Clinical Trial Protocol

Clinical Trial Protocol Number	MS200095-0032
Title	Phase I, Open-label, Single Sequence, Two-Period Study to Evaluate the Effect of Tepotinib on P-Glycoprotein by Investigating the Pharmacokinetics of the P-Glycoprotein Probe Substrate Dabigatran Etexilate in Healthy Subjects
Phase	I
IND Number	Not applicable
EudraCT Number	2017-004074-34
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	23 April 2018 / Version 3.0 including Amendment 1.0 to Version 1.0 and Amendment 2 to Version 2.0
Replaces Version	6 March 2018 / Version 2.0

- Confidential –

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List of Abbreviations

Abbreviation	Definition of Terms
AE	Adverse event
anti-HCV	Hepatitis C virus antibody
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
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
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero (= dosing time) extrapolated to infinity
AUC_{extra}	The AUC from time t_{last} extrapolated to infinity
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0-\infty}$) x 100
AUC_{τ}	The area under the plasma concentration-time curve (AUC) over the dosing interval from T_1 = 0 h to $T_2 = \tau$ h
beta-HCG	Beta-human chorionic gonadotrophin
bpm	Beats per minute
CI	Confidence Interval
CK MB	Creatinine phosphokinase myocardium/brain type
CL/f	Apparent total body clearance considering the fraction of dose (f) absorbed
CL_{SS}/f	Apparent total body clearance of drug at steady state following oral administration, considering the fraction of dose (f) absorbed.
C_{max}	Maximum plasma concentration observed
$C_{max,SS}$	Maximum plasma concentration observed in steady state

Abbreviation	Definition of Terms
$C_{min,SS}$	Minimum plasma concentration observed in steady state
c-Met	Mesenchymal-epithelial transition factor
CRO	Contract research organization
CV	Coefficient of variation
DDI	Drug-drug interaction
ECG	Electrocardiograms
eGFR	Estimated glomerular filtration rate
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GeoCV	Coefficient of variation of the geometric mean
GeoMean	geometric mean
h	hours
HBsAg	Hepatitis B surface antigen
HCC	Hepatocellular carcinoma
HGF	Hepatocyte growth factor
HIV1/HIV2	Human immunodeficiency virus 1 and 2
IC_{50}	Half maximal inhibitory concentration
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
λ_z	Apparent terminal rate constant

Abbreviation	Definition of Terms
LLOQ	Lower limit of quantification
min	minutes
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for AEs
NSCLC	Non-small cell lung cancer
P-gp	P-glycoprotein
PGx	Pharmacogenetics
PK	Pharmacokinetics
QTcF	Corrected QT interval per Fridericia's formula
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SD	Standard deviation
SS	Steady state
$t_{1/2}$	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
$t_{max,SS}$	Time to reach the maximum plasma concentration in steady state
T/R ratio	Test/Reference ratio
TSH	Thyroid stimulating hormone
TT	Thrombin time
ULN	Upper limit of normal range
V_Z/f	Apparent volume of distribution during the terminal phase

1 Synopsis

Clinical Trial Protocol Number	MS200095-0032
Title	Phase I, Open-label, Single Sequence, Two-Period Study to Evaluate the Effect of Tepotinib on P-Glycoprotein by Investigating the Pharmacokinetics of the P-Glycoprotein Probe Substrate Dabigatran Etexilate in Healthy Subjects
Trial Phase	I
IND Number	Not applicable
FDA covered trial	No
EudraCT Number	2017-004074-34
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)	Q1-Q2 2018
Trial Registry	EU Clinical Trials Register, ClinicalTrials.gov

Primary Objective:

- To investigate the effect of tepotinib on the primary pharmacokinetic (PK) endpoints of dabigatran following oral administration of the P-gp probe substrate dabigatran etexilate after multiple dose administration of tepotinib in healthy subjects.

Secondary Objectives:

- To investigate the PK effect of tepotinib on the secondary PK endpoints of dabigatran following oral administration of dabigatran etexilate
- To assess the safety and tolerability of tepotinib alone and upon co-administration of dabigatran etexilate.

Exploratory Objectives:

- To investigate the multiple dose PK of tepotinib and its metabolites (MSC2571109A and MSC2571107A)

- To explore the effect of pharmacogenetics (PGx) and variations of associated genes on the PK profile of dabigatran and/or tepotinib (if applicable; participation is optional).

Methodology: Open-label, single-sequence, 2-period drug-interaction trial.

The study will be divided into 2 periods: Period 1 will evaluate the PK of dabigatran after single dose administration of 75 mg dabigatran etexilate (Pradaxa®, given as mesilate). In Period 2, tepotinib will be administered for 7 days. On Day 8, dabigatran etexilate and tepotinib will be co-administered and PK of total dabigatran (unconjugated plus conjugated) will be evaluated over 72 hours (h) post-dose.

The subjects will be admitted to the study site on Day -1. They will be resident at the study site under medical supervision from Days -1 of Period 1 until Day 11 of Period 2. After the first 6 subjects completed administration in Period 2, safety and PK data will be reviewed by the responsible functional representatives.

Planned number of subjects: Overall, 20 healthy subjects are planned to be included.

Primary endpoint:

- PK profile of dabigatran in terms of area under the concentration-time curve (AUC) from time zero to the last sampling time (AUC_{0-t}), AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}) of total dabigatran (unconjugated plus conjugated) at Day 1 of Period 1 and Day 8 of Period 2 from time zero to 72 h post-dose.

Secondary endpoints:

- PK profile of total dabigatran (unconjugated plus conjugated) in terms of time of the maximum drug concentration (t_{max}), terminal half-life ($t_{1/2}$), percentage of $AUC_{0-\infty}$ obtained by extrapolation ($AUC_{extra\%}$), apparent total body clearance (CL/f), apparent volume of distribution during terminal phase (V_Z/f) at Day 1 of Period 1 and Day 8 of Period 2 from time zero to 72 h post-dose.
- Occurrence of treatment emergent adverse events (TEAEs, incidence, frequency, intensity and causality), occurrence of changes in safety laboratory assessments, 12-lead electrocardiograms (ECGs) and vital signs in subjects receiving tepotinib alone and together with dabigatran etexilate assessed from Day -1 of Period 1 until the End of Trial Visit.

Exploratory endpoints:

- PK profile of tepotinib and its metabolites MSC2571109A and MSC2571107A in terms of AUC over the dosing interval (AUC_{τ}), C_{max} at steady state ($C_{max,SS}$), minimum concentration at steady state ($C_{min,SS}$), t_{max} at steady state ($t_{max,SS}$), CL/f at steady state (CL_{SS}/f) (parent drug only), and $t_{1/2}$ if appropriate
- Genetic variants and mutations in genes that potentially influence the PK of tepotinib and/or dabigatran.

Pharmacokinetics:

Blood samples for determination of plasma concentrations of total dabigatran will be taken at pre-dose until 72 h after dosing on Day 1 of Period 1 and Day 8 of Period 2.

Blood samples for determination of plasma concentrations of tepotinib and its metabolites MSC2571109A and MSC2571107A will be taken pre-dose on Day 6 and at pre-dose until 24 h after dosing on Day 7 of Period 2.

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.

Dabigatran etexilate 75 mg hard capsules, provided as mesilate salt.

Period 1: A single oral dose of 75 mg dabigatran etexilate will be administered together with 240 mL of water in the morning of Day 1 of Period 1, 30 minutes (min) after start of a standardized breakfast (which must be consumed completely within 25 min).

Period 2: Single doses of 500 mg tepotinib will be administered together with 240 mL of water in the morning of Days 1 to 7 of Period 2, 30 min after start of a standard breakfast (which must be consumed completely within 25 min).

On Day 8 of Period 2, 500 mg tepotinib and 75 mg dabigatran etexilate will be administered together with 240 mL of water 30 min after start of the breakfast (which must be consumed completely within 25 min).

Reference therapy: dose/mode of administration/dosing schedule: Not applicable

Planned trial and treatment duration per subject: About 7 weeks from Screening to End of Trial Visit, treatment on Day 1 of Period 1 and Days 1 to 8 of Period 2.

Statistical methods: A general linear model with TREATMENT and SUBJECT as fixed effects will be applied to log-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of dabigatran (measured as total dabigatran) based on the PK analysis set. Treatment differences on the log scale of dabigatran with tepotinib vs dabigatran 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.

Individual estimates of relative bioavailability of dabigatran will be calculated for each subject.

Summary statistics will be provided for all parameters.

Table 1 Schedule of Assessments - Period 1 (Administration of Dabigatran Etexilate alone)

Assessment/ Activity	Screening	Study Period 1				
	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3	Day 4 [f]
Written informed consent [a]	X					
Hospitalization		X	X	X	X	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 [i]
12-lead ECG	X	X	X [b]			X [i]
Clinical laboratory (hematology, biochemistry, urinalysis)	X	X				X [i]
Coagulation	X		X [g]	X [g]		
Test for occult blood in feces	X					
Serology (HIV/hepatitis)	X					
Alcohol breath test	X	X				
Pregnancy test [c]	X	X				
Drugs of abuse	X	X				
Administration of dabigatran etexilate			X [d]			
PK blood sampling total dabigatran (unconjugated and conjugated)			X [e]	X [e]	X [e]	X [e]
PGx blood sampling (optional)			X [h]			
Adverse event (AE) monitoring	X ←----------→ X					
Prior and concomitant medication	X ←----------→ X					

ECG = electrocardiogram, HIV = human immunodeficiency virus, PK = pharmacokinetics, PGx = pharmacogenetics

Adverse events and concomitant medication will be assessed from screening throughout the whole study until End of Trial Visit.

a Written informed consent must be obtained prior to any screening activities.

b Vital signs (blood pressure and pulse rate) and ECG will be measured after at least 5 min rest at pre-dose (within 60 min prior to dosing).

c Women of nonchildbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Day -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, or bilateral oophorectomy or bilateral salpingecectomy.**

d A standardized breakfast will be administered 30 min prior to dabigatran etexilate administration and must be consumed completely within 25 min. 30 min after start of the breakfast, 75 mg dabigatran etexilate will be taken together with 240 mL of water.

e PK blood samples for determination of total dabigatran will be collected at pre-dose (within 60 min prior to dosing) and 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose.

f Day 4 measurements (72 h measurements) may be performed (within 60 min, PK sampling within 30 min) prior to tepotinib dosing on Day 1 of Period 2.

g Coagulation parameters will be determined pre-dose and 4 h post-dose on Day 1 and 24 h post-dose on Day 2.

h PGx blood samples of 2 x 2 mL (optional) to be drawn at pre-dose Day 1.

i Only to be performed in case of a prolonged interval of more than 7 days between Period 1 (Day 4) and Period 2 (Day 1)

