

Clinical Trial Protocol

Clinical Trial Protocol Number	MS200095-0044
Title	Phase 1, Open-label, 3-Parts Study with Crossover Design in each part to Investigate the Bioequivalence of the Tablet Formulation of Tepotinib TF3 compared to TF2 (Part A), and to Investigate the Influence of Food on the Pharmacokinetics of each Tablet Formulation TF2 (Part B) and TF3 (Part C) of Tepotinib in Healthy Subjects
Phase	1
IND Number	Not applicable
EudraCT Number	2017-005056-29
Principal Investigator	PI [REDACTED], PI [REDACTED] PI [REDACTED] Germany
Sponsor	Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany
	Medical Responsible: PI [REDACTED], PI [REDACTED] Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany Phone: PI [REDACTED] Mobile: PI [REDACTED]
Clinical Trial Protocol Version	29 May 2018 / Version 1.0
Replaces Version	Not applicable

- Confidential -

This document is the property of Merck KGaA, Darmstadt, Germany, or one of its subsidiaries. It is intended for restricted use only and may not – in full or part – be passed on, reproduced, published or used without express permission of Merck KGaA, Darmstadt, Germany, or its subsidiary. Copyright © 2018 by Merck KGaA, Darmstadt, Germany, or its subsidiary. All rights reserved.

Protocol Table of Contents

6.2	Dosage and Administration	27
6.3	Assignment to Treatment Groups.....	28
6.4	Non-investigational Medicinal Products to be Used	29
6.5	Concomitant Medications and Therapies	29
6.5.1	Permitted Medicines	29
6.5.2	Prohibited Medicines	29
6.5.3	Permitted / Prohibited Procedures	30
6.5.4	Other Interventions	30
6.5.5	Special Precautions	31
6.5.6	Management of Specific Adverse Events or Adverse Drug Reactions.....	31
6.6	Packaging and Labeling of the Investigational Medicinal Product....	31
6.7	Preparation, Handling, and Storage of the Investigational Medicinal Product.....	31
6.8	Investigational Medicinal Product Accountability	31
6.9	Assessment of Investigational Medicinal Product Compliance	32
6.10	Blinding	32
6.11	Emergency Unblinding.....	32
6.12	Treatment of Overdose	33
6.13	Medical Care of Subjects after End of Trial.....	33
7	Trial Procedures and Assessments.....	33
7.1	Schedule of Assessments.....	33
7.1.1	Screening Examination.....	33
7.1.2	Treatment Periods.....	34
7.1.3	End of Trial Visit	36
7.2	Demographic and Other Baseline Characteristics	36
7.3	Efficacy Assessments	37
7.4	Assessment of Safety	37
7.4.1	Adverse Events	37
7.4.2	Pregnancy and In Utero Drug Exposure	41
7.4.3	Clinical Laboratory Assessments	42
7.4.4	Vital Signs, Physical Examinations, and Other Assessments.....	44
7.5	Pharmacokinetics	45

7.5.1	Blood Sampling	45
7.5.2	Calculation of Pharmacokinetic Variables	45
7.6	Biomarkers.....	46
7.7	Pharmacogenetics	46
7.8	Other Assessments.....	47
8	Statistics	47
8.1	Statistical Hypotheses	47
8.2	Sample Size	47
8.2.1	Part A (Bioequivalence)	47
8.2.2	Parts B and C (Food Effect).....	50
8.3	Randomization.....	50
8.4	Endpoints	51
8.4.1	Primary Endpoints	51
8.4.2	Secondary Endpoints	51
8.4.3	Exploratory Endpoints	52
8.5	Analysis Sets.....	52
8.5.1	Safety Analysis Set	52
8.5.2	Definition of Pharmacokinetic Analysis Set.....	52
8.6	Description of Statistical Analyses.....	52
8.6.1	General Considerations.....	52
8.6.2	Analysis of Primary Endpoints	53
8.6.3	Analysis of Secondary Endpoints	54
8.6.4	Analysis of Safety and Exploratory Endpoints.....	54
8.7	Interim and Additional Planned Analyses	55
9	Ethical and Regulatory Aspects.....	55
9.1	Responsibilities of the Investigator	55
9.2	Subject Information and Informed Consent	55
9.3	Subject Identification and Privacy.....	56
9.4	Emergency Medical Support and Subject Card.....	56
9.5	Clinical Trial Insurance and Compensation to Subjects.....	56
9.6	Independent Ethics Committee or Institutional Review Board	57
9.7	Health Authorities.....	57

10	Trial Management.....	57
10.1	Case Report Form Handling	57
10.2	Source Data and Subject Files	58
10.3	Investigator Site File and Archiving.....	58
10.4	Monitoring, Quality Assurance and Inspection by Health Authorities	59
10.5	Changes to the Clinical Trial Protocol.....	59
10.6	Clinical Trial Report and Publication Policy.....	59
10.6.1	Clinical Trial Report	59
10.6.2	Publication	59
11	References Cited in the Text.....	60
12	Appendices	61
Appendix I	Signature Pages and Responsible Persons for the Trial.....	62
	Signature Page – Protocol Lead.....	63
	Signature Page – Principal Investigator.....	64
	Sponsor Responsible Persons not Named on the Cover Page	65
Appendix II	Blood Volume Sampled in the Clinical Trial	66
Appendix III	Contraception Guidance	67

