1.5 to 5) h. T_{max} is delayed after non-fasting administration. The terminal half-life ($t_{1/2}$) of the active metabolite is 8 to 10 h [4]. Its anxiolytic, muscle-relaxant, sedative and sleep-inducing effects are mediated via enhancing the effect of the neurotransmitter gamma-aminobutyric acid (GABA) on the GABAA receptors. It is prescribed as a sleep-inducing agent for adults and children in situations requiring sedation or anesthesia. It also exerts anticonvulsant effects and is indicated as a treatment of prolonged, acute, convulsive seizures in pediatric patients with epilepsy. The sedative effect would last about 7 to 8 h, paralleling the fast decline phase. It is available in both oral and intravenous formulations. The recommended clinical oral dose for sedation in adults is ranging from 7.5 to 15 mg.

There is extensive clinical experience of the use of midazolam [5] and full information about the potential side effects of midazolam treatment are described in the currently approved Summary of Product Characteristics (SmPC) [6]. There are a number of contraindications and precautions within the prescribing information (eg contraindication in patients with severe respiratory failure or acute respiratory depression, or liver insufficiency, use with caution in patients with impaired respiratory function and other patients at higher risk of alteration to vital functions). Respiratory

depression and severe cardiorespiratory adverse events (AEs) have been reported, including respiratory depression, apnea, respiratory arrest and cardiac arrest. Such life-threatening incidents are more likely to occur when a high dose is administered or when an intravenous injection is given rapidly. Midazolam can also cause anterograde amnesia and paradoxical reactions, and long-term use can also lead to tolerance, dependence and withdrawal syndromes. There is also the potential for clinically important DDIs between midazolam and a number of other medications. Most of these interactions are the result of reduction of midazolam metabolism by inhibitors of CYP3A leading to elevated midazolam exposure. If the trial compound inhibits CYP3A, the risk for the listed side effects of midazolam could be increased.

Antidote

Midazolam may cause somnolence, confusion, lethargy, muscle relaxation and paradoxical excitation. Treatment, if needed, of overdosing or overreaction of midazolam will be performed as per SmPC, ie monitoring of vital signs, symptomatic treatment of cardiorespiratory or central nervous adverse events; in case of severe central nervous depression, Flumazenil, a specific benzodiazepine-receptor antagonist, is an antidote available at the site for midazolam.

3.1 Trial Rationale

This trial will generate human data on the potential of DDI of tepotinib as potential perpetrator toward CYP3A on the PK of the CYP3A probe substrate midazolam at the RP2D of 500 mg. As the intended target population, patients suffering from malignancies such as HCC and NSCLC, often receives multiple concomitant drugs, including drugs that are metabolized by CYP3A4, characterization of the DDI perpetrator potential toward CYP3A4 is clinically relevant.

In vitro, tepotinib caused increases in CYP3A4 mRNA levels of 7-fold in one out of three hepatocyte preparations, and its major metabolite MSC2571109A induced 7- and 21-fold increases in two out of three hepatocyte preparations. Mechanistic static modeling for tepotinib and its metabolite MSC2571109A for CYP3A induction based on maximal exposure observed in Trial EMR 200095-001 resulted in an R_{AUC} value of 0.25 for tepotinib and 0.07 for MSC2571109A, ie tepotinib is currently meeting the Food and Drug Administration (FDA) definition of a potential inducer. This meets the criteria given in the FDA guideline for the conduct of a clinical DDI trial using a sensitive index substrate.

In addition, the tepotinib metabolite, MSC2571109A was found to be a mechanism-based inhibitor of CYP3A4/5 enzymes based on increased percent of inhibition observed at the highest tested concentration of 15 µM (Trial XT155037) after preincubation in vitro in human liver microsomes. However, due to limited solubility, K_i and K_{inact} values could not be determined, preventing the proper evaluation of the risk associated with this mechanism based inhibition of CYP3A4/5.

The trial design is based on the regulatory guidance of the FDA [7, 8] and of the European Medicines Agency (EMA) [9]. Midazolam is well characterized [5, 6], and has been established as a selective and sensitive probe index substrate for CYP3A commonly used in clinical DDI studies and considered as an index substrate in the most recent update of the FDA guidance [7, 8] and EMA guideline [9].

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP [14] and any additional applicable regulatory requirements.

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

4 Trial Objectives

4.1 Primary Objective

- To investigate the effect of multiple doses of tepotinib on AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of the CYP3A substrate midazolam in healthy subjects.

4.2 Secondary Objectives

- To further investigate effects of multiple doses of tepotinib on the PK of midazolam
- To investigate the effect of multiple doses of tepotinib on the PK of the main midazolam metabolite 1-hydroxymidazolam
- To assess the safety and tolerability of tepotinib alone and upon co-administration of midazolam.

4.3 Exploratory Objective

- To explore the effect of pharmacogenetics (PGx) and variations of associated genes on the PK profile of tepotinib and/or midazolam.

5 Investigational Plan

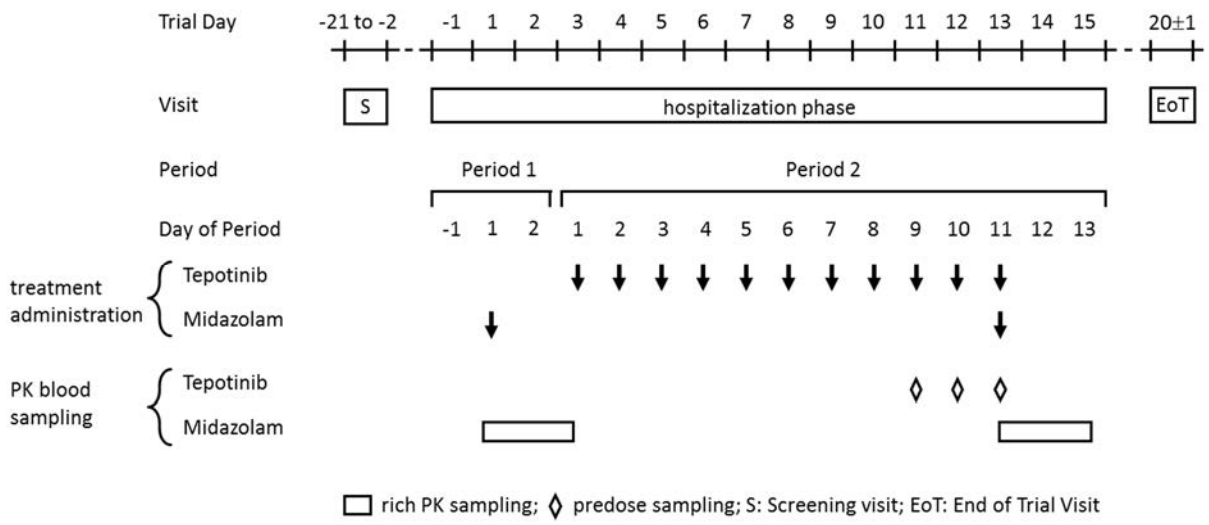
5.1 Overall Trial Design and Plan

This is a Phase 1, open-label, single-sequence, 2-period, crossover trial to investigate the effect of tepotinib on the PK of the CYP3A substrate midazolam determined from concentrations of midazolam and its main metabolite 1-hydroxymidazolam in 12 healthy subjects. A flowchart summarizing the overall trial design is shown in Figure 1.

The trial will be divided into 2 periods: Period 1 will evaluate the PK of midazolam and 1-hydroxymidazolam after single dose administration of midazolam over a sampling period of 48 h post-dose, which covers > 5 times the geometric mean (GeoMean) $t_{1/2}$ of about 2.5 h [6]. In Period 2, tepotinib will be administered alone for 10 days. On Day 1 1 of Period 2, midazolam and tepotinib will be co-administered and the PK of midazolam and 1-hydroxymidazolam will be evaluated again over 48 h post-dose (see Figure 1). Dosing of tepotinib will be performed after completion of breakfast. Midazolam will be administered 4 h after tepotinib administration, when tepotinib systemic exposure is building up, and a quasi-fasted condition is reached to minimize for food effects on midazolam absorption.

Day 1 of Period 2 will be 2 days after midazolam administration in Period 1.

Figure 1 **Treatment Overview**



A Screening period is implemented from Trial Day -21 to Day -2.

The subjects will be admitted to the trial site on Trial Day -1. They will be resident at the trial site under medical supervision from Day -1 of Period 1 until Day 13 of Period 2 (Trial Day 15).

Serial blood and urine samples will be collected for laboratory assessments (hematology, biochemistry, urinalysis), which will be performed at Screening, during the inpatient period and for the End of Trial Visit as explained in detail in Table 1 and Table 2 (see also Figure 1).

Serial blood samples for PK assessment of midazolam and 1-hydroxymidazolam will be collected for 48 h after administration of midazolam in Periods 1 and 2.

The End of Trial Visit is planned 7 days (± 1 day) after the last drug administration in Period 2 (Trial Day 20 ± 1). An Early Termination Visit will be conducted for subjects who withdraw prematurely. The same assessments as for the End of Trial Visit will be conducted at the Early Termination Visit.

A detailed schedule of trial procedures and assessments is provided in Table 1 and Table 2.