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

Assessment/ Activity	Study Period 2							End of Trial Visit [a]
	Day 1	Day 2 - 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 15 (±1)
Hospitalization	X	X	X	X	X	X	X [j]	
Ambulatory Visits								X
Physical examination								X
Vital signs (blood pressure, pulse rate, body temperature)	X [b]	X [b]	X [b]	X [c]	X [c]	X [c]	X [c]	X
12-lead ECG	X [d]	X [d]	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 [e]	X
Coagulation	X [i]			X [i]	X [i]			X
Serum pregnancy test								X
Administration of tepotinib	X [f]	X [f]	X [f]	X [f]				
Administration of dabigatran etexilate				X [f]				
PK blood sampling (tepotinib and its metabolites)		X [g]	X [g]	X [g]				
PK blood sampling total dabigatran (unconjugated and conjugated)				X [h]	X [h]	X [h]	X [h]	
Adverse events	←----------						----------→	X
Concomitant medication	←----------						----------→	X

ECG = electrocardiogram, PK = pharmacokinetics

Adverse events and concomitant medication will be assessed from screening throughout the whole study until End of trial Visit.

a 7 ± 1 days after last drug administration in Period 2 (Day 15).

b 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.

c Vital signs will be measured after at least 5 min rest before (within 60 min prior to dosing) as well as 4, 8, 24, 48 and 72 h after the combined dabigatran etexilate and tepotinib administration.

d After at least 5 min rest before each time point 12-lead ECGs will be recorded and printed out. Days 1 to 7 within 60 min prior to dosing and 6 h after each tepotinib administration. Day 8 within 60 min prior to dosing, as well as 4, 8, 24, 48 and 72 h after the combined dabigatran etexilate and tepotinib administration.

e Laboratory assessments will be performed on Day 1, 2, 7 and 8 pre-dose, and on Day 11.

f On Days 1 to 7, 500 mg tepotinib will be administered together with 240 mL of water 30 min after start of a standardized breakfast (completely consumed within 25 min).
On Day 8, a standardized breakfast will be administered 30 min prior to tepotinib and dabigatran etexilate administration and must be consumed completely within 25 min. 30 min after start of the breakfast, 500 mg tepotinib and 75 mg dabigatran etexilate will be taken together with 240 mL of water.

g PK blood samples for determination of tepotinib and its metabolites will be collected on Day 6 at pre-dose (within 60 min prior to administration), on Day 7 at pre-dose (within 60 min prior to administration) and 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12 and 24 h post-dose prior to dosing on Day 8 (within 60 min prior to administration).

h PK blood samples for determination of total dabigatran will be collected at pre-dose (within 60 min prior to administration) and 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose.

i Coagulation parameters: Pre-dose on Day 1, pre-dose and 4 h post-dose on Day 8, and 24 h after the last dose on Day 9.

j Discharge after completion of all 72 h post-dose activities.

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.

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.

The trial will appear in the following clinical trial registries: EU Clinical Trials Register, ClinicalTrials.gov.

Nuvisan GmbH, Wegenerstrasse 13, 89231 Neu-Ulm, Germany, a contract research organization, 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 a separate Monitoring and Data Management Plans which will be prepared by Nuvisan GmbH.

The Sponsor will provide the Investigational Medicinal Products (IMPs) tepotinib and dabigatran etexilate. 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. 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 I or Phase Ib/II 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.

Based on the currently available nonclinical as well as clinical safety data, short term multi-day dosing of tepotinib in healthy subjects is reasonable considering the preclinical safety pharmacology and toxicity data, and the absence of genotoxicity, in conjunction with the predicted exposures at steady state after multiple dosing of 500 mg/day in healthy subjects, and the clinical experience in oncology patient populations, and implementing close medical monitoring of safety and tolerability. It is recognized that healthy subjects will not get benefit by participating in this study. Considering the current clinical exposure after the recommended Phase II dose (RP2D) of 500 mg tepotinib once daily, and the non-clinical observation that tepotinib was identified as a substrate of the efflux transporter P-glycoprotein (P-gp), as well as an inhibitor of P-gp (half maximal inhibitory concentration, IC_{50} ~ 0.4 µM), the need to investigate tepotinib clinically for any potential to cause P-gp-mediated drug-drug interaction (DDI) was triggered. This study will generate human data about the potential of DDI of tepotinib as perpetrator on the pharmacokinetics (PK) of the P-gp probe substrate dabigatran etexilate. Drug interaction with P-gp is of importance in the context of concomitant medication in tumor patients treated with tepotinib. This is basic information to safeguard the further clinical development of tepotinib in patients suffering from malignancies such as HCC and NSCLC. Healthy subjects (n = 9) well tolerated a single dose or 3 single doses of tepotinib (different dose levels up to 500 mg single dose). All treatment emergent adverse events (TEAEs) were mild to moderate, except one Grade 3 asymptomatic transient lipase elevation in 1 subject. TEAEs 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 identified risks for subjects administered tepotinib. These elevations were observed in 5 of 79 healthy subjects exposed to tepotinib and were mild to moderate in severity (exception: one Grade 3 lipase elevation) and without apparent dose dependency. All increases of serum amylase/lipase were asymptomatic and not associated with a pancreatitis.

Subjects enrolled in this study might be exposed to a risk, including pancreatic enzyme elevation. However, inclusion of healthy subjects is justified when the administration of tepotinib is limited to a single dose or short term multiple administrations that will be given under close monitoring conditions to reduce the risk for untoward effects.

Knowing that the inhibition of c-Met shows teratogenic effects in knockout mice, stringent criteria are applied to ensure exclusion of women of childbearing potential in this study. Only healthy women that are known to be postmenopausal or surgically sterile (ie due to hysterectomy, or bilateral oophorectomy, or bilateral salpingectomy) will be enrolled in this study (for details see Section 5, Investigational Plan). Male subjects will be required to take precautions regarding female partners.

In this drug-drug interaction (DDI) study tepotinib will be administered the first time in multiple doses of the RP2D of 500 mg to healthy subjects. To achieve steady-state levels and robustly evaluate its potential as perpetrator on the P-gp probe substrate dabigatran etexilate, further risk mitigation measures are incorporated. A close safety monitoring will be implemented in this healthy subject study. Subjects will be admitted to the study site and remain resident there for at least 72 h after dabigatran etexilate administration in Period 1 and until at least 72 h after last administration in Period 2, to allow continuous safety monitoring of the clinical laboratory parameters, ECG, and vital signs. After the first 6 subjects completed administration in Period 2, safety and PK data will be reviewed by the responsible functional representatives. In addition, frequent monitoring of subjects is ensured by subsequent Ambulant Visits and by choosing a contract research organization (CRO) experienced in the conduct of clinical pharmacology trials.

The 500 mg tepotinib single oral dose has been studied 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 500mg tepotinib in crossover) and was well tolerated. A dose of 500 mg once daily is the RP2D. Refer to the Investigator's Brochure for further information about the nonclinical and clinical programs and the implemented Guidance for the Investigator.

Dabigatran

Dabigatran, the active principle of the prodrug dabigatran etexilate, which is formulated as mesilate salt in Pradaxa® (DE; Pradaxa®, Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany), is an oral, direct thrombin inhibitor with potent antithrombotic effects. After oral administration, the prodrug dabigatran etexilate, which is pharmacologically inactive, is rapidly absorbed and nearly completely converted to the pharmacologically active dabigatran by esterase-catalyzed hydrolysis in plasma and in the liver. The pro-drug dabigatran etexilate but not dabigatran is a substrate of the efflux transporter P-gp. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran inhibits free thrombin, as well as fibrin-bound thrombin, and thrombin-induced platelet aggregation.

After oral administration of dabigatran etexilate in healthy subjects, the PK profile of dabigatran will be determined as total dabigatran (unconjugated plus conjugated) in plasma. It is

characterized by a rapid increase in plasma concentration with C_{max} attained within 0.5 and 2.0 h post administration. The absolute bioavailability of dabigatran following oral administration of Pradaxa® was approximately 6.5%. Dabigatran is subject to conjugation forming pharmacologically active acylglucuronides, but is eliminated primarily in the unchanged form in the urine (85%). Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations of dabigatran by 2 h. C_{max} and AUC were dose proportional. Plasma concentrations of dabigatran showed a bi-exponential decline with a terminal half-life of 8.4 h (coefficient of variation for the geometric mean, GeoCV = 12.0%) in healthy subjects [1].

Since dabigatran etexilate has been previously studied in healthy subjects in single dose as well as in multiple dose settings with up to 400 mg 3 times daily [2], and since the thrombin inhibitory effects in the current study will be closely monitored, the 2 single dose administrations of 75 mg dabigatran etexilate in healthy subjects is reasonable and considered safe.

Dabigatran etexilate (Pradaxa®, provided as mesilate) is currently approved in the USA, European Union, Canada and Japan for the prevention of stroke and systemic emboli in patients with non-valvular atrial fibrillation. Furthermore, Pradaxa® is also approved for the primary prevention of thromboembolism in adults after elective total hip or knee replacement surgery in more than 75 countries, including Europe and Canada [1].

For reference see Summary of Product Characteristics Pradaxa® 75 mg hard capsules [2].

3.1 Trial Rationale

Tepotinib was identified as a substrate of the efflux transporter P-glycoprotein (P-gp), as well as an inhibitor of P-gp. Nonclinical data indicate that tepotinib inhibits P-gp with IC_{50} values of about 0.4 µM, which is several folds lower than the plasma concentrations, and magnitudes lower than the expected intestinal concentrations. This represents potential to cause P-gp-mediated DDI considering the current clinical exposure after the RP2D of 500 mg tepotinib once daily.

This study will investigate the effect of tepotinib on P-gp by measurement of the PK of the P-gp probe substrate dabigatran etexilate. The study design is based on the regulatory guidance of the Food and Drug Administration (FDA) [4] and of the European Medicines Agency (EMA) [5]. Per guidance from both authorities, dabigatran etexilate is presently recommended as probe for P-gp inhibition.

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP 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 tepotinib on the primary pharmacokinetic (PK) endpoints of dabigatran following oral administration of the P-gp probe substrate dabigatran etexilate after multiple dose administration of tepotinib in healthy subjects.

4.2 Secondary Objectives

- To investigate the PK effect of tepotinib on the secondary PK endpoints of dabigatran following oral administration of dabigatran etexilate
- To assess the safety and tolerability of tepotinib alone and upon co-administration of dabigatran etexilate.

4.3 Exploratory Objectives

- To investigate the multiple dose PK of tepotinib and its metabolites (MSC2571109A and MSC2571107A).
- To explore the effect of pharmacogenetics (PGx) and variations of associated genes on the PK profile of dabigatran and/or tepotinib (if applicable; participation is optional).

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a Phase I, open-label, single-sequence, 2-period, crossover study to investigate the effect of tepotinib on the PK of the P-gp probe substrate dabigatran etexilate determined from concentrations of total dabigatran (unconjugated plus conjugated) in 20 healthy subjects. A flowchart summarizing the overall study design is shown in Figure 1.