Table of In-Text Tables

Table 1	Schedule of Assessments – Parts A, B and C	13
Table 2	Clinical Laboratory Evaluations	43
Table 3	Time Windows.....	45
Table 4	Definition of PK Parameters for Tepotinib and its Metabolites After Single Dose Administration	46
Table 5	Overview of the PK-Variability Observed in the Previous Tepotinib Studies	48
Table 6	Power and Mean n for Declaring Bioequivalence for Individual PK Parameters	49
Table 7	90% Confidence Intervals for Estimated Test/Reference Ratios, n = 12 per Group.....	50

Table of In-Text Figures

Figure 1	Overall Trial Design	20
Figure 2	Design of the Trial Parts	20
Figure 3	Diagram of Two-Stage Adaptive Design	48

List of Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ALU	Aluminum
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC _{0-∞}	Area under the plasma concentration-time curve from time zero (= dosing time) extrapolated to infinity
AUC _{0-t}	Area under the plasma concentration-time curve from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification.
AUC _{extra}	The AUC from time t_{last} extrapolated to infinity
AUC _{extra%}	AUC _{extra} / AUC _{0-∞} in percent
beta-HCG	Beta-human chorionic gonadotropine
BMI	Body mass index
CI	Confidence interval
CK-MB	Creatine phosphokinase - myocardium/brain type
CL/f	Apparent total body clearance considering the fraction of dose (f) absorbed
C _{max}	Maximum plasma concentration
c-Met	Mesenchymal-epithelial transition factor
CRO	Contract research organization
CTCAE	Common Terminology Criteria for AEs
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EudraCT	European Union Clinical Trials Register
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GeoMean	Geometric mean

GMR	Geometric Mean Ratio
h	Hour(s)
HCC	Hepatocellular carcinoma
HGF	Hepatocyte growth factor
HIV1/HIV2	Human immunodeficiency virus 1 and 2
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
LLOQ	Lower limit of quantification
min	Minute(s)
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
PGx	Pharmacogenetics
PK	Pharmacokinetics
QTcF	Corrected QT interval according to Fridericia
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reactions
T/R	Test/Reference
$t_{1/2}$	Terminal half-life
TEAE	Treatment emergent adverse event
TF1; TF2; TF3	Tablet Formulation 1; Tablet Formulation 2; Tablet Formulation 3
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
ULN	Upper limit of normal range
V_z/f	Apparent volume of distribution during terminal phase (after oral/extravascular administration)

1 Synopsis

Clinical Trial Protocol Number	MS200095-0044
Title	Phase 1, Open-label, 3-Parts Study with Crossover Design in each part to Investigate the Bioequivalence of the Tablet Formulation of Tepotinib TF3 compared to TF2 (Part A), and to Investigate the Influence of Food on the Pharmacokinetics of each Tablet Formulation TF2 (Part B) and TF3 (Part C) of Tepotinib in Healthy Subjects
Trial Phase	1
IND Number	Not applicable
FDA covered trial	No
EudraCT Number	2017-005056-29
Principal Investigator	PI [REDACTED], MD PI [REDACTED] Germany
Sponsor	Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany
Trial center	PI [REDACTED] Germany
Planned trial period (first subject in-last subject out)	Q3-Q4 2018
Trial Registry	ClinicalTrial.gov, EU Clinical Trials Register
Primary Objectives:	
<ul style="list-style-type: none">Part A: To demonstrate bioequivalence between the new tablet formulation (TF3, test treatment) and the tablet formulation used in clinical studies (TF2, reference treatment) after single dose administration in healthy subjects under fasting conditionsParts B and C: To investigate the food effect, ie the difference in pharmacokinetics (PK) between administration after a high-calorie, high-fat breakfast and administration under fasting conditions in healthy subjects, for both TF3 and TF2.	
Secondary Objectives:	
<ul style="list-style-type: none">To further investigate the PK of tepotinibTo assess the safety and tolerability of tepotinib (TF3 and TF2) under fasting and non-fasting conditions.	

Exploratory Objectives:

- Part A: To investigate the PK of metabolites after administration of both tablet formulations (TF3 and TF2) of tepotinib
- Parts B and C: To investigate the effect of food on the PK of metabolites of tepotinib
- To explore the effect of pharmacogenetics (PGx) and variations of associated genes on the PK profile of tepotinib (if applicable).

Methodology: This is a Phase 1, mono-center, single-dose, open-label trial in 3 parts (Parts A, B and C).

Part A investigates the bioequivalence of TF3 and TF2 under fasted condition and is designed in 2 stages. If the PK-variability in Stage 1 is larger than initially assumed, the sample size will be re-calculated (with alpha-correction) and additional subjects may be randomized in Stage 2.