After the first 6 subjects completed administration up to Day 11 of Period 2 (including), safety and PK data will be reviewed by the responsible functional representatives before remaining subjects will be treated. The decision will be documented and will be filed in the trial documentation files.

The following stopping rules apply throughout the trial:

- Further dosing will be temporarily stopped after occurrence of an SAE. Dosing will only be restarted if further investigation of the SAE clearly demonstrates another plausible clinical reason for the SAE other than the trial drug

- The trial will be permanently stopped if 4 or more subjects were withdrawn from the trial because they fulfill the individual stopping criteria as defined in Section 5.5.2
- Dosing will be permanently stopped if clinically relevant TEAEs of moderate or severe intensity occur in at least 50% of subjects which are considered related to the trial drug by the Investigator.

Primary endpoint:

- Area under the plasma concentration-time curve from time zero to the last sampling time (AUC_{0-t}), area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$) and maximum plasma concentration (C_{max}) of midazolam (at Day 1 of Period 1 and Day 11 of Period 2 from time zero to 48 h post-dose).

Secondary endpoints:

- t_{max} and $t_{1/2}$ of midazolam
- AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max} and $t_{1/2}$ of 1-hydroxymidazolam; metabolic ratio (MR)
- Occurrence of TEAEs (incidence, frequency, intensity and causality), occurrence of changes in clinical laboratory assessments, 12-lead ECGs and vital signs in subjects receiving tepotinib alone and together with midazolam assessed from Day 1 of Period 2 until the End of Trial Visit.

Exploratory endpoint:

- Genetic variants and mutations in genes that potentially influence PK of tepotinib and/or midazolam

  Note: Pharmacogenetic sample collection is mandatory. The results of the pharmacogenetic analysis, as applicable, will be described in a separate report.

5.2 Discussion of Trial Design

The trial design is based on the regulatory guidelines of the FDA and the EMA (see Section 3.1).

5.2.1 Inclusion of Special Populations

Not applicable.

5.2.2 Scientific Rationale for Trial Design

The trial design and endpoints are typical for a drug interaction trial of this type. The effect of tepotinib on CYP3A will be investigated by measurement of the PK of the sensitive CYP3A substrate midazolam and its main metabolite 1-hydroxymidazolam. Midazolam will be administered as a single dose once alone (Day 1 of Period 1) and once after 11 days of daily tepotinib administration (Day 11 of Period 2). Oral administration of the probe drug midazolam is expected to be the most sensitive test for CYP interaction as reflects effects on both, presystemic and systemic clearance.

The trial will utilize a crossover design to minimize the influence of covariates, with both treatments applied to the same subject. A single-sequence crossover design was chosen as the potential effects of tepotinib on CYP3A4, including mRNA induction and mechanism-based inhibition, may be long-lasting. Therefore, multiple doses of tepotinib will only be administered in the second period of the trial. It is anticipated that a possible period effect is very small and negligible compared to relevant treatment effects.

No carryover of midazolam is expected between the periods due to the wash-out time of at least 12 days between midazolam administrations. In addition, the midazolam plasma concentrations are expected to be below the quantification limit at the start of the first tepotinib administration in Period 2 (considering an apparent elimination $t_{1/2}$ of about 2.5 h for midazolam and 8 to 10 h for 1-hydroxymidazolam in healthy adult subjects [4, 6]).

Tepotinib will be administered for 11 days. Considering its apparent half-life of 30 h, exposure to tepotinib is expected to be at steady state on Day 11 of Period 2. The apparent half-life of the metabolite MSC2571109A is around 45 h. Simulations based on the population-PK model indicate that stable trough concentrations for MSC2571109A are reached only beyond 50 days of treatment. After 11 daily administrations, 77% of the steady-state exposure are expected. In line with t_{max} and $t_{1/2}$ only small peak to trough fluctuations around the average concentration values were observed at steady state, therefore an interval of 4 h between tepotinib and midazolam administration is considered adequate to reach the maximum inhibition/induction by tepotinib.

This trial will be conducted in healthy subjects to standardize the trial population and to minimize exposure variability.

Although multiple doses of up to 1400 mg were found safe and well tolerated in patients (Trial EMR200095-001), tepotinib 500 mg has been administered so far to healthy volunteers only as single doses (Trial EMR200095-007, single dose; trial MS200095-0012, two single doses). To assess the safety profile of multiple doses of 500 mg tepotinib in healthy subjects, the safety, tolerability and PK data from the first 6 subjects up to Day 11 of Period 2 will be reviewed by the responsible functional representatives. Only if tepotinib was safe and well tolerated by these subjects, the remaining subjects will be treated.

Nonclinical safety investigations did not reveal a genotoxicity potential or other findings with relevance for human use. Knowing that tepotinib shows teratogenic effects in animals, only healthy women who are postmenopausal or surgically sterile (ie due to hysterectomy, or bilateral oophorectomy, or bilateral salpingectomy) will be enrolled in this trial, and male subjects must agree to use and have his female partner use highly effective methods of contraception.

Close safety monitoring including clinical laboratory parameters, ECG and vital signs will be conducted. Special attention will be paid to the clinical laboratory parameters, including serum amylase and lipase.

Midazolam is a well-established and safe drug with overall low toxicity. Owing to these properties, it has been safely used as a sensitive probe substrate in CYP3A4 interaction studies and is recommended by the relevant guidelines [7, 9].

Subjects will be admitted to the trial site and remain resident there until at least 48 h after the last administration, to allow continuous safety monitoring. A monitoring period of 48 h after the last dose of tepotinib is regarded as sufficient to ensure the safety of the subjects. If there are any safety concerns the Investigator can extend the inpatient period as appropriate. In addition, monitoring of subjects is ensured by choosing a CRO experienced in the conduct of clinical pharmacology studies.

An open-label design is deemed appropriate as the primary endpoint relates to pharmacokinetic parameters.

5.2.3 Justification for Dose

The dose of 500 mg tepotinib has been selected to reflect the RP2D dose for the treatment of human malignant tumors and will be administered to the trial subjects for 11 days during Period 2 of the trial. Given the lack of genotoxic effects of tepotinib, and the large clinical database, which revealed asymptomatic transient increases of amylase and/or lipase as the only identified risk, short term multi-day administration in this trial of 500 mg tepotinib in healthy subjects is expected to be safe and well tolerated. Up to two single doses of 500 mg (MS200095-0012) have been studied in previous studies in healthy subjects and were found to be well tolerated. Multiple dosing of 500 mg tepotinib was well tolerated in patients (see Section 3). Also, multiple doses of tepotinib up to 1400 mg daily have been explored in 7 patients and were well tolerated.

The recommended therapeutic dose of midazolam is 7.5 mg to 15 mg for premedication before induction of anesthesia or for conscious sedation before and during diagnostic and therapeutic procedures. A dose of 7.5 mg midazolam was used in several studies investigating the effect on CYP3A and proved to be sensitive enough to detect such an effect [4, 10]. Midazolam will be administered as a single oral dose of 7.5 mg midazolam tablet (ie Dormicum® 7.5 mg film-coated tablet) on Day 1 of Period 1 and Day 11 of Period 2.

On Day 11 of Period 2, midazolam will be administered 4 h after tepotinib dosing ie about 4 h after completion of a standardized continental breakfast. Thus, dosing of midazolam can be regarded as quasi-fasted administration.

5.2.4 Rationale for Endpoints

The peak (C_{max}) and extent (area under the plasma concentration-time curve [AUC]) of exposure of midazolam after single dose administration are considered adequate endpoints to evaluate the effect of tepotinib on the PK on the CYP3A probe substrate midazolam. These endpoints are in line with the regulatory guidance of the FDA and the EMA (see Section 3.1).

5.3 Selection of Trial Population

Only subjects meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as participants. Prior to performing any trial assessments, the Investigator will ensure that the subject has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

To be eligible, the subject must fulfill all the following criteria:

1. Male or female, aged 18 to 44 years inclusive (at Screening)
2. Body mass index (BMI) ≥ 18.5 and ≤ 29.9 kg/m^2 and body weight between 50 to 100 kg, inclusive (at Screening)
3. A female participant is eligible to participate if she is not pregnant, not breastfeeding and of non-childbearing potential, confirmed at Screening by fulfilling at least one of the following criteria:
   - Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL)
   - Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy
4. A male participant must agree to use and to have his female partners of childbearing potential to use highly effective methods of contraception (ie methods with a failure rate of less than 1% per year) as detailed in the Clinical Trial Facilitation Group (CTFG) recommendations [11] during the period of participation in the trial and for at least 3 months after the last IMP administration (see Appendix III). Males must also refrain from donating sperm during this period and should always use a barrier method such as condom concomitantly. The male participants will be asked to report pregnancies in their female partners up to 3 months after the last IMP intake
5. Subject must be healthy, as assessed by the Investigator, with no clinically significant abnormality identified on physical examination and no active clinically significant disorder, condition, infection or disease that would pose a risk to subject safety or interfere with the trial evaluation, procedures, or completion (at Screening and Day -1)
6. Subject must have given written informed consent before any trial-related activities are carried out and must be able to understand the full nature and purpose of the trial, including possible risks and adverse effects
7. All values for hematology and biochemistry tests of blood and urinalysis should be within the normal range (at Screening). Minor (solitary) nonclinically relevant deviation(s) are allowed as judged by the Investigator, however amylase, lipase, alanine aminotransferase [ALT] and aspartate aminotransferase [AST] values should not exceed the upper limit of normal range (ULN).