The study will be divided into 2 periods: Period 1 will evaluate the PK of total dabigatran after single dose administration of 75 mg dabigatran etexilate (Pradaxa®, given as mesilate) over a sampling period 72 h post-dose, which covers > 5 times the geometric mean $t_{1/2}$ of 8.4 h [1]. In Period 2, tepotinib will be administered for 7 days and the PK of tepotinib and its metabolites will be evaluated on Day 7. On Day 8, dabigatran etexilate and tepotinib will be co-administered and the PK of total dabigatran will be evaluated again over 72 h post dose. Dosing will be performed 30 min after start of a standardized breakfast (completely consumed within 25 min). Considering that in Period 2 dabigatran etexilate will be administered on Day 8 (= 168 h), the resulting interval between the 2 administrations of dabigatran etexilate will be 240 h (= 72 h [Day 1 to Day 4 of Period 1] + 168 h [Day 1 to Day 8 of Period 2]) or 10 days (see Figure 1).

A Screening period will occur from Day -28 to Day -2.

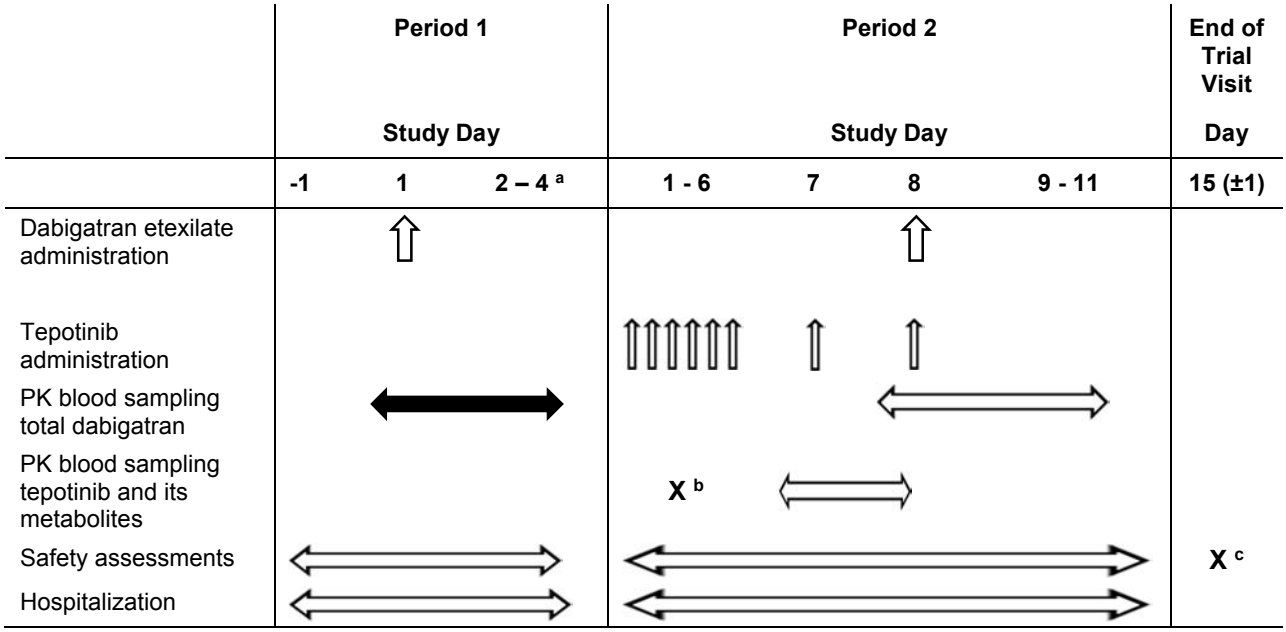
The subjects will be admitted to the study site on Day -1. They will be resident at the study site under medical supervision from Day -1 of Period 1 until Day 11 of Period 2.

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

Serial blood samples for PK assessments will be collected for 72 h after administration of 75 mg dabigatran etexilate (Pradaxa®, given as mesilate) in Periods 1 and 2. Tepotinib PK will be assessed in Period 2.

The End of Trial Visit is planned 7 days (± 1 day) after the last drug administration in Period 2 (Day 15 ± 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.

Figure 1 **Study Design**



a Day 4 of Period 1 = Day 1 of Period 2.
b PK sample prior to dosing on Day 6.
c End of Trial Visit safety assessments

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

Since to date tepotinib 500 mg was administered to healthy subjects only as single doses (study EMR200095-007, single dose; study MS200095-0012, 2 single doses), the safety and tolerability as well as the PK of multiple dose tepotinib (up to Day 8 inclusive in Period 2) will first be assessed in a subgroup of 6 subjects, followed by group(s) of the remaining subjects. Dosing of the subsequent group(s) will only be started if the safety and tolerability of multiple dosing of tepotinib was assessed as reasonable and no stopping rules applied. The decision will be documented and will be filed in the trial documentation files.

Stopping rules of the study:

- 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 scientific reason for the SAE other than the study drug.

- The trial will be permanently stopped if 4 or more subjects were withdrawn from the study 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 of similar nature occur in at least 50% of subjects which are considered related to the study drug by the Investigator.

Primary endpoint:

- PK profile of dabigatran in terms of AUC from time zero to the last sampling time (AUC_{0-t}), AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}) of total dabigatran (unconjugated plus conjugated) at Day 1 of Period 1 and Day 8 of Period 2 from time zero to 72 h post-dose.

Secondary endpoints:

- PK profile of total dabigatran (unconjugated plus conjugated) in terms of time of the maximum drug concentration (t_{max}), terminal half-life ($t_{1/2}$), percentage of $AUC_{0-\infty}$ obtained by extrapolation ($AUC_{extra\%}$), apparent total body clearance (CL/f), apparent volume of distribution during terminal phase (V_Z/f) at Day 1 of Period 1 and Day 8 of Period 2 from time zero to 72 h post-dose.
- Occurrence of TEAEs (incidence, frequency, intensity and causality), occurrence of changes in safety laboratory assessments, 12-lead ECGs and vital signs in subjects receiving tepotinib alone and together with dabigatran etexilate assessed from Day -1 of Period 1 until the End of Trial Visit.

Exploratory endpoints:

- PK profile of tepotinib and its metabolites MSC2571109A and MSC2571107A in terms of AUC over the dosing interval (AUC_{τ}), C_{max} at steady state ($C_{max,SS}$), minimum concentration at steady state ($C_{min,SS}$), t_{max} at steady state ($t_{max,SS}$), CL/f at steady state (CL_{SS}/f) (parent drug only), and $t_{1/2}$, if appropriate.
- Genetic variants and mutations in genes that potentially influence the PK of tepotinib and/or dabigatran.

  Note: Pharmacogenetic sample collection is optional. 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 study design and endpoints are typical for a drug interaction study of this type. The effect of tepotinib on P-gp by measurement of the PK of the P-gp substrate dabigatran etexilate will be investigated. Thus, dabigatran etexilate will be administered as a single dose once alone and once at steady state of tepotinib.

The study will utilize a single sequence crossover design with both treatments applied to the same subject. No carryover of dabigatran is expected between the first and second dose due to sufficient wash-out time. Moreover, the total dabigatran concentration should be below the quantification limit when starting the multiple dosing of tepotinib (period of 72 h, considering a mean elimination $t_{1/2}$ [GeoMean] of about 8.4 h for dabigatran in healthy adult subjects [1]). It is anticipated that a possible period effect is very small and negligible compared to relevant treatment effects. The potential drug-drug interaction investigated in this study is expected to occur mainly in the intestine, where the P-gp mediated efflux of dabigatran etexilate could be inhibited by tepotinib. However, the effect on dabigatran will only be measured indirectly by the concentration-time profile of total dabigatran (unconjugated plus conjugated) in plasma.

Healthy subjects will be included in the study to minimize variability, which is expected to be higher in a patient population. Non-clinical safety investigations did not reveal a genotoxicity potential or other findings with relevance for human use. Therefore, it is reasonable that tepotinib can be administered to healthy subjects such as in this study in which careful safety monitoring is conducted. Knowing that tepotinib shows teratogenic effects, only healthy women that are postmenopausal or surgically sterile (ie, due to hysterectomy, or bilateral oophorectomy, or bilateral salpingectomy) will be enrolled in this study and male subjects must take precautions with female partners.

The study will be performed as an open-label study. This is not considered to introduce bias, because the main assessment criteria are based on PK parameters. For risk mitigation, an initial group of 6 subjects will be dosed first. Only if tepotinib multiple dosing was considered reasonable safe and tolerated by these subjects, the remaining group(s) will be dosed. A close monitoring of the safety laboratory parameters, ECG, and vital signs will be performed in all subjects. Subjects will be admitted to the study site and remain resident there until at least 72 h after the last administration, to allow continuous safety monitoring. A hospitalization period of 72 h after the last dose of tepotinib is regarded as sufficient to ensure close safety monitoring of the subjects during the initial elimination of about 70 - 80%. The end of trial visit is set at 7 (± 1) days after last dose of tepotinib, hence covering full elimination of tepotinib. 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.

5.2.3 Justification for Dose

Up to 2 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 (refer to Section 3). Also, multiple doses of tepotinib up to 1400 mg daily have been explored in few patients and were well tolerated. The tepotinib dose of 500 mg is the RP2D for the treatment of human malignant tumors. Tepotinib will be administered for 8 days. Considering an apparent elimination $t_{1/2}$ of about 30 h, tepotinib should be at steady state on Day 7. This is the first time that multiple doses of tepotinib are administered to healthy subjects.

Dabigatran will be administered as a single dose of a 75 mg dabigatran etexilate (Pradaxa®, given as mesilate) film-coated tablet on Day 1 of Period 1 and Day 8 of Period 2.

The recommended daily therapeutic dose of dabigatran etexilate is 220 mg once daily for the prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery, and 300 mg taken as one 150 mg capsule twice daily for treatment of deep vein thrombosis and pulmonary embolism and prevention of recurrent deep vein thrombosis and pulmonary embolism in adults. A dose of 150 mg dabigatran etexilate was used in several DDI studies investigating the effect on P-gp and proved to be sensitive enough to detect such an effect [6] [7]. The fact that only the pro-drug dabigatran etexilate is a substrate of the efflux transporter P-gp, but not the pharmacologically active dabigatran or its acylglucuronides, renders dabigatran etexilate very specific and sensitive to intestinal inhibition of P-gp efflux transport.

Factors which may increase the hemorrhagic risk (refer to the Summary of product characteristics [2]) will be excluded in this study. Recommended doses of dabigatran etexilate are up to 300 mg daily. In this study, a single dose of 75 mg dabigatran etexilate will be administered, which will minimize the hemorrhagic risk but is high enough to result in measurable plasma concentration time profiles. Therefore, safety concern due to higher exposure of dabigatran, should pronounced DDI occur, and is not expected after a single dose of 75 mg dabigatran etexilate.