Parts B and C investigate the effect of food on the PK of tepotinib after administration of TF2 (Part B) and TF3 (Part C), respectively.

Each trial part has a 2-period, 2-sequence cross-over design. All 3 trial parts may be performed concurrently.

For each subject, the study consists of a screening period (Day -21 to Day -2) and 2 treatment periods, each lasting 21 days. Eligible subjects will be admitted to the clinical unit on Day -1. Subjects who continue to meet the eligibility criteria will be randomized to 1 treatment sequence on Day 1 of Period 1.

In each study period, the subjects will be hospitalized from Day -1 to Day 4 for safety assessments and PK blood sampling and return to the site on Days 5 - 8 for additional PK blood sampling and monitoring of AEs and concomitant medication. Study drug will be administered on Day 1 of each period. An End of Trial Visit will be performed at the end of Period 2 (21 days after dosing in Period 2).

Planned number of subjects:

At least 64 subjects; more subjects may be enrolled in accordance with the adaptive study design (Part A: 40 subjects in Stage 1, additional subjects in Stage 2, if required; Parts B and C: 12 subjects each).

Primary Endpoints:

- Part A: Area under the plasma concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time at which the concentration is at or above the lower limit of quantification (AUC_{0-t}), AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$) and maximum plasma concentration (C_{max}) of tepotinib observed from time zero to 168 h post-dose of each period
- Parts B and C: AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} of tepotinib observed from time zero to 168 h post-dose of each period.

Secondary Endpoints:

- Time to reach C_{max} (t_{max}), terminal half-life ($t_{1/2}$), apparent total body clearance considering the fraction of dose absorbed (CL/f) and apparent volume of distribution during terminal phase (V_z/f) of tepotinib observed from time zero to 168 h post-dose of each period
- 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.

Exploratory Endpoints:

- PK profiles of tepotinib metabolites:
 AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , t_{max} , $t_{1/2}$ of tepotinib metabolites observed from time zero to 168 h post-dose of each period
- Genetic variants and mutations in genes that potentially influence PK of tepotinib.

Pharmacokinetics:

Plasma concentrations of tepotinib and its metabolites MSC2571109A and MSC2571107A will be determined in each study period from pre-dose until 168 h post-dose. PK parameters will be calculated using non-compartmental analysis.

Pharmacogenetics: PGx analysis on Day -1 of Period 1

Other assessments: Not applicable

Diagnosis and key inclusion and exclusion criteria:

Healthy males and females (of non-childbearing potential) between 18 to 55 years (inclusive) with a body mass index (BMI) ≥ 18.5 and $\leq 29.9 \text{ kg/m}^2$ and a total body weight between 50 and 100 kg (inclusive) at the time of Screening examination may be enrolled in the trial.

Investigational Medicinal Product: dose/mode of administration/ dosing schedule:

- Tepotinib film-coated tablet (Tablet Formulation 2, TF2) containing 500 mg of drug substance for oral administration
- Tepotinib film-coated tablet (Tablet Formulation 3, TF3) containing 250 mg of drug substance for oral administration

Part A: Single doses of 500 mg tepotinib administered as 1 tablet of TF2 and 2 tablets of TF3 in fasted state.

Part B: Single dose of 1 tablet (500 mg) of TF2 will be administered in fasted state and with a high-fat, high-calorie breakfast.

Part C: Single dose of 2 tablets (500 mg) of TF3 will be administered in fasted state and with a high-fat, high-calorie breakfast.

The washout period between single doses will be at least 21 days.

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

Planned trial and treatment duration per subject:

For Parts A, B and C about 9 weeks each from Screening to End of Trial Visit, including 2 treatment periods of 21 days each.

Statistical methods:

Primary Endpoints:

Part A (Bioequivalence): An analysis of variance (ANOVA) model will be fitted for the log-transformed PK parameters C_{max} , AUC_{0-t} , $AUC_{0-\infty}$ based on the PK analysis set. The model will include treatment, period, sequence and subject within sequence as fixed effects. If a Stage 2 is required and the number of subjects in Stage 2 is sufficiently large, stage will be included as additional effect to the ANOVA model for the analysis of the pooled data of both stages.

Treatment differences on the log scale of tepotinib will be estimated for C_{max} , AUC_{0-t} , $AUC_{0-\infty}$ together with their CIs with coverage probability according to the planned 2-stage procedure. The variance estimate from Stage 1 will be used to evaluate the power at Stage 1. Bioequivalence will be assessed after Stage 1 using Stage 1 data, or after Stage 2 using the pooled data of both stages.

The null hypothesis will be rejected if the CI corresponding to the α -level (either 90% or 94.12%) for the ratio of the geometric mean lies within the interval 0.8000 to 1.2500.

Parts B and C (Food Effect): PK parameters will be compared between study drug administration (Part B: TF2; Part C: TF3) in fasted vs fed state using a mixed model with treatment, period and sequence as fixed effects and a random effect for subject within sequence based on log-transformed PK parameters.

Treatment differences on the log scale of tepotinib will be estimated for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ together with their 90% confidence intervals (CIs). Point estimates and CIs will be back-transformed to the original scale for the comparisons.