5.3.2 Exclusion Criteria

Subjects are not eligible for this trial if they fulfill any of the following exclusion criteria:

1. Participation in the treatment phase of a clinical trial within 60 days or 5 half-lives after last dosing of the previous trial drug, whatever is longer, before administration of trial drug
2. Whole blood donation or loss of > 450 mL within 60 days before administration of trial drug

3. Any surgical or medical condition, including findings in the medical history or in the screening assessments, or any other significant disease, that in the opinion of the Investigator, constitutes a risk or a contraindication for the participation of the subject in the trial or that could interfere with the trial objectives, conduct, or evaluation
4. Supine systolic blood pressure (SBP) > 140 or < 90 mmHg, diastolic blood pressure (DBP) > 90 or < 50 mmHg, and pulse rate > 90 or < 50 beats per minute at Screening and at admission on Day -1. (Any abnormal vital signs 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)
5. 12-lead ECG showing a QTcF > 450 ms, PR > 215 ms, or QRS > 120 ms (at Screening)
6. Creatinine clearance estimated glomerular filtration rate (eGFR) < 90 mL/min as assessed by using the estimated measure with the Cockcroft-Gault equation. In case of a borderline result between ≥ 80 and < 90 mL/min, Cystatin C will be determined in addition, and the subject will only be included if the Cystatin C value is below the ULN
7. Subjects with gall bladder removal or other relevant surgery of gastrointestinal tract. (Appendectomy is not considered as relevant)
8. History of any malignancy except for adequately treated superficial basal cell carcinoma
9. History of epilepsy
10. Ascertained or presumptive allergy/hypersensitivity to tepotinib or midazolam 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 subject and/or outcome of the trial
11. Positive screen for alcohol or drugs of abuse (at Screening and Day -1 of Period 1)
12. Positive screen for hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (anti-HCV), and human immunodeficiency virus 1 and 2 antibodies (HIV1/HIV2 antibodies) (at Screening)
13. 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 Day -1)
14. Receipt of any prescription or nonprescription medication within 14 days or 5 half-lives, whatever is longer, before trial drug administration (apart from paracetamol up to 1500 mg per day, as judged appropriate by the Investigator)
15. Smoker (cigarettes, pipes, cigars, or others) or former smoker who stopped smoking less than 6 months before the time of the Screening Visit
16. Intake of grapefruit, Seville orange, cranberry or juices of these fruits, or St. John's Wort, from 14 days prior to Day -1
17. Inability to communicate or cooperate with the Investigator (eg language problem, illiteracy, poor mental status) or to comply with the requirements of the entire trial, including dietary restrictions
18. Other factors, which in the opinion of the Investigator may interfere with trial conduct (at Screening and Day -1 only)

19. Legal incapacity or limited legal capacity
20. Subjects kept in detention
21. Any contraindications according to midazolam label (ie hypersensitivity to the active substance, benzodiazepines or to any of the excipients listed in the SmPC, severe respiratory insufficiency, sleep apnea syndrome, severe hepatic impairment, myasthenia gravis.

5.4 Criteria for Initiation of Trial Treatment

Inclusion and exclusion criteria will be checked within the screening period and again on Day -1 of Period 1. Subjects meeting all the inclusion and none of the exclusion criteria will be enrolled in the trial.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Trial Treatment

A subject must be withdrawn from IMPs administration if any of the following occur:

- The subject requires treatment with any medication suspected or known to interfere with the IMPs
- The subject is suspected or known not to comply with the protocol directives (use of prohibited medication, noncompliance with the sampling schedule, nonadherence to dietary rules, and nonattendance at trial assessments).

Withdrawal of a subject from trial drug due to any of the above reasons means that this subject prematurely discontinues the trial, ie before completion of the full profiling and all safety investigations. Subjects who dropped out, must be encouraged to attend the End of Trial examination for safety reasons (see Table 2).

Subjects who dropped out must be replaced.

5.5.2 Withdrawal from the Trial

Subjects must be withdrawn from the trial by the Investigator at any time for any of the following reasons:

- Subject withdrew consent
- Subject lost to Follow-up
- Participation in another clinical trial
- Relevant AEs, especially SAEs, occur that do not justify the subject's continuation in the trial
- Pregnancy
- Protocol noncompliance judged as significant by the Investigator and/or Sponsor

- Use of a non-permitted concomitant drug as defined in Section 6.5. However, any medications that are considered necessary for the subject's wellbeing (eg paracetamol up to 1500 mg per day) may be given at the discretion of the Investigator
- Subject is no longer able to participate for other medical reasons (eg surgery, intercurrent illness)
- Any other condition which to the opinion of the Investigator no longer justifies or permits a safe participation of the subject.
- Any of the following individual stopping criteria is met unless deemed unrelated to IMPs by the Investigator with alternate etiology identified:
  - Abnormal clinically relevant vital signs confirmed on 2 or more measurements (min. 5 minute intervals), including abnormal blood pressure
    - hypotension defined as systolic < 80 mmHg and/or diastolic < 40 mmHg, or
    - hypertension defined as systolic > 160 mmHg and/or diastolic > 100 mmHg
  - Abnormal clinically relevant ECG findings, including a corrected QT-interval (ad modus Fridericia; QTcF) > 500 ms or an increase in QTcF > 60 ms compared to baseline, confirmed on ≥ 2 repeat measurements
  - Marked increases in liver or renal parameters (ALT/AST ≥ 3 x ULN, total bilirubin ≥ 2 x ULN), creatinine > 1.5 x (ULN) confirmed by ≥ 2 repeat measurements
  - Any clinically relevant symptom or sign which in the opinion of the Investigator and/or Sponsor warrants subject withdrawal.

If a subject has failed to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case a subject should be withdrawn from the trial, the medical monitor and clinical trial leader at the Sponsor will be informed immediately.

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

In case of premature withdrawal from the trial, the assessments scheduled for the last End of Trial Visit should be performed, as Early Termination Visit, if possible with focus on the most relevant assessments (see Table 2). In any case, the appropriate electronic Case Report Form (eCRF) section must be completed.

Subjects who withdraw from the trial must be replaced.

5.6 Premature Termination of the Trial

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk benefit judgment for any IMP. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of an IMP or withdrawal of an IMP or comparator from the market for safety reasons.

Health Authorities and IECs will be informed about the discontinuation of the trial in accordance with applicable regulations.

5.7 Definition of End of Trial

The End of Trial is defined by the last contact (related to this trial) with the last subject who participates in this trial (last subject's End of Trial Visit or telephone call, independent of whether the subject is in End of Trial Visit or discontinued from the trial).

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" refers to any active substance or a placebo being tested or used as a reference treatment or therapy in a clinical trial, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

6.1 Description of the Investigational Medicinal Product

Investigational Medicinal Product:

- Tepotinib (MSC2156119J), 3-(1-{3-[5-(1-methylpiperidin-4-ylmethoxy)-pyrimidin-2-yl]-benzyl}-1,6-dihydro-6-oxo-pyridazin-3-yl)-benzonitrile hydrochloride (HCl) hydrate, is supplied as 500 mg (oblong, light yellow) film-coated tablets (Tablet Formulation 2, TF2) for oral administration

  Tepotinib 500 mg film-coated tablets have a drug load of approximately 50% and contain the excipients D-mannitol, silica colloidal anhydrous, crospovidone, magnesium stearate, and Opadry® II yellow

  All excipients used in the tablet formulation are of compendial grade. Supplier's certificates show that there is no transmissible spongiform encephalopathy risk. Tepotinib is provided in aluminum (ALU)/ALU blisters and storage at or below 25°C.

- Midazolam: Commercially available midazolam will be used, ie Dormicum 7.5 mg film-coated tablets.

Reference product: Not applicable.

Specific rules for treatment modifications: Not applicable.

6.2 Dosage and Administration

Subjects will receive the following 2 treatments.

Treatment A (Period 1): Administration of Midazolam Alone

On Day 1 of Period 1, a single oral dose of 7.5 mg midazolam as tablet will be administered in a quasi-fasted state 4 h after completion of a standardized breakfast together with 240 mL water. Time of breakfast and midazolam administration should be the same as planned for Day 11 of Period 2 (eg breakfast from 06:30 h to 06:55 h, midazolam dosing at 11:00 h).

The standardized breakfast is a continental breakfast consisting of: 2 rolls, 20 g butter, 25 g jam, 1 slice of cheese, 1 slice of cold cut, fruit tea or decaffeinated coffee without milk and sugar.

Subjects will stay in a semi-recumbent position for 4 h post-dose, except for use of toilet, when the subjects can leave the bed without undue physical stress/activity. If necessary subjects may stay in bed for a longer period at the discretion of the Investigator.

Standardized meals will be served 4 h (light meal) and 8 h (dinner) after administration of midazolam on Day 1 of Period 1; thereafter, meals will be served at customary times during the inpatient period.