As dabigatran reduces the thrombin activity and therefore could prolong the thrombin time (TT) and activated partial thromboplastin time (aPTT), these coagulation parameters and the Hemoclot Thrombin Inhibitor (Anti-Factor II) will be measured. In case of dabigatran-induced bleeding, subjects will be referred to a collaborating clinic for treatment with the dabigatran antidote idarucizumab, as appropriate.

5.2.4 Rationale for Endpoints

The peak exposure (C_{max}) and extent (AUC) of exposure of total dabigatran (unconjugated plus conjugated) after single dose administration are considered adequate endpoints to evaluate the effect of tepotinib on the PK on the P-gp probe substrate dabigatran etexilate. 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 persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments, the Investigator will ensure that the subject or the subject's legal representative 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 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, or bilateral oophorectomy, or bilateral salpingectomy
4. A male participant must agree to use and to have his female partner of childbearing potential to use highly effective method of contraception (ie methods with a failure rate of less than 1% per year) as detailed in the Clinical Trial Facilitation Group (CTFG) recommendations [8] during the period of participation in the study and for at least 3 months after the last investigational medicinal product (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 study evaluation, procedures, or completion (at Screening and Day -1)
6. Subject must have given written informed consent before any study-related activities are carried out and must be able to understand the full nature and purpose of the study, including possible risks and adverse effects
7. All values for hematology, coagulation, and biochemistry tests of blood and urinalysis within the normal range (at Screening). Minor (solitary) non-clinically relevant deviation(s) are allowed as judged by the Investigator; however, amylase, lipase and alanine-amino-transferase [ALT] or aspartate-amino-transferase [AST] values should not exceed the upper limit of normal (ULN).

5.3.2 Exclusion Criteria

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

1. Participation in the treatment phase of a clinical study within 60 days or 5 half-lives after last dosing of the previous study drug, whatever is longer, before administration of study drug within this study
2. Whole blood donation or loss of > 450 mL within 60 days before administration of study drug
3. Any surgical or medical condition, including findings in the medical history or in the prestudy 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 study or that could interfere with the study objectives, conduct, or evaluation
4. Supine systolic blood pressure (SBP) > 140 mmHg or < 90 mmHg, diastolic blood pressure (DBP) > 90 or < 50 mmHg, and pulse rate > 90 or < 50 bpm 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 (at Screening)
7. Subjects with gall bladder removal or other relevant surgery of gastrointestinal tract
8. History of any malignancy except for adequately treated superficial basal cell carcinoma
9. History of epilepsy
10. Ascertained or presumptive allergy/hypersensitivity to the active drug substance and/or excipients; history of anaphylaxis to drugs or serious allergic reactions leading to hospitalization or any other allergy reaction in general, which the Investigator considers may affect the safety of the subject and/or outcome of the study
11. Subjects who in the Investigator's judgment were perceived as having an increased risk of bleeding, for example because of:
    - Hemorrhagic disorders or bleeding diathesis
    - Occult blood in feces
    - Trauma or surgery within the last month or if an excessive risk of bleeding persisted after these events
    - History of arteriovenous malformation or aneurysm
    - History of gastroduodenal ulcer disease, gastrointestinal hemorrhage, and hemorrhoids
    - History of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intraarticular bleeding

- Use of drugs that may have interfered with hemostasis during trial conduct (eg acetylic salicylic acid or other non-steroidal anti-inflammatory drugs) within 14 days or 5 half-lives after last dosing, whatever is longer, prior to start of dosing or during the trial

12. Positive screen for alcohol or drugs of abuse (at Screening and Day -1)
13. 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)
14. Excessive consumption of xanthine-containing food or beverages (> 5 cups of coffee or equivalent a day) or inability to stop consuming caffeine, from 48 h before study drug administration until collection of last PK sample in each period (at Screening and Day -1)
15. Receipt of any prescription or nonprescription medication within 14 days or 5 half-lives, whatever is longer, before study drug administration (apart from paracetamol up to 1500 mg per day, as judged appropriate by the Investigator)
16. Smoker (cigarettes, pipes, cigars, or others) or former smoker who stopped smoking less than 6 months before the time of the Screening Visit
17. Intake of grapefruit, Seville orange, cranberry or juices of these 3 fruits, or St. John's Wort, from 14 days prior to Day -1
18. Inability to communicate or cooperate with the Investigator (eg, language problem, illiteracy, poor mental status) or to comply with the requirements of the entire study, including dietary restrictions
19. Other factors, which in the opinion of the Investigator may interfere with study conduct (at Screening and Day -1 of first Period only)
20. Legal incapacity or limited legal capacity
21. Subjects kept in detention.

5.4 Criteria for Initiation of Trial Treatment

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

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 study assessments).

Withdrawal of a subject from study drug due to any of the above reasons means that this subject prematurely discontinues the study, 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).

If the number of evaluable subjects decreased below 16 a discussion should occur between the Investigator and the Sponsor regarding whether a replacement may be considered.

5.5.2 Withdrawal from the Trial

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

- Subject withdrew consent
- Subject lost to Follow-up
- Participation in another clinical study
- Relevant adverse events (AEs) occur that do not justify the subject's continuation in the study
- 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 study drug 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 upper limit of normal range (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
- Coagulation tests that may be associated with an increased risk of bleeding except for thrombin inhibitory effects expected due to dabigatran but not exceeding 3-fold prolongation in the aPTT upper limit of normal at peak.

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 eCRF section must be completed.

Subjects who withdraw from the trial prior to the first administration of IMPs, or for any reason do not have a full PK dataset may be replaced. A discussion should occur between the Investigator and the Sponsor regarding whether a replacement may be considered.

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 IMPs. 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 IEC will be informed about the discontinuation of the trial in accordance with applicable regulations.

5.7 Definition of End of Trial

The end of the 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 study).

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 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 hydrate, is supplied as 500 mg (oblong, light yellow) film-coated tablets (Tablet Formulation 2, TF2) for oral administration.

  The percentage of active ingredient is approximately 50%. Tepotinib 500 mg film-coated tablets 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 blisters and should be stored at or below 25°C.

- Dabigatran etexilate: Commercially available dabigatran etexilate ie Pradaxa® (provided as mesilate salt) will be used. Each Pradaxa® hard capsule contains 86.48 mg dabigatran etexilate mesilate equivalent to 75 mg of the prodrug dabigatran etexilate.

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): Dabigatran Etexilate alone

In the morning of Day 1 of Period 1, a single oral dose of 75 mg dabigatran etexilate capsule will be administered in a fed state.

A standardized breakfast (see below) will be administered 30 min prior to dabigatran etexilate administration and must be consumed completely within 25 min. 30 min after start of the breakfast, the 75 mg dabigatran etexilate capsule will be taken together with 240 mL of water.

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 are allowed to leave the bed without undue physical stress/activity.

Standardized meals will be served 4 h (lunch), 8 h (snack) and 10 h (dinner) after administration of dabigatran etexilate; thereafter, meals will be served at customary times during the inpatient period.

Treatment B (Period 2): Tepotinib and Dabigatran Etexilate

On Days 1 to 7 of Period 2, 500 mg tepotinib will be administered together with 240 mL of water after a standard breakfast (about 30 min after start of breakfast). A standardized breakfast must be consumed completely within 25 min.

On Day 8 of Period 2, a single dose of 75 mg dabigatran etexilate and 500 mg tepotinib will be administered concomitantly in a fed state with 240 mL water. A standardized breakfast will be administered 30 min prior to tepotinib and dabigatran etexilate dosing and must be consumed completely within 25 min. 30 min after start of the breakfast, 500 mg tepotinib and 75 mg dabigatran etexilate will be administered together with 240 mL of water.

The minimum washout period after administration of dabigatran etexilate as mesilate in Period 1 is at least 72 h (Day 4) from dosing on Day 1 of Period 1 to prevent PK carryover effects between periods. Considering that in Period 2 dabigatran etexilate will be administered on Day 8 (= 168 h) of Period 2, the resulting interval between the 2 administrations of dabigatran etexilate will be 240 h (= 72 h [Day 1 to Day 4 of Period 1] + 168 h [Day 1 to Day 8 of Period 2]) or 10 days.

On Days 7 and 8 of Period 2, subjects will stay in a semi-recumbent position for 4 h post-dose, except for use of the toilet, when the subjects will be allowed to leave the bed without undue physical stress/activity.

Standardized meals will be served 4 h (lunch), 8 h (snack) and 10 h (dinner) after dosing on Days 7 and 8; other meals will be served at customary times during the inpatient period.

6.3 Assignment to Treatment Groups

Not applicable.

6.4 Noninvestigational 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's welfare and 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 2 weeks or 5 half-lives, whichever is longer, prior to the first IMPs 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 and will be reminded regularly.

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

- Drug administration of dabigatran etexilate as well as tepotinib will be performed after intake of a standardized breakfast. Subjects will be fasting the 10 hours before intake of the breakfast
- Drinking is not allowed 1 h after administration of dabigatran etexilate or tepotinib
- Chewing gum is not allowed during the PK profile days.

Throughout the study, the following restrictions must be met:

- No smoking or use of tobacco products
- No alcohol intake
- No intake of food or beverages other than that provided to the subjects by the CRO during the inpatient period
- No intake of caffeine- and xanthine-containing food and beverages (eg coffee, black or green tea, chocolate or chocolate-containing food or beverages) 48 h before first administration of study drug until collection of last PK sample in 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 until final examination.
- No intake of concomitant medication within 14 days before first administration of study 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 before first administration of study drug until final examination.
- No exhausting physical activities (body building, sports) from at least 72 h before the first administration of study drug until the final examination.
- No sun baths, solarium or sauna at least 12 h before first administration of study 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.

Dabigatran etexilate 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 the interaction drug will be supplied in ready to use oral formulations. The responsible pharmacist will dispense the necessary amount of the IMP. Detailed guidance will be provided in an IMP handling manual.

The IMPs supplies will be recorded in an IMPs 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 IMPs

should not be used until authorization has been received from the Sponsor. The preparation, handling and storage of the IMPs will be documented.

Detailed recommendations for the use and storage of dabigatran etexilate are described in the Summary of Product Characteristics.

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 IMPs accountability, including reconciliation of drugs and maintenance of records. Drug accountability will also be confirmed by the study monitor.

- Upon receipt of IMP, 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 and in the defined temperature range
  - 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 trial 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.

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

Blinding is not applicable as this is a single arm open-label trial.

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.

Antidote in case of unexpected bleeding risk for the reversal of anticoagulant effects of dabigatran etexilate:

- Idarucizumab (Praxbind®) 2.5 g/50 mL solution for injection/infusion.