Secondary and exploratory endpoints will be analyzed with summary statistics.

Table 1 Schedule of Assessments – Parts A, B and C

Assessment/ Activity	Screening	All periods				End of Trial Visit
		Day -21 to -2	-1	1	2 - 4	
Written informed consent ^a						
Hospitalization		X -----		X		
Ambulatory visits	X				X	X
In-/exclusion criteria	X	X (Period 1 only)				
Demographic data (incl. height, weight, BMI)	X					
Medical history	X					
Physical examination	X	X		Day 2, Day 4 ^e		X
Vital signs (blood pressure, pulse rate, body temperature)	X	X	pre-dose, 2 h, 8 h	Day 2, Day 4 ^e		X
12-lead safety ECG	X ^b	X	pre-dose, 2 h, 8 h	Day 2, Day 4 ^e		X
Clinical laboratory (hematology, biochemistry, urinalysis)	X	X	pre-dose	Day 2, Day 4 ^e		X
Serology (HIV/hepatitis)	X					
Pregnancy test (in serum at Screening and End of Trial Visit, in urine on Day -1)	X	X				X
Urine drug screen; Alcohol breath test	X	X				
Administration of tepotinib			X			
PK blood sampling			X ^c	X ^c	X ^c	
PGx blood sampling		X (Period 1 only)				
Adverse events monitoring	X	X ←-----→ X ^d				
(Prior and) concomitant medication	X	X ←-----→ X ^d				

BMI = body mass index, ECG = electrocardiogram, h = hours, HIV = human immunodeficiency virus, min = minutes, PK = pharmacokinetics, PGx = pharmacogenetics

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

^b ECGs at screening will be recorded in triplicate

Tepotinib (MSC2156119J) Bioequivalence (TF3/TF2) and Effect of Food on the PK of Tepotinib
MS200095-0044

- c PK blood samples for determination of tepotinib and its metabolites 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, 16 and (Day 2) 24, 36, (Day 3) 48, 60, (Day 4) 72, (Day 5) 96, (Day 6) 120, (Day 7) 144 and (Day 8) 168 h post-dose
- d Adverse events and concomitant medication will be assessed from signing of the informed consent form throughout the whole study until End of Trial.
- e All safety assessments on Day 4 before discharge.

2 Sponsor, Investigators and Trial Administrative Structure

This clinical trial will be sponsored by:

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

Single trial site at ^{PI} [REDACTED], Germany.

The Principal Investigator (^{PI} [REDACTED], ^{PI} [REDACTED], Germany) will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report consistent with the International Council for Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP) [7].

Signature pages for the Protocol Lead and the Principal Investigator as well as a list of Sponsor responsible persons are in [Appendix I](#).

The trial will appear in the following clinical trial registries: European Union Clinical Trials Register (EudraCT), ClinicalTrials.gov.

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

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

The Sponsor will provide the Investigational Medicinal Product (IMPs) tepotinib. Packaging, labeling and distribution of all IMPs to the trial site will be conducted by a designated contract manufacturing organization (Nuvisan GmbH). 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 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. Sixty subjects of these were exposed to a tepotinib + gefitinib combination. Five studies have been completed; 3 of these were conducted as single dose studies in healthy subjects (EMR200095-002, EMR200095-007, and MS200095-0012; n = 79 subjects), and 2 as multiple dose studies in subjects with different solid tumors (EMR200095-001 and EMR200095-003; n = 161). In addition, 4 studies in subjects with hepatocellular carcinoma (HCC; EMR200095-004, EMR200095-005) or epidermal growth factor receptor mutated or c-Met mutated non-small cell lung cancer (NSCLC; EMR200095-006, and MS200095-0022) are ongoing. In the ongoing studies, subjects with HCC received tepotinib as multidose monotherapy, and subjects with NSCLC received either multidose tepotinib monotherapy or a multidose combination with gefitinib in Phase 1 or Phase 1b/2 studies. Doses of tepotinib of up to 1400 mg daily in subjects with solid tumors (EMR200095-001) and up to 1000 mg daily in subjects with HCC (EMR200095-004) have been explored.

The 500 mg single dose of tepotinib has been studied in previous studies with 36 healthy subjects in total (EMR200095-007: 12 subjects, MS200095-0012: 24 subjects, 2 single doses of 500 mg) and was well tolerated. A dose of 500 mg once daily is the recommended Phase 2 dose. Refer to the Investigator's Brochure (IB) for further information about the nonclinical and clinical programs and the implemented Guidance for the Investigator.

Based on the currently available nonclinical as well as clinical safety data, and the lack of genotoxicity in non-clinical studies, there is no objection against administration of single doses of tepotinib to healthy subjects. It is recognized that healthy subjects will not get benefit by participating in this study. However, this study will investigate the bioequivalence of a new tablet formulation (tablet formulation 3, TF3) of tepotinib, which is the envisaged market formulation, compared to the formulation used in Phase 2 studies (tablet formulation 2, TF2). Moreover, the study will generate mandatory human data about the potential influence of food on pharmacokinetics (PK) of tepotinib.