Treatment B (Period 2): Administration of Tepotinib and Midazolam

On Days 1 to 10 of Period 2, 500 mg tepotinib will be administered together with 240 mL of water after a continental breakfast (about 30 min after start of breakfast). Some flexibility of the continental breakfast on Days 1 to 10 is allowed, but the breakfast should be not high caloric. Cooked egg and Müsli with milk will be allowed on these days.

Standardized meals will be served 4 h (light meal) and 8 h (dinner) after administration of tepotinib on Days 1 to 10 of Period 2, while some flexibility is allowed within the range of standardization on these days, ie meals should be light, and comparable with regard to composition and caloric content. Other meals will be served at customary times during the inpatient period.

On Day 11 of Period 2, the subjects will receive a standardized breakfast, which must match with the breakfast on Period 1, Day 1, with regard to composition and content, in order to minimize potential influence of covariates for the PK profiling of midazolam. The standardized breakfast must be consumed completely within 25 min. 30 min after start of the breakfast, 500 mg tepotinib will be administered together with 240 mL of water. A single oral dose of 7.5 mg midazolam will be administered 4 h after tepotinib administration together with 240 mL water.

On Day 11 of Period 2, subjects will stay in a semi-recumbent position for 4 h after midazolam administration, except for use of the toilet, when the subjects will be allowed to leave the bed without undue physical stress/activity. If necessary subjects may stay in bed for a longer period at the discretion of the Investigator.

Standardized meals will be served 4 h (light meal) and 8 h (dinner) after administration of midazolam on Day 11 of Period 2; other meals will be served at customary times during the inpatient period.

6.3 Assignment to Treatment Groups

The subjects willing to participate in the trial and signing the Informed Consent Form (ICF) will be assigned a subject number. They will only be included when all Screening examination procedures have demonstrated that all inclusion criteria and none of the exclusion criteria apply. Subjects eligible for the trial will receive an assignment number prior to the first administration. Randomization is not applicable in this trial.

According to CRO standard operational procedures (SOPs), the subjects will be assigned an assignment number in the order of their registration to the trial (first registration results in the lowest available assignment number, second registration results in the second lowest available assignment number, and so on). However, precedence will be given to subjects who participate in a trial at PI for the first time and for subjects who served as "stand-by" during a preceding trial.

The Investigator will keep a record (screening log) relating the subject numbers and the names of all subjects (including the Nuvisan GmbH ID number) who have given their informed consent, to allow easy checking of data in subject files, when required. This record will also include the date of screening and completion status, as well as subjects who could not be enrolled in the active treatment trial part (defined as screening failures) for whatever reason. On the enrollment log the subject number, assignment number and status are listed.

6.4 Non-investigational Medicinal Products to be Used

Not applicable.

6.5 Concomitant Medications and Procedures

All concomitant medications taken by the subject during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the eCRF, noting the name, dose, route, duration, regimen, status and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

6.5.1 Permitted Medicines

Paracetamol is the only permitted medication. Paracetamol will be permitted up to a maximum daily dosage of 1500 mg.

Any medications that are considered necessary to protect subject welfare and that will not interfere with the IMPs may be given at the Investigator's discretion. The potential DDIs with tepotinib are still under evaluation. Therefore, medically required concomitant medication might have to be adjusted based on tolerability and the clinical response.

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

6.5.2 Prohibited Medicines

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

The subjects are prohibited from using prescription or over-the-counter medications (apart from paracetamol up to 1500 mg per day, as judged appropriate by the Investigator) within 14 days or 5 half-lives, whichever is longer, prior to the first IMP administration during the trial, and until after the End of Trial Visit.

6.5.3 Permitted/Prohibited Procedures

Subjects should drink about 2 L fluids per day during the hospitalization phase (as provided by the trial site) and will be reminded regularly.

Throughout the PK profiling days of Periods 1 and 2, the following restrictions must be met:

- Subjects should be in the fasted state for at least 10 h before breakfast and at least 4 h after midazolam administration (= 8 h after breakfast) on Day 1 of Period 1 and on Day 11 of Period 2
- Drinking is not allowed for 1 h before and after administration of midazolam and for 1 h after administration of tepotinib
- Chewing gum is not allowed during the PK profile days.

Throughout the trial, the following restrictions must be met:

- No smoking or use of tobacco products
- No alcohol intake
- No intake of food and beverages other than provided to the subjects by the trial site during the inpatient period
- No intake of caffeine- and xanthine-containing food and beverages (eg coffee, black or green tea, cola, cocoa, chocolate or chocolate-containing food or beverages) from 48 h before first administration of trial drug until collection of last PK sample of each period
- No intake of herbs/fruits that can have an influence on PK (eg St. John's Wort, Seville oranges, grapefruits, cranberry or the juice of these fruits), from 14 days prior to Day -1 of Period 1 until final examination
- No intake of poppy seeds (eg poppy seed rolls, poppy seed cake, yoghurt containing poppy seed etc.) from 72 h before first administration of trial drug until completion of final examination
- No intake of concomitant medication within 14 days or 5 half-lives, whatever is longer, before first administration of trial drug until final examination (except for paracetamol up to 1500 mg per day, may be given at the discretion of the Investigator)
- No intake of recreational drugs within 14 days or 5 half-lives, whatever is longer, before first administration of trial drug until final examination

- No exhausting physical activities (body building, sports) from at least 72 h before the first administration of trial drug until the final examination
- No sun baths, solarium or sauna at least 12 h before first administration of trial drug until final examination.

6.5.4 Other Interventions

Not applicable.

6.5.5 Special Precautions

Not applicable.

6.5.6 Management of Specific Adverse Events or Adverse Drug Reactions

No specific measures are proposed at this stage. Standard medical care will be provided at the trial site for all AEs occurring during the trial.

6.6 Packaging and Labeling of the Investigational Medicinal Product

All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

The investigational product tepotinib will be provided by the Sponsor packed in alu/alu blister.

Midazolam will be purchased from commercially available supplies.

6.7 Preparation, Handling, and Storage of the Investigational Medicinal Product

The pharmacy or designee will receive the IMPs labeled and packaged according to the local regulatory requirements and the storage requirements. Tepotinib and midazolam will be supplied in ready to use oral formulations. The responsible pharmacist will dispense the necessary amount of the IMPs. Detailed guidance will be provided in an IMP handling manual.

The IMP supplies will be recorded in an IMP inventory.

Tepotinib must be carefully stored at the trial site in a closed room or cabinet with restricted access, safely and separately from other drugs and protected from environmental extremes until used in the trial. Tepotinib should be stored at or below 25°C. Any deviations from the recommended storage conditions should be immediately reported to the Sponsor, and the IMP should not be used until authorization has been received from the Sponsor. The preparation, handling and storage of the IMP will be documented.

Detailed recommendations for the use and storage of midazolam are described in the Summary of Product Characteristics [6].

The IMPs must not be used for any purpose other than the trial in question.

It must be ensured at the trial site that the IMPs are not used after the use-by date. This is to be closely monitored by the responsible monitor.

6.8 Investigational Medicinal Product Accountability

The Clinical Trial Supply Department of Nuvisan GmbH is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records. Drug accountability will also be confirmed by the Trial Monitor.

- Upon receipt of IMPs, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File
- IMP dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit
- Trial site IMP accountability records will include the following:
    - Confirmation of IMP receipt, in good condition
    - The inventory of IMPs provided for the clinical trial and prepared at the site
    - The use of each dose by each subject
    - The disposition (including return, if applicable) of any unused IMP
    - Dates, quantities, batch numbers, kit numbers, expiry dates, formulation (for IMP prepared at the site), and the individual subject assignment numbers.

The Investigator site should maintain records, which adequately document that subjects were provided the doses specified in this protocol, and all IMPs provided were fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present trial. No IMP that is dispensed to a subject may be redispensed to a different subject.

A Trial Monitor will periodically collect the IMP accountability forms.

At the conclusion or termination of this trial, all used and unused IMP kits will be destroyed at the trial site according to local regulations and institutional guidelines. All used and unused medications will be carefully recorded and documented before destruction.

6.9 Assessment of Investigational Medicinal Product Compliance

During the treatment periods, drug administrations will be performed by a Nuvisan GmbH staff member in accordance with the specifications of the Investigator. This includes checking the oral

and buccal cavity with the aid of a flashlight and tongue depressor. The proper administration of the trial medication will be documented on the individual eCRF.

6.10 Blinding

This is an open-label trial by design. Therefore, blinding is not applicable. (Note: the bioanalytics will be performed without knowledge of treatment information. Access to treatment information will be restricted and defined in a Data Access Plan).

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol or planned for an individual subject enrolled in the trial. Even if it does not meet other criteria for an SAE, any overdose must be recorded in the trial medication section of the eCRF and reported to Patient Safety in an expedited manner using the SAE Report Form, and following the procedure in Section 7.4.

The effects of an overdose of tepotinib are unknown, and therefore no standard treatment is currently established. In the event of an overdose, the Investigator or treating physician should use appropriate clinical judgment for the management of any clinical symptoms or evaluation results.

Midazolam may cause somnolence, confusion, lethargy, muscle relaxation and paradoxical excitation. Treatment, if needed, of overdosing or overreaction of midazolam will be performed as per SmPC, ie monitoring of vital signs, symptomatic treatment of cardiorespiratory or central nervous adverse events; in case of severe central nervous depression, Flumazenil, a specific benzodiazepine-receptor antagonist, is an antidote available at the site for midazolam.