Praxbind® is a specific reversal agent for dabigatran and is indicated in adult patients treated with Pradaxa® (dabigatran etexilate) when rapid reversal of its anticoagulant effects is required. The recommended dose of Praxbind® is 5 g (2 x 2.5 g/50 mL). The administration is restricted to hospital use only. An administration of a second 5 g dose of Praxbind® may be considered. Relevant coagulation parameters are aPTT, diluted TT or Hemoclot Thrombin Inhibitor.

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 (Period 1) and Table 2 (Period 2).

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 study. This Screening examination will be conducted not more than 28 days prior to the planned first drug administration, ie between Day -28 to Day -2 before commencing to study Period 1. Only subjects who meet the inclusion criteria and none of the exclusion criteria will be admitted to the trial.

During the Screening examination, the subjects are identified by a screening number.

There is a notification on the subject's card as well as in the electronic subject's data base 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 informed consent form. This Screening examination will consist of the following:

- Demographic information including body height and body weight and BMI
- Medical history
- Physical examination
- Vital signs
- 12-lead ECG
- Blood and urine samples for safety laboratory assessments
- Blood sampling for coagulation parameters
- Test for occult blood in feces
- Serological tests for hepatitis B, C, and HIV1/HIV2
- Serum pregnancy test for women
- Urine drug screen (including test for cotinine) and an alcohol breath test
- Prior medication and concomitant medication
- 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. They will be assigned a subject number within the trial prior to the first administration.

For time points and assessments please refer to Table 1 and Table 2.

Period 1: Dabigatran Etexilate alone

Day -1 (admission)

Subjects will be hospitalized from the morning of Day -1 until completion of the 72 h assessments in the morning of Day 11 of Period 2.

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

- Physical examination
- Vital signs
- 12-lead ECG
- Blood and urine samples for safety laboratory assessments (including drugs of abuse and a urine pregnancy test in females)
- Alcohol breath test
- Prior medication and concomitant medication
- AEs
- Evaluation of inclusion and exclusion criteria.

Days 1 to 4 (inpatient)

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

- Vital signs
- 12-lead ECG
- Blood sample for PGx (optional)
- Pre-dose PK blood sample for determination of total dabigatran and coagulation parameters.

After completion of the pre-dose assessments breakfast will be served and dabigatran etexilate will be administered 30 min after start of breakfast. At 4 h after administration the subjects will consume a standardized lunch.

After dosing blood samples for determination of total dabigatran, coagulation parameters will be taken (please refer to Table 1).

Subjects will be asked regularly about their well-being and any concomitant medication taken.

Day 4 measurements (72 h measurements) may be performed immediately (within 60 min, PK sampling within 30 min) prior to tepotinib dosing on Day 1 of Period 2.

In case of a prolonged interval between Day 4 of Period 1 and Day 1 of Period 2 of more than 7 days, safety laboratory parameters will be determined, a physical examination will be performed as well as vital signs measured and an ECG recorded.

Period 2: Tepotinib and Dabigatran Etexilate

Days 1 to 6 (inpatient)

The subjects will be dosed with tepotinib in the morning of Days 1 to 6 of Period 2, 30 min after a standardized breakfast. Before and after dosing safety assessments (vital signs, 12-lead ECGs) will be performed regularly on each dosing day. Blood and urine samples for safety laboratory assessments (including coagulation) will be performed on Days 1 and 2 at pre-dose (coagulation on Day 1 only); in the morning of Day 6 a blood sample will be taken pre-dose for determination of tepotinib and metabolites (please refer to Table 2). Subjects will be asked regularly about their well-being and any medication taken.

Day 7 (inpatient)

Prior to dosing of tepotinib on Day 7 the following will be done:

- Vital signs
- 12-lead ECG
- Blood and urine samples for safety laboratory assessments
- Pre-dose PK blood sample for determination of tepotinib and metabolites parameters

After completion of the pre-dose assessments a standardized breakfast will be served and tepotinib will be administered 30 min after start of breakfast. At 4 h after administration the subjects will consume a standardized lunch. Six hours after drug administration, vital signs will be measured and an ECG recorded.

After dosing blood samples for determination of tepotinib and its metabolites will be taken (please refer to Table 2). Subjects will be asked regularly about their well-being and any medication taken.

Day 8 to 11 (inpatient)

Prior to dosing on Day 8 the following will be done:

- Vital signs

- 12-lead ECG
- Blood and urine samples for safety laboratory assessments
- Pre-dose PK blood sample will be taken for determination of total dabigatran, tepotinib and its metabolites and coagulation parameters

After completion of the pre-dose assessments a standardized breakfast will be served and dabigatran etexilate and tepotinib will be administered 30 min after start of breakfast. At 4 h after administration of study drugs the subjects will consume a standardized lunch.

After dosing safety assessments (vital signs, 12-lead ECGs) will be performed regularly and blood samples for determination of total dabigatran and coagulation parameters will be taken (please refer to Table 2). Prior to discharge on Day 11 blood and urine samples will be taken in addition for safety laboratory assessments. Subjects will be asked regularly about their well-being and any medication taken.

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

Dietary Regimen:

The subjects will be fasting at least 10 h before a standardized breakfast will be provided. Thereafter administration of dabigatran etexilate and/or tepotinib will occur (see Section 6.2). Four (4) hours after administration of dabigatran etexilate, a standardized lunch will be served. An afternoon snack will be provided 8 h and dinner 10 h post-dose.

On Day 1 of Period 1 and on Day 1 to 8 of Period 2, tepotinib and/or dabigatran etexilate will be administered 30 min after a defined standardized breakfast. All other meals during the inpatient period will be served as customary at the trial center.

During hospitalization subjects are not allowed to eat other than the provided meals.

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:

Foods, sweets and beverages:

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) are not allowed from 14 days before Day -1 of Period 1 until final examination. Methylxanthines (eg coffee, tea, cola, and cocoa) and alcohol containing food or beverages are not allowed from 48 h prior to the intended start of trial drug administration until the last PK blood sample. Poppy seeds (eg poppy seed rolls, poppy seed cake, yoghurt containing poppy seed etc.) will not be allowed from 72 h prior to dosing until completion of final examinations.

Drinking of fluids:

Drinking of fluids is not allowed 1 h after administration of dabigatran etexilate or tepotinib.

Smoking:

Only non-smokers or smokers who stopped smoking at least 6 months before the time of the Screening Visit will be included in the trial. Moreover, smoking is not allowed from Screening Visit until completion of End of Trial Visit.

Exercise Regimen:

Subjects will be advised to avoid heavy physical exertion 72 h prior to first drug administration until completion of all post trial examinations.

7.1.3 End of Trial Visit

The End of Trial examination should verify that all values tested in the Screening have remained within a clinically acceptable range. The assessments will be performed on 7 ± 1 day 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 and coagulation parameters (including a serum pregnancy test)
- 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 (contraception, postmenopausal, sterilization).

7.3 Efficacy Assessments

Not applicable.

7.4 Assessment of Safety

The safety profile of the IMPs 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, 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 regarding Safety Report notifications to Investigators will be considered.

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 SAEs 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, coagulation, 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. In addition, feces samples will be collected.

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:

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
Coagulation	Thrombin Time Activated partial thromboplastin time Hemoclot Thrombin Inhibitor (Anti-Factor II)		
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]: Basophiles Eosinophiles Lymphocytes Monocytes Neutrophiles
Urinalysis	pH Nitrite Protein Glucose	Ketone bodies Urobilinogen Bilirubin Urine pregnancy test	White blood cell count Red blood cell count 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 B core antibody Hepatitis C antibody HIV1/HIV2 antibodies Follicle stimulating hormone (if applicable) Thyroid stimulating hormone Serum pregnancy test (beta-HCG) eGFR [e] Breath Alcohol test (at Screening and Admission)		
Feces	Occult blood in feces (Haemoccult)		

HIV = human immunodeficiency virus, HCG = human chorionic gonadotropin

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.

The Sponsor should receive a list of laboratory normal ranges before shipment of the IMPs. 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 study, see Appendix II.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

7.4.4.1 Vital Signs

Blood pressure (systolic blood pressure [mmHg] and diastolic blood pressure [mmHg]) will be measured according to the oscillometric method using an automated device, which also indicates the corresponding pulse rate (bpm). 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).

Body temperature will be measured auricular.

Further vital sign measurements during the course of the study 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 must be signed and dated 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 study 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 study flow chart (see Table 1 and Table 2). Further physical examinations during the course of the study 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).

7.5 Pharmacokinetics

7.5.1 Blood Sampling

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

Blood samples will be taken and plasma levels of total dabigatran will be determined as closely as possible to the following time points:

- Day 1 of Period 1 at pre-dose (within 60 min prior to dosing) and 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose, and
- Day 8 of Period 2 at pre-dose (within 60 min prior to dosing) and 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose.

Blood samples will be taken and plasma levels of tepotinib and its metabolites MSC2571109A and MSC2571107A will be determined as closely as possible to the following time points:

- Day 6 of Period 2 at pre-dose (within 60 min prior to dosing), and
- Day 7 of Period 2 at pre-dose (within 60 min prior to dosing) and 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12 and 24 h post-dose (prior to dosing on Day 8, within 60 min prior to administration).

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 Time Windows

Planned Blood Sampling	Time Windows (min)
Pre-dose	- 60
15, 30, 45 and 60 min post-dose	± 2
90 min, and 2, 3, 4, 6, 8 and 12 h post-dose	± 5
24, 36 and 48 h post-dose	± 15
72 h post-dose	± 30

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 study 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 total dabigatran and tepotinib and its metabolites MSC2571109A and MSC2571107A will be measured using validated liquid chromatography and tandem mass spectrometry (LC-MS/MS) methods at Nuvisan. The assays will be carried out in accordance with GLP regulations and the EMA reflection paper (GCP). A separate bioanalytical protocol will be provided before the start of the analytical part of the study. Full details of the bioanalytical method used will be described in a separate bioanalytical report.

7.5.2 Calculation of Pharmacokinetic Variables

The following non-compartmental PK parameters (see Table 5 and Table 6) will be calculated from the individual plasma total dabigatran (unconjugated plus conjugated) and tepotinib concentration-time data using commercial software such as Phoenix®/WinNonlin® (Version 6.2 or higher) at Nuvisan GmbH.

Table 5 Definition of PK Parameters for Dabigatran 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 plasma 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
CL/f	Apparent total body clearance of drug from plasma following extravascular administration, calculated as dose/$AUC_{0-\infty}$
V_z/f	Apparent volume of distribution during the terminal phase following extravascular administration
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0-\infty}$) x100.