Further, justification based on the accumulated safety experience is provided. During the development of tepotinib, in all 3 studies performed in healthy subjects (n = 79), the subjects well tolerated a single or 3 doses of tepotinib (different dose levels up to 500 mg single dose). All treatment-emergent adverse events (TEAEs) were mild to moderate, except 1 Grade 3 asymptomatic 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 according to Fridericia (QTcF) values were noted.

Elevations in serum lipase and amylase are considered as the only identified risks for subjects administered tepotinib so far. These elevations were observed in 5 of 79 healthy subjects exposed to tepotinib and were mild to moderate in severity (exception: 1 Grade 3 lipase elevation), transient

and without apparent dose dependency. All increases of serum amylase/lipase were asymptomatic and not associated with pancreatitis.

Subjects enrolled in this study might be exposed to a potential 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.

Since loss of c-Met induces teratogenic effects in c-Met knockout mice, and since a pilot embryofetal development study in rabbits revealed maternotoxic effects and a dose-dependent increased number of skeletal malformations (teratogenicity), stringent criteria are applied to ensure exclusion of women of childbearing potential in this study. Only healthy women that are known to be postmenopausal or surgically sterile (ie due to hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) will be enrolled in this study (for details see Section 5.3.1). Male subjects will be required to take precautions with regards to female partners.

To further mitigate any risk, a close monitoring of the safety laboratory parameters, ECG, and vital signs will be performed in all healthy subjects. Subjects will be admitted to the study site and remain resident there for at least 72 h after administration of a single dose in each treatment period, to allow continuous safety monitoring. In addition, frequent monitoring of subjects is ensured by subsequent ambulant visits and by choosing a CRO experienced in the conduct of clinical pharmacology studies.

For the PK of tepotinib refer to the IB.

3.1 Trial Rationale

This trial will investigate the bioequivalence of a new tablet formulation (Tablet Formulation 3, TF3, test treatment) of tepotinib, which is the envisaged market formulation, compared to the formulation used in Phase 2 studies (Tablet Formulation 2, TF2, reference treatment). In addition, the study will generate human data about the potential influence of food on the PK of tepotinib.

This trial consists of 3 parts: the bioequivalence part (Part A with 2 stages) and the food effect parts (Parts B and C).

Part A of the trial will investigate the bioequivalence of a new tablet formulation of tepotinib (TF3) in comparison to the tablet formulation used in the Phase 2 studies (TF2) using an open-label, 2-period crossover, 2-stage design under fasted conditions.

In Parts B and C of the study the effect of food on the PK of tepotinib will be investigated using an open-label, 2-period crossover design in Part B (TF2) and Part C (TF3) each. Tepotinib drug substance is a hydrochloride salt and a mono hydrate. Food administered together with the respective formulation might have an influence on the rate and extent of absorption in the target population.

The trial design is based on the regulatory guidelines of the Food and Drug Administration (FDA) [1, 2] and the European Medicines Agency (EMA) [3].

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP [7], 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 Objectives

- Part A: To demonstrate bioequivalence between the new tablet formulation (TF3, test treatment) and the tablet formulation used in clinical studies (TF2, reference treatment) after single dose administration in healthy subjects under fasting conditions
- Parts B and C: To investigate the food effect, ie the difference in PK between administration after a high-calorie, high-fat breakfast and administration under fasting conditions in healthy subjects, for both TF3 and TF2.

4.2 Secondary Objectives

- To further investigate the PK of tepotinib
- To assess the safety and tolerability of tepotinib (TF3 and TF2) under fasting and non-fasting conditions.

4.3 Exploratory Objectives

- Part A: To investigate the PK of metabolites after administration of both tablet formulations (TF3 and TF2) of tepotinib
- Parts B and C: To investigate the effect of food on the PK of metabolites of tepotinib
- To explore the effect of pharmacogenetics (PGx) and variations of associated genes on the PK profile of tepotinib (if applicable).

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a Phase 1, single-dose, open-label, 3 parts trial (Parts A, B and C; see [Figure 1](#)). In each of the parts, a 2-way, 2-period, 2-sequence cross-over design will be conducted. Part A has 2 stages. The procedure will follow the method C described by Montague [4] and Potvin [5]. All 3 study parts are planned to be conducted concurrently.

Part A has a two-stage adaptive design (see section [8.2.1](#)). This design is chosen due to the residual risk with respect to the PK-variability of tepotinib in the fasted state.

Stage 1 will be sufficiently powered to show the bioequivalence of the new tablet formulation (TF3) and the tablet formulation used in clinical studies (TF2), based on an assumption for PK-variability in the fasted state as data is not available. The Stage 2 will be performed only, if after

Stage 1, the PK-variability turns out larger than initially assumed. For Stage 2, additional subjects will be randomized based on the newly estimated PK-variability.

More details are given in Section [8.2.1](#).