6.13 Medical Care of Subjects after End of Trial

Not applicable in a trial with healthy subjects.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

Detailed schedule of trial procedures/assessments is provided in Table 1 (administration of midazolam alone) and Table 2 (administration of tepotinib and midazolam).

Prior to performing any trial assessments, the Investigator will obtain written informed consent as described in Section 9.2.

7.1.1 Screening Examination

All subjects will undergo an entry examination to evaluate their health status and their eligibility for inclusion in the trial. The Screening examination will be conducted not more than 21 days prior to the planned first drug administration, ie between Day -21 to Day -2 before commencing to first trial period. Only subjects who meet the inclusion criteria and none of the exclusion criteria will be admitted to the trial.

Prior to Screening examination, the subjects will receive a subject number for identification. Eligible subjects will receive an assignment number prior to the first drug administration.

There is a notification on the subject's card as well as in the electronic subjects' database on the last participation in a trial. In addition, all subjects are reported to a central checking organization (VIP Check) before inclusion into the trial.

Prior to any Screening examinations the subjects must sign the ICF. This Screening examination will consist of the following:

- Demographic information including body height, body weight and BMI
- Medical history
- Physical examination
- Vital signs
- 12-lead ECG
- Blood and urine samples for safety laboratory assessments
- Serological tests for hepatitis B, C, and HIV1/HIV2
- Serum pregnancy test for women
- Urine drugs of abuse screen (including test for cotinine)
- Alcohol breath test
- Prior medication and concomitant medication
- Assessment of AEs
- Preliminary evaluation of inclusion and exclusion criteria.

7.1.2 Treatment Periods

The subjects willing to participate in the trial will only be included when all Screening examination procedures have demonstrated that all inclusion criteria and none of the exclusion criteria apply. Subjects will be assigned an assignment number within the trial prior to the first administration.

For detailed time points and assessments please see Table 1 (Treatment A) and Table 2 (Treatment B).

Adverse event monitoring is generally assessed between Trial Day -1 and Trial Day 15.

Subjects will be hospitalized from the morning of Trial Day -1 (= Day -1 of Period 1) until completion of the assessments of Trial Day 15 (= Day 13 of Period 2).

Treatment A (Period 1 - Midazolam alone)

Day -1 of Period 1 (admission)

On admission on Day -1 of Period 1 the following will be done:

- Physical examination
- Vital signs
- 12-lead ECG
- Blood and urine samples for safety laboratory assessments
- Pregnancy test for women (in urine)
- Urine drugs of abuse screen (including test for cotinine)
- Alcohol breath test
- Evaluation of inclusion and exclusion criteria
- Assessment of AEs
- Documentation of concomitant medication.

Days 1 to 2 of Period 1 (inpatient)

Prior to dosing of midazolam on Day 1 of Period 1 the following will be done:

- Vital signs
- 12-lead ECG
- Pulse oximetry from about 30 min before until 6 h after midazolam administration
- Pre-dose PK blood sample for determination of midazolam and 1-hydroxymidazolam
- Blood sample for PGx.

Midazolam will be administered together with 240 mL water, 4 h after completion of a standardized breakfast.

After dosing of midazolam on Day 1 of Period 1 the following will be done:

- PK blood samples for determination of midazolam and 1-hydroxymidazolam will be taken regularly until 48 h post-dose (for time points please see Table 1)
- Vital signs will be measured and 12-lead ECGs will be recorded from 4 h until 48 h post-dose (for time points please see Table 1)

- Regular assessment of AEs and documentation of concomitant medication.

Treatment B (Period 2 - Tepotinib and Midazolam)

Days 1 to 10 of Period 2 (inpatient)

Prior to the daily dosing of tepotinib the following will be done on specific days as detailed in the Schedule of Assessments (see Table 2):

- Vital signs
- 12-lead ECG
- Blood and urine samples for safety laboratory assessments
- Pre-dose PK blood sample for determination of trough levels of tepotinib and its metabolites on Days 9 and 10 of Period 2
- Day 1 of Period 2: PK blood sample for determination of midazolam and 1-hydroxymidazolam (= 48 h sample for Period 1).

After completion of the pre-dose assessments a continental breakfast will be served and 500 mg tepotinib will be administered together with 240 mL water 30 min after start of breakfast on Days 1 to 10.

Additionally, the following will be done on specific days as detailed in the Schedule of Assessments (see Table 2):

- Vital signs (6 h post-dose)
- 12-lead ECG (6 h post-dose)
- Regular assessment of AEs and documentation of concomitant medication.

Day 11 of Period 2 (inpatient)

Prior to dosing of tepotinib the following will be done:

- Pre-dose PK blood sample for determination of trough levels of tepotinib and its metabolites is taken
- Blood and urine samples for safety laboratory assessments.

Thereafter, 500 mg tepotinib will be administered together with 240 mL of water, 30 min after start of a standardized breakfast, which must be consumed completely within 25 min.

Prior to dosing of midazolam the following will be done:

- Vital signs
- 12-lead ECG
- Pulse oximetry from about 30 min before until 6 h after midazolam administration

- Pre-dose PK blood sample for determination of midazolam and 1-hydroxymidazolam.

After completion of the pre-dose assessments a single oral dose of 7.5 mg midazolam will be administered together with 240 mL water 4 h after tepotinib administration.

After dosing of midazolam the following will be done

- Vital signs will be measured and 12-lead ECGs will be recorded from 4 h until 48 h post-dose (for time points please see Table 2).
- PK blood samples for determination of midazolam and 1-hydroxymidazolam will be taken regularly until 12 h post-dose (for time points please see Table 2).
- Regular assessment of AEs and documentation of concomitant medication.

Days 12 to 13 of Period 2 (inpatient)

The following activities will be done:

- Physical examination (on Day 13 of Period 2 only)
- Vital signs
- 12-lead ECG
- Blood and urine samples for safety laboratory assessments (on Day 12 of Period 2 only)
- PK blood samples for determination of midazolam and 1-hydroxymidazolam will be taken regularly from 24 h until 48 h post-dose (for time points please see Table 2)
- Regular assessment of AEs and documentation of concomitant medication.

After completion of all assessments on Day 13 of Period 2, the subjects will be discharged.

Details about the measurements are provided in Sections 7.4 and 7.5.1.

Subjects should drink about 2 L fluids per day during the hospitalization phase (as provided by the site) and will be reminded regularly (for restrictions of fluids see below).

Restrictions:

A detailed listing of restrictions during the trial is provided in Section 6.5.

7.1.3 End of Trial Visit

The End of Trial examination must verify that all values tested in the Screening have remained within a clinically acceptable range. The assessments will be performed 7 ± 1 days after last drug administration in Period 2 or upon premature termination. Unacceptable values and AEs will be followed up until they return to the reference ranges/resolved or there is an adequate explanation which is not related to the trial.

The End of Trial examination will consist of the following:

- Physical examination
- Vital signs
- 12-lead ECG
- Blood and urine samples for safety laboratory assessments
- Serum pregnancy test for women
- Concomitant medication
- Assessment of AEs.

No medical treatment is planned after the end of the trial.

The end of the trial is defined as the last contact (related to this trial) of the last subject undergoing the trial.

7.2 Demographic and Other Baseline Characteristics

At Screening, the following demographic data will be collected: age (year of birth), height, weight, BMI, gender, race and ethnicity.

Furthermore, the following will be documented:

- Clinically relevant findings in the medical history are recorded
- Prior medication within 14 days (any prescribed medicine or over-the-counter drug or dietary supplement including herbal remedies, vitamins, and minerals)
- Smoking status, alcohol intake
- Female status (postmenopausal, sterilization).

7.3 Efficacy Assessments

Not applicable.

7.4 Assessment of Safety

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

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2). The reporting period for AEs is described in Section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE. Investigators will reference the **National Cancer Institute - Common Terminology Criteria for AEs (NCI-CTCAE)**, Version 5.0 (publication date: 27 Nov 2017), a descriptive terminology that can be used for AE reporting. A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided. If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

Grade 1 or Mild
Grade 2 or Moderate
Grade 3 or Severe
Grade 4 or Life-threatening
Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as hemoglobin decreased or neutrophils count decreased, is considered serious only if the condition meets one of the serious criteria specified below.

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

Investigators must also systematically assess the causal relationship of AEs to IMPs (including any other non-IMPs, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMPs include, but may not be limited to, temporal relationship between the AE and the IMPs known side effects of IMPs, medical history, concomitant medication, course of the underlying disease, trial procedures.

Unrelated: Not reasonably related to the IMPs. AE could not medically (pharmacologically/clinically) be attributed to the IMP/trial treatment under trial in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the IMPs. AE could medically (pharmacologically/clinically) be attributed to the IMPs under trial in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (Note: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.)
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.).

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE, as described in Section 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (for example, an overnight stay to facilitate chemotherapy and related intravenous fluid administration) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be additionally documented and reported using the appropriate Report Form as described in Section 7.4.1.4.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and times when it is important to assess the time of AE onset relative to the recorded treatment administration time), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the IMP, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of informed consent) and continues until the End of Trial Visit.