Table 6 Definition of PK Parameters for Tepotinib and Metabolites MSC2571109A and MSC2571107A after Multiple Dose Administration

Symbol	Definition
AUC_{τ}	The area under the plasma concentration-time curve (AUC) at steady state over the dosing interval from T_1 = 0 h to T_2 = τ h. Calculated using the mixed log linear trapezoidal rule (linear up, log down), τ = 24 h
CL_{SS}/f	Apparent total body clearance of drug at steady state following extravascular administration, considering the fraction of dose absorbed. CL_{SS}/f = Dose po / AUC_{τ} (parent drug only)
$C_{max,SS}$	Maximum observed plasma concentration during a complete dosing interval at steady state
$C_{min,SS}$	Minimum observed plasma concentration during a complete dosing interval at steady state
$t_{max,SS}$	The time to reach the maximum observed plasma concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)

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

Plasma concentrations below LLOQ before the last quantifiable data point will be taken as zero for calculating the AUC (ie embedded BLQ values set to zero). Plasma concentrations below LLOQ after the last quantifiable data point will not be considered for the determination of λ_z.

7.6 Biomarkers

Not applicable.

7.7 Pharmacogenomics

Pharmacogenetic sample collection is optional. An additional separate Informed Consent Form (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

8.1 Sample Size

A total of 20 subjects will be dosed in this study to obtain at least 16 evaluable subjects for the primary endpoint analysis. Four subjects will be added for drop-out compensation.

For the statistical analysis of AUC, data a-priori ordered hypotheses will be tested. The procedure is intended to classify tepotinib as a P-gp inhibitor.

Test 1 H_{01}: T/R ratio ≥ 2.0 versus H_{A1}: T/R ratio < 2.0

Test 2 H_{02}: T/R ratio ≥ 1.5 versus H_{A1}: T/R ratio < 1.5

In published studies of dabigatran, coefficient of variations (CVs) up to 30% were observed for the AUC following a single dose of dabigatran etexilate; after fed administration CV may be slightly lower [2] [9]. With 16 evaluable subjects and CV = 30%, Test 1 would have at least 80% power to reject H_{01}, if the true T/R ratio is 1.5 or smaller, and Test 2 would have at least 80% power to reject H_{02}, if the true T/R ratio is 1.14 or smaller. The one-sided significance level was set to alpha = 0.05.

8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Primary Endpoints

- PK profile of dabigatran in terms of AUC_{0-t}, $AUC_{0-\infty}$, C_{max} of total dabigatran (unconjugated plus conjugated) at Day 1 of Period 1 and Day 8 of Period 2 from time zero to 72 h post-dose.

8.3.2 Secondary Endpoints

- PK profile of total dabigatran (unconjugated plus conjugated) in terms of t_{max}, $t_{1/2}$, CL/f, V_z/f, $AUC_{extra\%}$ at Day 1 of Period 1 and Day 8 of Period 2 from time zero to 72 h post-dose
- Occurrence of TEAEs (incidence, frequency, intensity and causality), occurrence of changes in safety laboratory assessments, 12-lead ECGs and vital signs in subjects receiving tepotinib alone and together with dabigatran etexilate assessed from Day -1 of Period 1 until the End of Trial Visit.

8.3.3 Exploratory Endpoints

- PK profile of tepotinib and its metabolites MSC2571109A and MSC2571107A in terms of AUC_{τ}, $C_{max,ss}$, $C_{min,ss}$, $t_{max,ss}$, CL_{ss}/f (parent drug only), and $t_{1/2}$, if appropriate.
- Genetic variants and mutations in genes that potentially influence the PK of tepotinib and/or dabigatran.

  Note: Pharmacogenetic sample collection is optional. 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
Screening	The screening analysis set will include all subjects who provided signed informed consent, regardless of treatment status in the trial. This set will be used for subject disposition.
Safety	The Safety Analysis Set will include all subjects who have received at least 1 dose of planned IMP. Subjects will be analyzed according to the actual treatment they receive.
Pharmacokinetic	The PK Analysis Set will include all subjects who have completed at least 1 period without any relevant protocol violations with respect to factors likely to affect the comparability of PK results, with adequate study medication compliance, and with evaluable dabigatran PK data. Assessment of data sufficiency will be done by the responsible pharmacokineticist before database lock, ie PK data will be available and included in the database before data base lock. 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/or 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 [Q1 and Q3], minimum, and maximum) and categorical data will be summarized by means of frequency tables (ie count and percentages), if not stated otherwise.

Concentrations of total dabigatran, 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 (SEM), 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 geometric mean (GeoMean), the geometric coefficient of variation (GeoCV), and the 95% confidence interval (CI) for the GeoMean.

Since the statistical analyses will be predominantly descriptive presentations in tables and individual data listings, 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 and in the clinical trial report.

8.5.2 Analysis of Primary Endpoint

A general linear model with TREATMENT and SUBJECT as fixed effects will be applied to log-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of dabigatran (measured as total dabigatran) based on the PK analysis set. Treatment differences on the log scale of dabigatran with tepotinib vs dabigatran 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.

Individual estimates of relative bioavailability of dabigatran will be calculated for each subject.

The primary endpoint will be descriptively summarized. Scatterplots will be produced by treatment also showing the median, Q1 and Q3.

8.5.3 Analysis of Secondary Endpoints

Summary statistics will be provided for all secondary PK parameters as well as for the concentrations of dabigatran in plasma by time point.

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

PK variables will be evaluated and listed for all subjects of the PK population.

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

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 AE 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 post-dose

shifts relative to baseline, and data listings of abnormalities as per the NCI-CTCAE severity scale.

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.

PK concentrations will be descriptively summarized. Individual and mean concentration-time plots will be produced in linear and log-linear scale.

Analysis of exploratory endpoints

Summary statistics will be provided for all exploratory PK parameters as well as for the concentrations of the tepotinib and metabolites in plasma by time point. PK variables of tepotinib and the metabolites will be evaluated and listed for all subjects who provide sufficient concentration-time data. Graphical displays will be given, where appropriate. Further details of the statistical analysis will be described in the statistical analysis plan.

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, 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 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 Informed Consent Form 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 Informed Consent Form 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 Informed Consent Form 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 I 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 or Institutional Review Board

Prior to commencement of the trial, this clinical trial protocol will be submitted together with its associated documents (for example, Informed Consent Form, 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 Informed Consent Form 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, Investigational Medicinal Product Dossier, Subject Information and Informed Consent Form) 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 Informed Consent Forms. 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, 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 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 (no-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 [10].

10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoints. The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results.

Posting of data on ClinicalTrials.gov and 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. Härtter S, Sennewald R, Nehmiz G, et al. Oral bioavailability of dabigatran etexilate (Pradaxa®) after co-medication with verapamil in healthy subjects. BJCP 2013;75(4), 1053-1062.
2. Stangier J. Clinical Pharmacokinetics and Pharmacodynamics of the Oral Direct Thrombin Inhibitor Dabigatran Etexilate. Clin Pharmacokinet 2008;47(5): 285-295.
3. Summary of product characteristics Pradaxa 75 mg hard capsules. Updated 02 November 2017 Boehringer Ingelheim Limited. Downloaded from 'www.medicines.org.uk' on 07 November 2017.
4. Guidance for Industry; Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, Food and Drug Administration 2012.
5. Guideline on the investigation of drug interactions, CPMP/EWP/560/95/Rev. 1 Corr. 2**, European Medicines Agency 2012.
6. Drug Interaction Study With Dabigatran Etexilate and Dronedarone in Healthy Subjects. NCT01306162 (ClinTrials.gov). Homepage visited on 07 November 2017.
7. Drug Interaction Study Between Bosutinib And Dabigatran. NCT02102633 (ClinTrials.gov). Homepage visited on 07 November 2017.
8. 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.
9. Stangier J, Stähle H, Rathgen K, et al. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. Clin Pharmacokinet. 2008;47:47-59.
10. ICH Topic E 3 Note for Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95); July 1996.

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 Study to Evaluate the Effect of Tepotinib on P-Glycoprotein by Investigating the Pharmacokinetics of the P-Glycoprotein Probe Substrate Dabigatran Etexilate in Healthy Subjects
EudraCT Number:	2017-004074-34
Clinical Trial Protocol Date / Version:	23 April 2018 / Version 3.0

Protocol Lead:

I approve the design of the clinical trial:

PI	PI
Signature	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 I, Open-label, Single Sequence, Two-Period Study to Evaluate the Effect of Tepotinib on P-Glycoprotein by Investigating the Pharmacokinetics of the P-Glycoprotein Probe Substrate Dabigatran Etexilate in Healthy Subjects
EudraCT Number	2017-004074-34
Clinical Trial Protocol Date / Version	23 April 2018 / Version 3.0
Center Number	PI
Principal Investigator	PI

I, the undersigned, am responsible for the 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 of Harmonization Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PI

Signature

PI

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

Function / Title: PI

Institution: Merck KGaA

Address: Frankfurter Strasse 250, 64293 Darmstadt, Germany

Telephone number: PI

E-mail address: PI

Name: PI

Function / Title: PI

Institution: Merck KGaA

Address: Frankfurter Strasse 250, 64293 Darmstadt, Germany

Telephone number: PI

E-mail address: PI

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]	5[b]	1	8	37.6
Hematology	2.7	1	1[a]	5[b]	1	8	21.6
Coagulation	3.0	1	3[c]	4[d]	1	9	27.0
PK total dabigatran (unconjugated and conjugated	2.0		16[e]	16[f]		32	64.0
PK tepotinib and its metabolites	2.0			14[g]		14	28.0
PGx	2.0		2[h]			2	4.0
Total		**3**	**23**	**44**	**3**	**73**	**182.2**
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 study that will not be exceeded in this planned trial as by experience of the Investigating institution							**250**

Clinical laboratory (biochemistry and hematology) blood samples

a Period 1: Day -1 = 1 sample

b Period 2: pre-dose on Days 1, 2, 7 and 8 and on Day 11 = 5 samples

Coagulation

c Period 1: pre-dose and 4 h post-dose on Day 1 and 24 h post-dose on Day 2 = 3 samples

d Period 2: pre-dose on Day 1, pre-dose and 4 h post-dose on Day 8 and 24 h after the last dose on Day 9 = 4 samples

Dabigatran (unconjugated plus conjugated) **PK blood samples:**

e Period 1, Day 1: at pre-dose, 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose = 16 samples

f Period 2, Day 8: at pre-dose, 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose = 16 samples

Tepotinib and its metabolites PK blood sampling:

g Period 2: Day 6 pre-dose and Day 7 pre-dose, 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24 h post-dose = 14 samples

PGx blood samples:

h PGx blood samples of 2 x 2 mL (optional) to be drawn in Period 1 Day 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

Appendix IV Protocol Amendments and List of Changes

Previous Protocol Amendments

None

Table of Amendments

Amendment Number	Substantial (Y/N)	Date	Region or Country	Included in the current document (Y/N)
1	Y	06 March 2018	Global	Y
2	Y	23 April 2018	Global	Y

Amendment 1

Rationale

This amendment is written to include an additional exclusion criterion as requested by the Ethics Committee.

Major Scientific Changes

The following exclusion criterion is added:

22. Abnormal liver function tests (alanine-amino-transferase [ALT] or aspartate-amino-transferase [AST] values above 1.1 x upper limit of normal [ULN]) at Screening. In case of marginal deviation, a re-testing is allowed for confirmation.