Parts B and C will investigate the effect of food on the PK of tepotinib using a 2-way, 2-period, 2-sequence cross-over design following administration of the previous tablet formulation (TF2, Part B) and administration of the new tablet formulation (TF3, Part C), in 12 healthy subjects each. Each subject will receive the tablet under fasted and fed conditions.

Common Visit Schedule

Trial procedures are the same for all periods in all parts except for the food intake on Day 1.

The washout period will be at least 21 days between Day 1 of each period (see [Figure 2](#)).

A screening period is implemented from Day -21 to Day -2.

Subjects will be admitted to the study site on Day -1 of each period and will be resident at the study site under medical supervision from Days -1 to 4. They must visit the site on the morning of Days 5 to 8 for further blood sampling.

Blood and urine samples will be collected for laboratory assessments (hematology, biochemistry, urinalysis), which will be performed at Screening, throughout the in-patient period of each treatment period and for the End of Trial Visit.

Serial blood samples for PK assessments will be collected for 168 h after tepotinib administration in all periods.

The End of Trial Visit is planned 21 days (\pm 1 day) after tepotinib administration in the second period. 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 Overall Trial Design

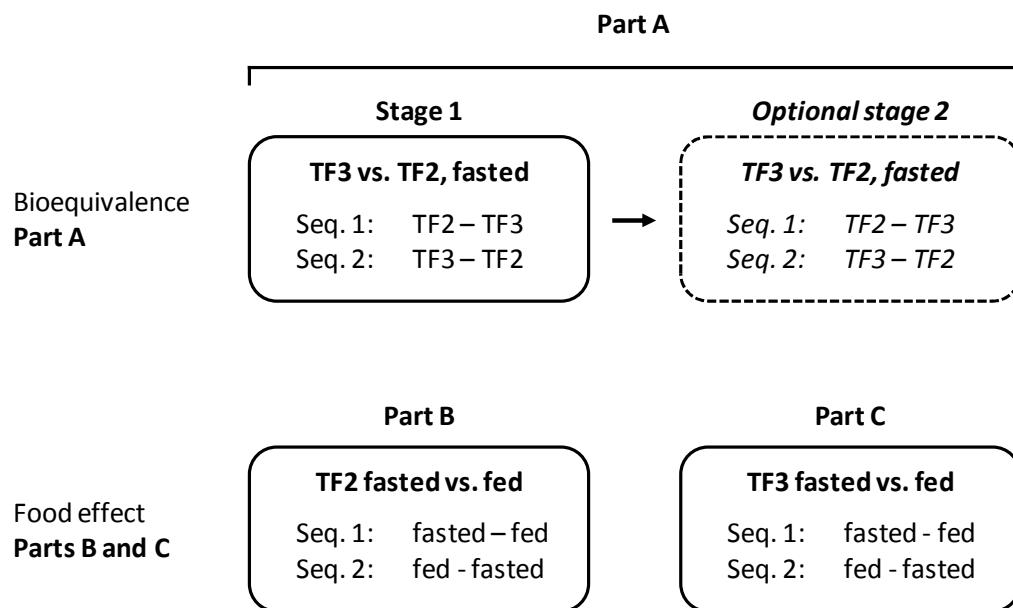


Figure 2 Design of the Trial Parts

Procedure	Parts A, B and C - All Periods			
	-1	1	2 - 4	5 - 8
Tepotinib administration		↑		
PK blood sampling		↔		
Safety assessments ^a	↔			
AE monitoring	↔			
Hospitalization	↔			

AE = adverse event, PK = pharmacokinetics

The washout period will be at least 21 days between Day 1 of each period.

^a Safety assessments: Vital signs, 12-lead electrocardiogram, clinical laboratory during hospitalization.

A detailed schedule of study procedures and assessments is provided in [Table 1](#).

5.2 Discussion of Trial Design

The trial design is based on the regulatory guidelines of the FDA [1, 2] and the EMA [3]. The primary objectives are to demonstrate the bioequivalence under fasting conditions of the new formulation TF3 versus the current formulation TF2 (Part A), and to investigate the food effect for

both TF2 (Part B) and TF3 formulations (Part C). The new formulation TF3 has been developed aiming for a robust and reliable manufacturing process. While TF2 is administered under fed conditions in the Phase 2 studies due to its higher bioavailability under fed state conditions, the bioequivalence of TF3 versus TF2 will be investigated in this study Part A under fasted conditions, in line with the regulatory recommendations for bioequivalence studies with immediate-release formulations (see [1, 2, 3]). Hence, demonstration of bioequivalence of TF3 versus TF2, and knowledge of the extent of any food effect on both formulations are essential information for further clinical development of TF3.

5.2.1 Inclusion of Special Populations

Not applicable.

5.2.2 Scientific Rationale for Trial Design

The trial design and endpoints are typical for bioequivalence or food interaction studies of this type. The single dose design is more sensitive in showing changes in the PK as compared to multiple dose designs.