Any SAE assessed as related to the IMPs must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMPs.

7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of **24 hours** after becoming aware of the event) inform the Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately thereafter by fax or e-mail. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the trial-specific SAE Report Form.

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report and autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

Adverse Events of Special Interest

Healthy subjects might experience asymptomatic elevations in serum lipase and amylase. Any elevation in serum lipase and amylase of Grade ≥ 3 will lead to the recording of an adverse event of special interest (AESI). The severity of these AEs should be defined based on clinical judgment of the Investigator and defined according to NCI-CTCAE Severity Scale.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial subjects to the IEC that approved the trial.

In accordance with ICH GCP [14], the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC's approval/favorable opinion to continue the trial." In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regards to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

7.4.1.6 Monitoring of Subjects with Adverse Events

AEs are recorded and assessed continuously throughout the trial (see Section 7.4.1.3) and are assessed for final outcome at the End of Trial Visit. All AEs ongoing at the End of Trial Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to trial treatment (for example, resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.4.1.4.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the trial.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The Sponsor/designee must be notified without delay and the subject must be followed as mentioned above.

7.4.3 Clinical Laboratory Assessments

Fasted blood samples and urine samples will be collected for the clinical laboratory tests (hematology, biochemistry, virology, drugs of abuse, hormones, and urinalysis, Table 3) following the timing noted in the Schedule of Assessments (Table 1 and Table 2). Additional laboratory safety examinations during the trial are at the discretion of the Investigator. All blood and urine samples will be worked up and analyzed in Nuvisan's clinical laboratory. Any abnormalities in any of the laboratory parameters will be judged by a physician individually in relation to the reference ranges from the laboratory.

For all findings with major deviation and/or possible pathological relevance, follow-up examinations will be carried out until the deviation returns to normal or the absence of pathological relevance can be confirmed. If a deviation considered clinically relevant has not returned to a normal or not clinically relevant value when it is checked during the screening laboratory tests, the subject will not be included in the trial.

Laboratory abnormalities considered clinically relevant by the Investigator will be reported as AE. The following parameters will be determined as summarized in Table 3.

The Sponsor should receive a list of laboratory normal ranges before shipment of the IMP. Any change in laboratory normal ranges during the trial should be forwarded to the Sponsor, including laboratory certificates.

For the amount of blood taken in this trial see Appendix II.

Table 3 Safety Laboratory Evaluations

Biochemistry	Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase γ-Glutamyl-transferase Lactate dehydrogenase Creatine phosphokinase [b] Amylase Lipase	Bilirubin (total) [a] Cholesterol Triglycerides Uric acid	Sodium Potassium Creatinine Urea Glucose Cystatin C (if applicable)
Hematology	Hematocrit Hemoglobin Red blood cell count Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration	Platelet count White blood cell count	White blood cell differentials and absolute counts [c]: Basophils Eosinophils Lymphocytes Monocytes Neutrophils
Urinalysis	pH Nitrite Protein Glucose	Ketone bodies Urobilinogen Bilirubin Urine pregnancy test, females only	Leucocytes Blood Microscopic examination [d]
Urine drug screen	Cocaine Amphetamines Methamphetamines Opiates	Barbiturates Benzodiazepines Methadone Cannabinoids	Tricyclic antidepressants Cotinine Ecstasy
Other tests	Hepatitis B surface antigen Hepatitis C antibody HIV1/HIV2 antibodies Follicle stimulating hormone (if applicable), only females Thyroid stimulating hormone Serum pregnancy test (beta-HCG), only females eGFR [e] Alcohol breath test		

HIV = human immunodeficiency virus, beta-HCG = beta-human chorionic gonadotropine, eGFR = Estimated glomerular filtration rate

a In case of an increased Bilirubin (total) the direct Bilirubin will be determined.

b In case of an increased creatine phosphokinase (CK), myocardium/brain type (CK-MB) will be determined; if the ratio of CK/CK-MB is above 6, troponin will be determined as well.

c In case of abnormal findings, manual differential blood count can be requested by the Investigator.

d Only if blood, protein, nitrite, or leucocytes are positive on the dipstick.

e Estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

7.4.4.1 Vital Signs

Blood pressure (SBP [mmHg] and DBP [mmHg]) will be measured according to the oscillometric method using an automated device, which also indicates the corresponding pulse rate. Blood pressure and pulse rate will be measured after at least 5 min in a supine position, according to the schedule of assessments (Table 1 and Table 2).

Pulse oximetry will be performed continuously from about 30 min before until 6 h after midazolam administration. Oxygen will be administered as determined by the Investigator in the event of a pulse oximetry reading of < 92% (confirmed by repeat measurement).

Body temperature will be measured auricular (Table 1 and Table 2).

Further vital sign measurements during the trial are at the discretion of the Investigator.

7.4.4.2 ECG

Twelve-lead ECGs will be recorded as scheduled in the trial schedule of assessments (Table 1 and Table 2) using the ECG system CardioPerfect®, Welch Allyn. The ECGs will be recorded in supine position after at least 5 min rest.

ECGs will be plotted with a paper speed of 50 mm/s and 10 mm/mV amplitude, with 10 seconds recording duration for all leads and at least 3 complexes, but preferably 5 complexes in each lead.

Per time-point, the ECG will be stored electronically, printed and reviewed in a timely manner by the Investigator. The original printout will be stored with the subject's source data. Electronic data may be transferred to a central ECG laboratory for central reading and further analysis; these results would be reported separately.

ECG printouts will be signed and dated electronically by the person evaluating the ECG. The ECG will be interpreted by the Investigator (normal/abnormal). For abnormal ECGs, the clinical significance (yes/no) must be judged by the Investigator and the abnormality is to be specified.

Additional ECGs during the course of the trial are at the discretion of the Investigator.

7.4.4.3 Physical Examination

The physical examination comprises general appearance, skin, head, neck (including thyroid), eyes, ears, nose, throat, abdomen, as well as neurological, peripheral vascular, musculoskeletal, cardiovascular and pulmonary system.

Physical examination will be scheduled according to the schedule of assessments (see Table 1 and Table 2). Further physical examinations during the course of the trial are at the discretion of the Investigator. Any relevant findings are to be recorded on the Medical History form in the

eCRF (for findings from the past that occurred prior to ICF signature) or on the AE form in the eCRF (for findings presently occurring; events existing but unresolved prior to drug administration).

7.4.4.4 Alcohol Breath Test

A commercially available breath analyzer (Alcotest 6510, Draeger Safety GmbH) will be used to determine the concentration of alcohol in the subject's breath per the schedule of assessments (see Table 1 and Table 2).

Additional alcohol breath tests during the course of the trial are at the discretion of the Investigator.

7.5 Pharmacokinetics

7.5.1 Blood Sampling

On the PK profiling days, an indwelling venous catheter will be positioned in a suitable forearm vein for blood sampling and should be kept, if possible, until 12 or 24 h after dosing. After removing the indwelling venous cannula, samples will be taken by venipuncture.

Plasma levels of midazolam and 1-hydroxymidazolam (Day 1 o f Period 1 and Day 1 1 of Period 2 from time pre-dose to 48 h post midazolam dosing) will be determined. Blood samples for determination of tepotinib and its metabolites trough levels will be taken before tepotinib administration on Days 9, 10 and 11. The sampling schedule is outlined in Table 1 and Table 2.

The exact date and time of sample collection must be recorded in the eCRF and will be used in the calculation of PK parameters. Blood samples should be taken as close as possible to the scheduled time points. Samples taken outside of the time periods shown in Table 4 need an explanation and will be considered a protocol violation.

Table 4 PK Blood Sampling - Allowed Time Windows

Planned Blood Sampling	Time Windows (min)
Pre-dose	-60 min
0-1 h post-dose	± 2 min
After 1 h - 12 h post-dose	± 5 min
After 12 h - 48 h post-dose	± 15 min

At visits where assessment time points coincide with each other, the vital signs and ECG assessments should be performed slightly before the specific time point and the PK blood sampling should be performed on time.

Details of blood sample collection, labeling, processing, storage and shipment requirements will be described in a separate laboratory manual. For the amount of blood taken in this trial see Appendix II.

All sample handling procedures, including the time of each sample collection, the time of placement into frozen storage (at the end of the sample preparation), and the date of transfer or shipment of the samples to the responsible analyst will be documented in detail.

Concentrations of midazolam, 1-hydroxymidazolam and tepotinib (and its metabolites) will be measured using validated Liquid Chromatography and Tandem Mass Spectrometry methods at Nuvisan. The assays will be carried out in accordance with Good Laboratory Practice Regulations and the EMA reflection paper. Separate bioanalytical protocols will be provided before the start of the analytical part of the trial. Full details of the bioanalytical methods used will be described in separate bioanalytical reports.

7.5.2 Calculation of Pharmacokinetic Variables

The following non-compartmental PK parameters (see Table 5) will be calculated from the individual plasma concentration-time data using commercial software such as Phoenix®/WinNonlin® (Certara, L.P., Princeton, New Jersey, Version 6.4 or higher) at Nuvisan GmbH.