The following laboratory assessment has been changed:

Ecarin Clotting Time was replaced by the more advanced Hemoclot Thrombin Inhibitor determination.

Administrative and Editorial Changes

Misleading footnotes in Table 3 “Safety Laboratory Evaluations” were corrected.

Packaging, labelling and distribution will now be handled by Nuvisan instead of Catalent.

In inclusion criterion #4 the reference to CTFG was corrected.

The wording of "Restrictions” were aligned with Exclusion Criterion.

A sentence was added to the clinical laboratory assessments, which allows Investigators to request analysis of additional blood samples.

Comparison with Clinical Trial Protocol Version 1.0, dated 07 December 2017 (Amendment No. 1, dated 06 February 2018)

Change	Section	Page (in CTP v1)	Previous Wording	New Wording
Major Scientific Changes				
Justification of Dose	5.2.3	26	As dabigatran prolongs the thrombin time (TT), the Ecarin Clotting Time (ECT) and the activated partial thromboplastin time (aPTT), appropriate coagulation-related parameters will be measured regularly.	As dabigatran ~~prolongs~~ **reduces the thrombin activity and therefore could prolong** the thrombin time (TT)~~,~~ ~~ecarin clotting time (ECT),~~ and activated partial thromboplastin time (aPTT), ~~appropriate~~ **these** coagulation ~~related~~ parameters **and the Hemoclot Thrombin Inhibitor (Anti-Factor II)** will be measured ~~regularly~~.
Additional exclusion criterion	5.3.2	29	-	**22. Abnormal liver function tests (alanine-amino-transferase [ALT] or aspartate-amino-transferase [AST] values above 1.1 x upper limit of normal [ULN]) at Screening. In case of marginal deviation, a re-testing is allowed for confirmation.**
Clinical Laboratory Assessments	7.4.3 – Table 3	48	Coagulation: Ecarin Clotting Time	Coagulation: ~~Ecarin Clotting Time~~ **Hemoclot Thrombin Inhibitor (Anti-Factor II)**
Administrative and Editorial Changes				
List of Abbreviations		8	ECT Ecarin clotting time	~~ECT Ecarin clotting time~~
Sponsor, Investigator and Trial Administrative Structure	2	18	Packaging, labeling and distribution of all IMPs to the trial site will be conducted by a designated contract manufacturing organization (Catalent Pharma Solutions, Inchwood, Bathgate, West Lothian, EH48 2FY, United Kingdom).	Packaging, labeling and distribution of all IMPs to the trial site will be conducted by a designated contract manufacturing organization (~~Catalent Pharma Solutions, Inchwood, Bathgate, West Lothian, EH48 2FY, United Kingdom~~ **Nuvisan GmbH, Wegenerstrasse 13, 89231 Neu-Ulm, Germany**).
Inclusion Criteria	5.3.1	27	4. A male participant must agree to use and to have his female partner of childbearing potential to use highly effective method of contraception (ie methods with a failure rate of less than 1% per year) as detailed in the EMA CTFG guidelines [8] during the period of participation in the study and for at least 3 months after the last investigational medicinal product (IMP) administration.	4. A male participant must agree to use and to have his female partner of childbearing potential to use highly effective method of contraception (ie methods with a failure rate of less than 1% per year) as detailed in the ~~EMA~~ **Clinical Trial Facilitation Group (**CTFG**)** ~~guideline~~ **recommendations** [8] during the period of participation in the study and for at least 3 months after the last investigational medicinal product (IMP) administration.

Change	Section	Page (in CTP v1)	Previous Wording	New Wording
Treatment of Overdose	6.12	37	Relevant coagulation parameters are aPTT, diluted TT or ECT.	Relevant coagulation parameters are aPTT, diluted TT or ~~ECT~~ **Hemoclot Thrombin Inhibitor**.
Treatment Periods Restrictions	7.1.2	41	Foods, sweets and beverages: 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) are not allowed from 14 days before first administration of study medication until final examination. Methylxanthines (eg coffee, tea, cola, cocoa) and alcohol containing food or beverages are not allowed from 48 h prior to the intended start of trial drug administration until the final examination.	Foods, sweets and beverages: 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) are not allowed from 14 days before ~~first administration of study medication~~ **Day -1 of Period 1** until final examination. Methylxanthines (eg coffee, tea, cola, cocoa) and alcohol containing food or beverages are not allowed from 48 h prior to the intended start of trial drug administration until the ~~final examination~~ **last PK blood sample**.
Clinical Laboratory Assessments	7.4.3	47	Fasted blood samples and urine samples will be collected for the clinical laboratory tests (hematology, biochemistry, coagulation, virology, drugs of abuse, hormones, and urinalysis, Table 3) following the timing noted in the Schedule of Assessments (Table 1 and Table 2). All blood and urine samples will be worked up and analyzed in Nuvisan's clinical laboratory.	Fasted blood samples and urine samples will be collected for the clinical laboratory tests (hematology, biochemistry, coagulation, 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.
Clinical Laboratory Assessments	7.4.3 – Table 3	48	Biochemistry: Creatine phosphokinase Hematology: White blood cell differentials and absolute counts: Urinalysis: Microscopic examination [b] Other tests: eGFR [c]	Biochemistry: Creatine phosphokinase [b] Hematology: White blood cell differentials and absolute counts [c]: Urinalysis: Microscopic examination [b] [d] Other tests: eGFR [e] [e]

Change	Section	Page (in CTP v1)	Previous Wording	New Wording
Clinical Laboratory Assessments	7.4.3 - Table 3	48	Footnotes to Table 3 a. In case of abnormal findings, manual differential blood count, direct/indirect bilirubin and CK MB (CK myocardium/brain type) can be requested by the Investigator. b. Only if blood, protein, nitrite, or white blood cell count are positive on the dipstick. c. Estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation.	Footnotes to Table 3 ~~a. In case of abnormal findings, manual differential blood count, direct/indirect bilirubin and CK MB (CK myocardium/brain type) can be requested by the Investigator.~~ **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.** ~~b~~ **d** Only if blood, protein, nitrite, or ~~white blood cell count~~ **leucocytes** are positive on the dipstick. ~~c~~ **e** Estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation.
Physical Examination	7.4.4.3	49	Further medical examinations during the course of the study are at the discretion of the Investigator.	Further ~~medical~~ **physical** examinations during the course of the study are at the discretion of the Investigator.
Planned Numbers of Blood Samples for Clinical Laboratory, PK, and PGx and Total Blood Sampling Volume	Appendix II	67	Previous Wording of Appendix II see below	New Wording of Appendix II see below

Previous Wording

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	
Viral serology	4.7	1				1	4,7
Clinical laboratory tests							
Biochemistry (incl. TSH and FSH levels, if applicable)	4.7	1	1[a]	5[b]	1	8	37.6
Hematology	2.7	1	1[a]	5[b]	1	8	21.6
Coagulation	3.0	1	3[c]	4[d]	1	9	27.0
PK total dabigatran (unconjugated and conjugated	2.0		16[e]	16[f]		32	64.0
PK tepotinib and its metabolites	2.0			14[g]		14	28.0
PGx	2.0		2[h]			2	4.0
Total		**4**	**23**	**44**	**3**	**74**	**186.9**
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 study that will not be exceeded in this planned trial as by experience of the Investigating institution							**250**

Clinical laboratory (biochemistry and hematology) blood samples

a Period 1: Day -1 = 1 sample

b Period 2: pre-dose on Days 1, 2, 7 and 8 and on Day 11 = 5 samples

Coagulation

c Period 1: pre-dose and 4 h post-dose on Day 1 and 24 h post-dose on Day 2 = 3 samples

d Period 2: pre-dose on Day 1, pre-dose and 4 h post-dose on Day 8 and 24 h after the last dose on Day 9 = 4 samples

Dabigatran (unconjugated plus conjugated) PK blood samples:

e Period 1, Day 1: at pre-dose, 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose = 16 samples

f Period 2, Day 8: at pre-dose, 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose = 16 samples

Tepotinib and its metabolites PK blood sampling:

g Period 2: Day 6 pre-dose and Day 7 pre-dose, 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24 h post-dose = 14 samples

PGx blood samples:

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

New Wording

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	
~~Viral serology~~	~~4.7~~	~~1~~				~~1~~	~~4,7~~
Clinical laboratory tests							
Biochemistry (incl. **viral serology,** TSH and FSH levels, if applicable)	4.7	1	1[a]	5[b]	1	8	37.6
Hematology	2.7	1	1[a]	5[b]	1	8	21.6
Coagulation	3.0	1	3[c]	4[d]	1	9	27.0
PK total dabigatran (unconjugated and conjugated	2.0		16[e]	16[f]		32	64.0
PK tepotinib and its metabolites	2.0			14[g]		14	28.0
PGx	2.0		2[h]			2	4.0
Total		~~4~~ **3**	**23**	**44**	**3**	~~74~~ **73**	~~186,9~~ **182.2**
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 study that will not be exceeded in this planned trial as by experience of the Investigating institution							**250**

Clinical laboratory (biochemistry and hematology) blood samples

a Period 1: Day -1 = 1 sample

b Period 2: pre-dose on Days 1, 2, 7 and 8 and on Day 11 = 5 samples

Coagulation

c Period 1: pre-dose and 4 h post-dose on Day 1 and 24 h post-dose on Day 2 = 3 samples

d Period 2: pre-dose on Day 1, pre-dose and 4 h post-dose on Day 8 and 24 h after the last dose on Day 9 = 4 samples

Dabigatran (unconjugated plus conjugated) PK blood samples:

e Period 1, Day 1: at pre-dose, 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose = 16 samples

f Period 2, Day 8: at pre-dose, 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h post-dose = 16 samples

Tepotinib and its metabolites PK blood sampling:

g Period 2: Day 6 pre-dose and Day 7 pre-dose, 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24 h post-dose = 14 samples

PGx blood samples:

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

Amendment 2

Rationale

This amendment is written including updates as requested by the German Competent Authority.

Major Scientific Changes

The 1st sentence in the 4th paragraph in Section 3 "Background Information" has been revised by deleting the term "showing a broad safety margin". The updated sentence is given in the table below.

As the SMC is not considered necessary for this study, all text related to the originally planned SMC has been deleted in the synopsis and in protocol sections 3 "Background Information" and 5.1 "Overall Trial Design and Plan".