As illustrated in [Figure 1](#), the study consists of 3 parts (Parts A, B, and C), and will utilize a randomized open-label, 2-period, 2-sequence crossover design in each part to minimize the influence of covariates. Part A will investigate the bioequivalence of TF3 (test) vs TF2 (reference) administered under fasted condition (Part A: TF3 fasted vs TF2 fasted). Part B will investigate the food effect on TF2 (Part B: TF2 fasted vs fed), and Part C will investigate the food effect on TF3 (Part C: TF3 fasted vs fed). The washout period will be at least 21 days between Day 1 of each treatment period. Despite the elimination terminal half-life ($t_{1/2}$) of about 30 h for the parent compound and about 45 h for the main metabolites MSC2571109A and MSC2571107A (Study MS200095-0012), very low concentrations (< 5% of the maximum plasma concentration [C_{max}]) were observed after 14 days in study MS200095-0012. Thus, no (or very low) concentrations above the detection limit are expected after a 21 days washout period as implemented in this study. This trial will be performed in healthy volunteers to standardize the trial population and minimize inter-subject variability.

Since relevant data on the variability of the tepotinib PK for TF2 at the relevant dose under fasted conditions are currently not available, Part A will utilize a 2-stage design with bioequivalence testing after Stage 1 and potential extension to Stage 2 with adjusted sample size if the PK variability is larger than expected (see [Section 8.2.1](#) for details).

5.2.3 Justification for Dose

The 500 mg single oral dose has been studied in previous studies in healthy subjects and was found to be safe and well tolerated. The tepotinib dose of 500 mg is the Phase 2 dose for the treatment of human malignant tumors.

5.2.4 Rationale for Endpoints

The peak (C_{\max}) and extent (area under the plasma concentration-time curve [AUC]) of exposure after single dose administration are considered adequate endpoints to evaluate the bioequivalence (Part A) and the effect of food (Parts B and C). These endpoints are in line with the regulatory guidance of the FDA and the EMA (see Section 3.1). In a previous clinical study with single-dose administrations in 23 subjects of 500 mg tepotinib as the TF2 formulation (EMR200095-0012), the median time to reach the maximum plasma concentration (t_{\max}) was 8 h (ranging from 4 h to 24 h), and the mean apparent half-life was 35 h (ranging from 28.3 h to 58.8 h). The PK sampling scheme (see Table 1) with sampling up to 168 h after administration is expected to adequately cover the absorption, distribution and elimination phases up to $> 80\%$ of the AUC from time zero (dosing time) extrapolated to infinity ($AUC_{0-\infty}$).

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 not part of the subject's routine medical care, the Investigator will ensure that the subject has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

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

1. Male or female, aged 18 to 55 years inclusive (at Screening)
2. Body mass index (BMI) ≥ 18.5 and $\leq 29.9 \text{ kg/m}^2$ and body weight between 50 to 100 kg, inclusive (at Screening)
3. A female participant is eligible to participate if she is not pregnant, not breastfeeding and of non-childbearing potential, confirmed at Screening, by fulfilling at least 1 of the following criteria:
 - Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] $> 40 \text{ mIU/mL}$)
 - Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy
4. A male participant must agree to use and to have his female partner of childbearing potential to use highly effective methods of contraception (ie methods with a failure rate of less than 1% per year) as detailed in the Clinical Trial Facilitation Group (CTFG) recommendations [6] during the period of participation in the study and for at least 3 months after the last IMP administration (see Appendix III). Males must also refrain from donating sperm during this period and should always use a barrier method such as condom concomitantly. The male participants will be asked to report pregnancies in their female partners up to 3 months after the last IMP intake.
5. Subject must be healthy, as assessed by the Investigator, with no clinically significant abnormality identified on physical examination and no active clinically significant disorder,

condition, infection or disease that would pose a risk to subject safety or interfere with the 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 and lipase should not exceed the upper limit of normal range (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should not exceed the ULN x 1.1.

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
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 pre-study 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 > 140 or < 90 mmHg, diastolic blood pressure > 90 or < 50 mmHg, and pulse rate > 90 or < 50 beats per minute (min) at Screening and at Admission on Day -1 (Any abnormal blood pressure results may be repeated once and if the repeat result is within the normal range, it is not considered to have met the exclusion criterion)
5. 12-Lead ECG showing a QTcF > 450 ms, PR > 215 ms, or QRS > 120 ms
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). In case of a borderline result between ≥ 80 and 90 mL/min, Cystatin C will be determined in addition, and the subject will only be included if the Cystatin C value is below the ULN.
7. Subjects with gall bladder removal or other relevant surgery of gastrointestinal tract. (Appendectomy is not considered as relevant)
8. History of any malignancy except for adequately treated superficial basal cell carcinoma
9. History of epilepsy
10. Ascertained or presumptive allergy/hypersensitivity to 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. Positive screen for alcohol and drugs of abuse (at Screening and Day -1 of Period 1)