Table 5 Definition of PK Parameters for Midazolam and 1-Hydroxymidazolam after Single Dose Administration

Symbol	Definition
AUC_{0-t}	Area under the plasma concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification (LLOQ), calculated per the mixed log linear trapezoidal rule (ie linear up/log down)
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero (= dosing time) extrapolated to infinity, calculated as AUC_{0-t} + AUC_{extra}. AUC_{extra} represents the extrapolated part of $AUC_{0-\infty}$ calculated by $C_{lastpred}/\lambda_z$, where $C_{lastpred}$ is the predicted plasma concentration at the last sampling time point, calculated from the log-linear regression line for λ_z determination at which the measured plasma concentration is at or above LLOQ
C_{max}	Maximum plasma concentration observed
t_{last}	The last sampling time at which the concentration is at or above the lower limit of quantification
t_{max}	Time to reach the maximum plasma concentration
$t_{1/2}$	Terminal half-life, calculated as $\ln(2)/\lambda_z$
λ_z	Terminal rate constant determined from the terminal slope of the log-transformed plasma concentration curve using linear regression on terminal data points of the curve
AUC_{extra}	The AUC from time t_{last} extrapolated to infinity
$AUC_{extra\%}$	AUC_{extra} / $AUC_{0-\infty}$ x 100
MR	Metabolic ratio of midazolam $AUC_{0-\infty}$ and 1-hydroxymidazolam $AUC_{0-\infty}$

Individual PK parameters will be calculated using actual sampling times. The pre-dose sample will be considered as if it had been taken simultaneously with the administration of trial drug. PK variables will be evaluated and listed for all subjects who provide sufficient concentration-time data.

Plasma concentrations below lower limit of quantification (LLOQ) before the last quantifiable data point will be taken as zero for calculating the AUC (ie embedded below the limit of

quantitation values set to zero). Plasma concentrations below LLOQ after the last quantifiable data point will not be considered for the determination of the terminal rate constant (λ_z).

7.6 Biomarkers

Not applicable.

7.7 Pharmacogenomics

Pharmacogenetic sample collection is mandatory. An additional separate ICF will be used. One blood sample should be collected in duplicate on Day 1 pre-dose administration. The pharmacogenetic samples will be analyzed conditionally in case of unexpected PK profiles. The results of the pharmacogenetic analysis, as applicable, will be described in a separate report.

7.8 Other Assessments

Not applicable.

8 Statistics

The sample size consideration and the statistical analysis are primarily aimed at the classification of the tepotinib effect (inducer and/or inhibitor of CYP3A) as strong/moderate/mild. Nevertheless, the calculated 90% confidence intervals for the treatment ratios will provide a more general description of the drug-drug interaction.

8.1 Sample Size

A total of 12 subjects will be treated in this trial. Drop-outs will be replaced.

The coefficient of variation for midazolam AUC_{0-t} has been reported between 31% [12] and 49% [13].

Assuming a coefficient of variation (CV) of 50% for AUC_{0-t}, a one-sided alpha of 0.05, and a treatment ratio for the GeoMeans ranging between 0.85 and 1.18, the power to exclude a moderate effect (the 90% confidence interval needs to be within [0.50 – 2.00]) will be 80% with 12 evaluable subjects. A test to exclude a mild effect (ie to demonstrate bioequivalence) is not considered since the required sample size is unacceptably high with around 80 subjects assuming a true treatment ratio of 1.00.

8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Primary Endpoint

- AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of midazolam (at Day 1 of Period 1 and Day 11 of Period 2 from time zero to 48 h post-dose).

8.3.2 Secondary Endpoints

- t_{max} and $t_{1/2}$ of midazolam
- AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max} and $t_{1/2}$ of 1-hydroxymidazolam; metabolic ratio (MR)
- Occurrence of TEAEs (incidence, frequency, intensity and causality), occurrence of changes in clinical laboratory assessments, 12-lead ECGs and vital signs in subjects receiving tepotinib alone and together with midazolam assessed from Day 1 of Period 2 until the End of Trial Visit.

8.3.3 Exploratory Endpoint

- Genetic variants and mutations in genes that potentially influence PK of tepotinib and/or midazolam

  Note: Pharmacogenetic sample collection is mandatory. The results of the pharmacogenetic analysis, as applicable, will be described in a separate report.

8.4 Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Safety	The Safety Analysis Set will include all subjects who have received at least 1 dose of planned IMP.
Pharmacokinetic	The PK Analysis Set will include all subjects without any relevant protocol deviations with respect to PK and absence of factors likely to affect the comparability of PK results, who have received at least one dose of midazolam and who have at least 3 post-dose concentration measurements. Subjects may be excluded after vomiting or following diarrhea in a particular period as this could render the plasma concentration-time profile unreliable. The use of a concomitant medication that might interfere with the PK of any investigational drug could be a reason for excluding a subject.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

Statistical analyses will be performed using the computer program package SAS® System for Windows™ (Version 9.4 or later; SAS Institute, Cary, North Carolina, USA).

The results of this trial will be reported using summary tables, figures, and data listings, as appropriate. All data will be summarized by treatment and scheduled time point, as appropriate.

For demographic, baseline and safety assessments, continuous measurements will be summarized by means of descriptive statistics (ie number and percentage of observations, number and percentage of missing observations, mean, standard deviation [SD], median, 25th and 75th percentiles, minimum, and maximum) and categorical data will be summarized by means of frequency tables (ie count and percentages), if not stated otherwise.

Concentrations of midazolam and 1-hydroxymidazolam and tepotinib (and its metabolites) in plasma will be presented in tables and descriptively summarized by treatment and nominal time point using n, arithmetic mean, SD, standard error of the mean, median, minimum, maximum, and CV%. Values below the LLOQ will be taken as zero for descriptive statistics of PK concentrations. Descriptive statistics of PK parameters will additionally show the GeoMean, the geometric coefficient of variation (GeoCV%), and the 95% confidence interval (CI) for the GeoMean. PK data flagged as "invalid" will be handled as missing in the analyses.

No action will be taken to handle missing data. A subject who withdraws prior to the last planned observation in a trial period will be included in the analyses up to the time of discontinuation.

Changes in the conduct of the trial or planned analyses, if any, will be reported in the appropriate section of the statistical analysis plan (SAP) and in the clinical trial report.

8.5.2 Analysis of Primary Endpoint

For the statistical analysis of AUC_{0-t} of midazolam data, a-priori ordered hypotheses will be tested.

Test 1	H_{01}: T/R ratio ≤ 0.2 or T/R ratio ≥ 5.0	effect stronger than moderate
	versus	
	H_{A1}: T/R ratio within [0.2 ; 5.0]	moderate effect
Test 2	H_{02}: T/R ratio ≤ 0.5 or T/R ratio ≥ 2.0	effect stronger than mild
	versus	
	H_{A2}: T/R ratio within [0.5 ; 2.0]	mild effect.

A general linear model with a fixed effect for TREATMENT and a random effect for SUBJECT will be applied to log-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of midazolam based on the PK analysis set. Treatment differences on the log scale of midazolam with tepotinib vs midazolam alone will be estimated for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ together with their 90% CIs. Point estimates and CIs will be back-transformed to the original scale. The confidence intervals for AUC will be compared to the acceptance ranges for moderate effects [0.2 ; 5.0] and mild effects [0.5 ; 2.0].

Individual estimates of relative bioavailability and metabolic ratio (MR) of midazolam will be calculated for each subject and summarized.

For t_{max} of midazolam the Hodges-Lehmann shift estimator will be calculated together with the 90% CI according to Tukey. PK variables will be evaluated and listed for all subjects of the PK Analysis Set.

Graphical displays will be given, where appropriate, individual and mean concentration-time plots will be produced in linear and log-linear scale. For the primary endpoints, boxplots will be given. Details of the statistical analysis will be described in the SAP.

8.5.3 Analysis of Secondary Endpoints

For t_{max} of midazolam the Hodges-Lehmann shift estimator will be calculated together with the 90% CI according to Tukey.

Summary statistics will be provided for all secondary PK parameters in plasma by time point.

PK variables will be listed for all subjects who provide sufficient concentration-time data. Invalid data will be flagged accordingly.

Graphical displays will be given, where appropriate. Details of the statistical analysis will be described in the SAP.

8.5.4 Analysis of Safety and Other Endpoints

Safety data analysis will be conducted on the Safety Analysis Set. The number and percentage of subjects experiencing at least 1 TEAE will be summarized by treatment as well as the number of events. Tables by relationship to trial drug and by severity will be generated. AEs will be coded using Medical Dictionary for Regulatory Activities terminology.

All laboratory data will be reported with SI units. Laboratory parameters will be summarized using descriptive statistics for absolute values and change from baseline over time, by postdose shifts relative to baseline, and data listings of clinically significant abnormalities/out of the normal range.

Vital signs and ECG data will be summarized by changes-from-baseline values by treatment using descriptive statistics. Clinical noteworthy ECG findings for individual subjects will be listed and summarized as appropriate.

8.5.5 Analysis of Exploratory Endpoint

Methods for the pharmacogenetic analysis will be separately planned and results will be described in a separate report.

8.6 Interim and Additional Planned Analyses

Not applicable.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the site and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP [14], and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained.