The following inclusion and exclusion criteria have been revised as listed below:

- Inclusion criterion #1: The upper limit of age has been reduced from 55 years to 44 years.
- Inclusion criterion #4: The inclusion criteria has been revised by adding the following sentence: "The male participants will be asked to report pregnancies in their female partners up to 3 months after the last IMP intake.".
  In addition, a Contraception Guidance was added (as Appendix III) to provide guidance to the Investigator.
- Inclusion criterion #7 / Exclusion criterion #22: The limits for ALT and AST as well as amylase and lipase has been reduced to the upper limit of normal (ULN). The Inclusion criterion #7 has been revised as well as the Exclusion criterion #22 has been deleted.
- Exclusion criterion #4: The pulse rate has been updated from > 100 or ≤ 40 bpm to > 90 or < 50 bpm at Screening and at admission on Day -1.
- Exclusion criterion #11.7: The wording "…5 half-lives after last dosing, whatever is longer, …" has been added to the sub-topic.

The updated wording in the Inclusion and Exclusion criteria is shown in the table below.

Administrative and Editorial Changes

Clarification on vital signs assessments including also body temperature measurement if not explicitly excluded.

Update of the NCI-CTCAE used for AE grading.

Comparison with Clinical Trial Protocol Version 2.0, dated 6 March 2018 (Amendment No. 2, dated 23 April 2018)

Change	Section	Page (in CTP v2)	Previous Wording	New Wording
Major Scientific Changes				
Synopsis	-	12	Methodology: The subjects will be admitted to the study site on Day -1. They will be resident at the study site under medical supervision from Days -1 of Period 1 until Day 11 of Period 2. A safety monitoring committee (SMC) will take the decision about stopping or continuing the trial, as in this trial multiple doses of tepotinib will be given for the first time to healthy subjects. Details of the SMC composition and roles and responsibilities will be described in an SMC charter.	Methodology: The subjects will be admitted to the study site on Day -1. They will be resident at the study site under medical supervision from Days -1 of Period 1 until Day 11 of Period 2. **After the first 6 subjects completed administration in Period 2, safety and PK data will be reviewed by the responsible functional representatives.** ~~A safety monitoring committee (SMC) will take the decision about stopping or continuing the trial, as in this trial multiple doses of tepotinib will be given for the first time to healthy subjects. Details of the SMC composition and roles and responsibilities will be described in an SMC charter.~~
Synopsis	-	13	Diagnosis and key inclusion and exclusion criteria: Healthy males and females (of non-childbearing potential) between 18 and 55 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.	Diagnosis and key inclusion and exclusion criteria: Healthy males and females (of non-childbearing potential) between 18 and ~~55~~ **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.
Background Information	3	19	Based on the currently available nonclinical as well as clinical safety data, short term multi-day dosing of tepotinib in healthy subjects is reasonable considering the preclinical safety pharmacology and toxicity data showing a broad safety margin, and the absence of genotoxicity, in conjunction with the predicted exposures at steady state after multiple dosing of 500 mg/day in healthy subjects, and the clinical experience in oncology patient populations, and implementing close medical monitoring of safety and tolerability.	Based on the currently available nonclinical as well as clinical safety data, short term multi-day dosing of tepotinib in healthy subjects is reasonable considering the preclinical safety pharmacology and toxicity data ~~showing a broad safety margin~~, and the absence of genotoxicity, in conjunction with the predicted exposures at steady state after multiple dosing of 500 mg/day in healthy subjects, and the clinical experience in oncology patient populations, and implementing close medical monitoring of safety and tolerability.

Change	Section	Page (in CTP v2)	Previous Wording	New Wording
Background Information	3	20	After the first 6 subjects completed administration in Period 2, a safety monitoring committee (SMC) meeting is scheduled before continuing with the next cohort.	After the first 6 subjects completed administration in Period 2, ~~a safety monitoring committee (SMC) meeting is scheduled before continuing with the next cohort.~~ **safety and PK data will be reviewed by the responsible functional representatives.**
Overall Trial Design and Plan	5.1	23	Since to date tepotinib 500 mg was administered to healthy subjects only as single doses (study EMR200095-007, single dose; study MS200095-0012, 2 single doses), the safety and tolerability of multiple dose tepotinib (Period 2) will first be assessed in a subgroup of 6 subjects, followed by group(s) of the remaining subjects. Dosing of the subsequent group(s) will only be started if the safety and tolerability of multiple dosing of tepotinib was assessed as reasonable and no stopping rules applied.	Since to date tepotinib 500 mg was administered to healthy subjects only as single doses (study EMR200095-007, single dose; study MS200095-0012, 2 single doses), the safety and tolerability **as well as the PK** of multiple dose tepotinib (**up to Day 8 inclusive in** Period 2) will first be assessed in a subgroup of 6 subjects, followed by group(s) of the remaining subjects. Dosing of the subsequent group(s) will only be started if the safety and tolerability of multiple dosing of tepotinib was assessed as reasonable and no stopping rules applied. **The decision will be documented and will be filed in the trial documentation files.**
Overall Trial Design and Plan	5.1	24	A SMC will take the decision about stopping or continuing the trial, as in this trial multiple doses of tepotinib will be given for the first time to healthy subjects. Details of the SMC composition and roles and responsibilities will be described in an SMC charter. The committee will be composed of at least: • The global patient safety project lead (chair of the SMC) • The medical responsible of the Sponsor • The clinical pharmacokineticist of the Sponsor • The Principal Investigator. Clinical safety and safety laboratory data (from the electronic case report form [eCRF]) up to Day 8 (including) will be provided to the SMC members for review. Based on the safety data the SMC decides whether the dosing of the remaining group can start. The decisions of these meetings/telephone conferences will be documented and will be filed in the trial documentation files.	~~A SMC will take the decision about stopping or continuing the trial, as in this trial multiple doses of tepotinib will be given for the first time to healthy subjects. Details of the SMC composition and roles and responsibilities will be described in an SMC charter.~~ ~~• The committee will be composed of at least: The global patient safety project lead (chair of the SMC)~~ ~~• The medical responsible of the Sponsor~~ ~~• The clinical pharmacokineticist of the Sponsor~~ ~~• The Principal Investigator.~~ ~~Clinical safety and safety laboratory data (from the electronic case report form [eCRF]) up to Day 8 (including) will be provided to the SMC members for review. Based on the safety data the SMC decides whether the dosing of the remaining group can start. The decisions of these meetings/telephone conferences will be documented and will be filed in the trial documentation files.~~

Change	Section	Page (in CTP v2)	Previous Wording	New Wording
Inclusion Criteria	5.3.1	27	1. Male or female, aged 18 to 55 years inclusive (at Screening)	1. Male or female, aged 18 to ~~55~~ **44** years inclusive (at Screening)
Inclusion Criteria	5.3.1	27	4. A male participant must agree to use and to have his female partner of childbearing potential to use highly effective method of contraception (ie methods with a failure rate of less than 1% per year) as detailed in the Clinical Trial Facilitation Group (CTFG) recommendations [8] during the period of participation in the study and for at least 3 months after the last investigational medicinal product (IMP) administration. Males must also refrain from donating sperm during this period and should always use a barrier method such as condom concomitantly.	4. A male participant must agree to use and to have his female partner of childbearing potential to use highly effective method of contraception (ie methods with a failure rate of less than 1% per year) as detailed in the Clinical Trial Facilitation Group (CTFG) recommendations [8] during the period of participation in the study and for at least 3 months after the last investigational medicinal product (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.**
Inclusion Criteria	5.3.1	28	7. All values for hematology, coagulation, and biochemistry tests of blood and urinalysis within the normal range (at Screening). Minor (solitary) non-clinically relevant deviation(s) are allowed as judged by the Investigator; however, amylase and lipase should not exceed the upper limit of normal.	7. All values for hematology, coagulation, and biochemistry tests of blood and urinalysis within the normal range (at Screening). Minor (solitary) non-clinically relevant deviation(s) are allowed as judged by the Investigator; however, amylase**,** lipase **and alanine-amino-transferase [ALT] or aspartate-amino-transferase [AST] values** should not exceed the upper limit of normal **(ULN)**.
Exclusion Criteria	5.3.2	28	4. Supine systolic blood pressure (SBP) > 140 mmHg or < 90 mmHg, diastolic blood pressure (DBP) > 90 mmHg or < 50, and pulse rate > 100 or ≤ 40 bpm 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)	4. Supine systolic blood pressure (SBP) > 140 mmHg or < 90 mmHg, diastolic blood pressure (DBP) > 90 ~~mmHg~~ or < 50 **mmHg**, and pulse rate > ~~100~~ **90** or ~~≤ 40~~ **< 50** bpm 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)
Exclusion Criteria	5.3.2	29	11. • Use of drugs that may have interfered with hemostasis during trial conduct (eg acetylic salicylic acid or other non-steroidal anti-inflammatory drugs) within 14 days prior to start of dosing or during the trial	11. • Use of drugs that may have interfered with hemostasis during trial conduct (eg acetylic salicylic acid or other non-steroidal anti-inflammatory drugs) within 14 days **or 5 half-lives after last dosing, whatever is longer,** prior to start of dosing or during the trial

Change	Section	Page (in CTP v2)	Previous Wording	New Wording
Exclusion Criteria	5.3.2	29	22. Abnormal liver function tests (alanine-amino-transferase [ALT] or aspartate-amino-transferase [AST] values above 1.1 x upper limit of normal [ULN]) at Screening. In case of marginal deviation, a re-testing is allowed for confirmation.	~~22. Abnormal liver function tests (alanine-amino-transferase [ALT] or aspartate-amino-transferase [AST] values above 1.1 x upper limit of normal [ULN]) at Screening. In case of marginal deviation, a re-testing is allowed for confirmation.~~
Contraception Guidance	Appendix III	-	-	New Wording added as Appendix III, see below
Administrative and Editorial Changes				
Abbreviation	-	9	SMC Safety monitoring committee	~~SMC Safety monitoring committee~~
Schedule of Assessments – Period 1	Table 1	14	Vital signs (blood pressure, pulse rate)	Vital signs (blood pressure, pulse rate**, body temperature**)
Schedule of Assessments – Period 2	Table 2	16	Vital signs (blood pressure, pulse rate)	Vital signs (blood pressure, pulse rate**, body temperature**)
Screening Examination	7.1.1	38	• Vital signs (supine blood pressure and pulse rate)	• Vital signs ~~(supine blood pressure and pulse rate)~~
End of Trial Visit	7.1.3	42	• Vital signs (supine blood pressure and pulse rate)	• Vital signs ~~(supine blood pressure and pulse rate)~~
Adverse Event	7.4.1.1	44	Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (NCI-CTCAE), Version 4.03 (publication date: 14 June 2010), a descriptive terminology that can be used for AE reporting.	Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (NCI-CTCAE), Version ~~4.03~~ **5.0** (publication date: ~~14 June 2010~~ **27 Nov 2017**), a descriptive terminology that can be used for AE reporting.
Procedure for Reporting Serious Adverse Events	7.4.1.4	46	Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, autopsy report).	Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, **and** autopsy report).
Protocol Amendments and List of Changes	Appendix III	70	Appendix III - Protocol Amendments and List of Changes	Appendix ~~III~~ **IV** - Protocol Amendments and List of Changes

New Wording

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

4. 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.

5. Premenarchal

6. 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