A subject information sheet must be prepared in the local language in accordance with ICH GCP [14] and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or a designate will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

After the information is provided by the Investigator, the ICF must be signed and dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IEC for review and opinion. Using the approved revised subject information sheet and other written information, the Investigator will explain the changes to the previous version to each trial subject and obtain new written consent for continued participation in the trial. The subject will be given sufficient time

to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

A separate subject information and ICF will be prepared and signed by the subjects for pharmacogenomic examination.

9.3 Subject Identification and Privacy

A unique number will be assigned to each subject, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. All subject data collected in the trial will be stored under the appropriate subject number. Only the Investigator will be able to link trial data to an individual subject via an identification list kept at the site. For each subject, original medical data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but subject confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

9.4 Emergency Medical Support and Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by Nuvisan GmbH for use during trial participation in order to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, he will answer any questions. Any subsequent action will follow the standard process established for Investigators.

In cases where 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 h contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage will be provided for the trial. Insurance conditions will meet good local standards, as applicable.

9.6 Independent Ethics Committee

Prior to commencement of the trial, this clinical trial protocol will be submitted together with its associated documents (for example, ICF, insurance certificate) to the responsible IEC for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File.

The IEC will document the date at which the favorable opinion or approval was given. A members list of the IEC will be provided. Written evidence of favorable opinion or approval that clearly identifies the clinical trial protocol version and the Subject Information and ICF version reviewed will be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC, before implementation of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (for example, IMP Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Trial Management

10.1 Case Report Form Handling

Refer to the Manual of Operations for eCRF handling guidelines.

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible and timely manner. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to data management contain no mention of any subject names.

The data will be entered into a validated database. Nuvisan GmbH will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Subject Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to ECG recordings, and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site.

10.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years after the end of the trial.

The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines [14], whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH GCP [14] and any other applicable regulations. The site Monitor will perform visits to the trial site at regular intervals.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all IMPs and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report will be written by Nuvisan GmbH following the guidance in ICH Topic E3 [15].

10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoints. The results of this trial 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 trial results.

Posting of data on ClinicalTrials.gov and EU Clinical Trials Register (EudraCT) is planned and will occur 12 months after the last clinic visit of the final trial subject or another appropriate date to meet applicable requirements.

11 References Cited in the Text

1. Gorski JC, Hall SD, Jones DR, et al. Regioselective biotransformation of midazolam by members of the human cytochrome P450 3A (CYP3A) subfamily. Biochem Pharmacol. 1994;47(9):1643-53.
2. Paine MF, Shen DD, Kunze KL, et al. First-pass metabolism of midazolam by the human intestine. Clin Pharmacol Ther. 1996;60(1):14-24.
3. Zhu B, Bush D, Doss GA, et al. Characterization of 1′-hydroxymidazolam glucuronidation in human liver microsomes. Drug Metab Dispos. 2008;36(2):331-8.
4. Juif PE, Boehler M, Donazzolo Y, et al. A pharmacokinetic drug–drug interaction trial between selexipag and midazolam, a CYP3A4 substrate, in healthy male subjects. Eur J Clin Pharmacol. 2017;73:1121-8.
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7. Clinical Drug Interaction Studies - Trial Design, Data Analysis, and Clinical Implications, Guidance for Industry, DRAFT GUIDANCE, U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), October 2017.
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9. EMA Guideline on the investigation of drug interactions, CPMP/EWP/560/95/Rev. 1 Corr. 2**, 21 June 2012.
10. Zdravkovic M, Olsen AK, Christiansen T, et al. A clinical trial investigating the pharmacokinetic interaction between NN703 (tabimorelin), a potential inhibitor of CYP3A4 activity, and midazolam, a CYP3A4 substrate. Eur J Clin Pharmacol. 2003;58: 683-8.
11. Recommendations related to contraception and pregnancy testing clinical trials. Clinical Trial Facilitation Group (CTFG), Heads of Medicines Agencies. 15 September 2014. Downloaded from ‘www.hma.eu’ on 07 November 2017.
12. Paulson SK, Wood-Horrall RN, Hoover R, et al. The Pharmacokinetics of the CYP3A Substrate Midazolam After Steady-state Dosing of Delafloxacin. Clin Therapeut. 2017;39:1182-90.
13. Syed S, Clemens PL, Lathers D, et al. Lack of Effect of Brivanib on the Pharmacokinetics if Midazolam, a CYP2A4 Substrate, Administered Intravenously and Orally in Healthy Participants. J Clin Pharmacol. 2012;52:914-21.
14. ICH Topic E6(R2) Guideline for good clinical practice E6(R2). EMA/CHMP/ICH/135/1995. London, 1 December 2016. 1-70.

15. ICH Topic E3. Structure and Content of Clinical Study Reports. CPMP/ICH/137/95, London July 1996. 1-47.

12 Appendices

Appendix I Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	Phase 1, Open-label, Single Sequence, Two-Period Crossover Trial to Evaluate the Effect of Tepotinib on Cytochrome P450 (CYP) 3A by Investigating the Pharmacokinetics of the CYP3A Substrate Midazolam in Healthy Subjects
EudraCT Number:	2017-005055-92
Clinical Trial Protocol Date / Version:	12 June 2018 / Version 1.0

Protocol Lead:

I approve the design of the clinical trial:

PI

Signature

PI

Date of Signature

Name, academic degree:	PI , PI
Function / Title:	Medical Responsible / PI
Institution:	Merck KGaA
Address:	Frankfurter Strasse 250, 64293 Darmstadt, Germany
Telephone number:	PI
E-mail address:	PI

Signature Page – Principal Investigator

Trial Title	Phase 1, Open-label, Single Sequence, Two-Period Crossover Trial to Evaluate the Effect of Tepotinib on Cytochrome P450 (CYP) 3A by Investigating the Pharmacokinetics of the CYP3A Substrate Midazolam in Healthy Subjects
EudraCT Number	2017-005055-92
Clinical Trial Protocol Date / Version	12 June 2018 / Version 1.0
Center Number	PI
Principal Investigator	PI

I, the undersigned, approve the design of the clinical trial and I understand and will conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PI PI

Signature Date of Signature

Name, academic degree: PI , PI

Function / Title: Principal Investigator

Institution: PI

Address: PI , Germany

Telephone number: PI

Fax number: PI

E-mail address: PI

Sponsor Responsible Persons not Named on the Cover Page

Name:	PI
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Appendix II Planned Numbers of Blood Samples for Clinical Laboratory, PK, and PGx and Total Blood Sampling Volume

Blood Sample	Amount per Sample (mL)	Number of Samples					Total Amount (mL)
		Screening	Period 1	Period 2	End of Trial Visit	Total	
Clinical laboratory tests							
Biochemistry (incl. viral serology, TSH and FSH levels, if applicable)	4.7	1	1 [a]	6 [b]	1	9	42.3
Hematology	2.7	1	1 [a]	5 [b]	1	8	21.6
PK midazolam	2.0		14 [e]	14 [f]		28	56.0
PK tepotinib	2.0			3 [g]		3	6.0
PGx	2.0		2 [h]			2	4.0
Total		**2**	**18**	**28**	**2**	**50**	**129.9**
Note: The number of blood samples may increase above the scheduled number. Blood samples for clinical laboratory follow-up determinations may become necessary. Technical failure of PK/PGx blood drawing may lead the Investigator to decide immediately to repeat a single blood drawing to have a sample. **Maximal blood volume drawn: Estimate per subject in this trial** that will not be exceeded in this planned trial as by experience of the Investigating Institution:							**180**

FSH = follicle stimulating hormone, PGx = pharmacogenetics, PK = pharmacokinetics, TSH = thyroid stimulating hormone.

Clinical laboratory (biochemistry and hematology) blood samples

a Period 1: Day -1 = 1 sample

b Period 2:
Biochemistry: pre-dose on Days 1, 2, 5, 8, 11 and on Day 12 = 6 samples
Hematology: pre-dose on Days 1, 5, 8, 11 and on Day 12 = 5 samples

Midazolam and 1-hydroxamidazolam PK blood samples

e Period 1, Day 1: at pre-dose, 15, 30, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose = 14 samples

f Period 2, Day 11: at pre-dose, 15, 30, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose = 14 samples

Tepotinib and its metabolites PK blood samples

g Period 2: pre-dose on Days 9, 10 and 11 = 3 samples

PGx blood samples

h PGx blood samples of 2 x 2 mL to be drawn on Day 1 of Period 1 at pre-dose = 2 samples.

Appendix III Contraception Guidance

Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered women of childbearing potential

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

     Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
2. Premenarchal
3. Postmenopausal female
   - Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), or who have undergone documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy. If necessary to confirm postmenopausal status, FSH will be re-tested at Screening.
   - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. However, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraceptive Guidance for Women of Childbearing Potential:

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of <1% per year when used consistently and correctly [a].

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation [b]
  • oral
  • intravaginal
  • transdermal

• Progestogen-only hormonal contraception associated with inhibition of ovulation [b]
  • oral
  • injectable

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
• Vasectomized partner (Bilateral vasectomy of the partner is a highly effective contraceptive method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case another highly effective (not hormone based) method of contraception must be utilized during the treatment period and for at least 3 months after the last dose of study treatment