12. Positive screen for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, and human immunodeficiency virus 1 and 2 antibodies (HIV1/HIV2 antibodies) (at Screening)
13. Excessive consumption of xanthine-containing food or beverages (> 5 cups of coffee or equivalent a day) or inability to stop consuming caffeine (at Screening and Day -1)
14. Receipt of any prescription or nonprescription medication within 14 days or 5 half-lives, whatever is longer, before study drug administration (apart from paracetamol up to 1500 mg per day, as judged appropriate by the Investigator)
15. Smoker (cigarettes, pipes, cigars, or others) or former smoker who stopped smoking for less than 6 months before the time of the Screening Visit
16. Intake of grapefruit, Seville orange, cranberry or juices of these fruits, or St John's Wort, from 14 days prior to Day -1 of Period 1
17. Inability to communicate or cooperate with the Investigator (eg, language problem, illiteracy, poor mental status) or to comply with the requirements of the entire study, including dietary restrictions
18. Other factors, which in the opinion of the Investigator may interfere with study conduct (at Screening and Day -1 of Period 1 only)
19. Legal incapacity or limited legal capacity
20. Subjects kept in detention
21. Subjects of Part B and Part C who are not able or willing to eat the entire high fat, high calorie breakfast.

5.4 Criteria for Initiation of Trial Treatment

Inclusion and exclusion criteria will be checked within the screening period and again on Day -1 of Period 1. Subjects meeting all the inclusion and none of the exclusion criteria will be randomized to a treatment sequence on Day 1 of the first treatment period.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Trial Therapy

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

- The subject requires treatment with any medication suspected or known to interfere with the IMP
- 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 1](#)).

Part A: Subjects who dropped out will not be replaced as per design specificity. A drop-out compensation of 4 subjects will be added for Stage 1. A drop-out compensation for Stage 2 will be considered, if appropriate.

Parts B and C: Subjects who dropped out will be replaced as needed to have at least 12 evaluable subjects as recommended by the guideline.

5.5.2 Withdrawal from the Trial

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

- Subject withdrew consent
- Subject lost to Follow-up
- Participation in another clinical study
- Relevant adverse events (AEs), especially SAEs, 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 6.5.2](#). However, any medications that are considered necessary for the subject's well-being (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 the IMP by the Investigator with alternate etiology identified:
 - Abnormal clinically relevant vital signs confirmed on 2 or more measurements (minimum 5 min intervals), including abnormal blood pressure
 - hypotension defined as systolic < 80 mmHg and/or diastolic < 40 mmHg, or
 - hypertension defined as systolic > 160 mmHg and/or diastolic > 100 mmHg
 - Abnormal clinically relevant ECG findings, including a corrected QT-interval (ad modus Fridericia; QTcF) > 500 ms or an increase in QTcF > 60 ms compared to baseline, confirmed on ≥ 2 repeat measurements
 - Marked increases in liver or renal parameters (ALT/AST ≥ 3 x ULN, total bilirubin ≥ 2 x ULN, creatinine > 1.5 x ULN confirmed by ≥ 2 repeat measurements

- Any clinically relevant symptom or sign which in the opinion of the investigator and/or sponsor warrants subject withdrawal.

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

In case a subject should be withdrawn from the trial, the medical monitor and clinical trial leader at the Sponsor will be informed immediately. If there is a medical reason for the withdrawal, appropriate medical care will be provided.

In case of premature withdrawal from the trial, the assessments scheduled for the last End of Trial Visit should be performed, as Early Termination Visit, if possible with focus on the most relevant assessments (see [Table 1](#)). In any case, the appropriate electronic case report form (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 IMP. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrolment, or because of discontinuation of clinical development of an IMP or withdrawal of an IMP or comparator from the market for safety reasons.

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

5.7 Definition of End of Trial

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

A clinical trial protocol may not be considered closed as long as:

- Any subject is still receiving any IMP
- Visits specified by the protocol are still taking place
- Procedures or interventions according to the protocol are still being undertaken in any subject
- The post-treatment follow up period, defined in the clinical trial protocol as being part of the trial, has not yet been completed for any subject.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

6.1 Description of the Investigational Medicinal Products

Investigational Medicinal Products:

Tepotinib (MSC2156119J), 3-(1-{3-[5-(1-Methyl-piperidin-4-ylmethoxy)-pyrimidin-2-yl]-benzyl}-1,6-dihydro-6-oxo-pyridazin-3-yl)-benzonitrile hydrochloride hydrate (HCl), is supplied as

- 250 mg (oblong, light pink) film-coated TF3 for oral administration (test formulation)
Tepotinib 250 mg film-coated tablets TF3 have a drug load of approximately 30% and contain the excipients D-mannitol, microcrystalline cellulose, crospovidone, magnesium stearate, silica colloidal anhydrous, and Opadry® II pink.
- 500 mg (oblong, light yellow) film-coated TF2 for oral administration (reference formulation).
Tepotinib 500 mg film-coated tablets (TF2) have a drug load of approximately 50% and contain the excipients D-mannitol, silica colloidal anhydrous, crospovidone, magnesium stearate, and Opadry II yellow.

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

For dosage and administration see Section [6.2](#).

Reference product: Not applicable.

Specific rules for treatment modifications: Not applicable.

6.2 Dosage and Administration

Subjects will receive the following treatments:

Part A - Bioequivalence

Subjects will receive the following single doses of tepotinib in randomized order:

- 1 film-coated tablet TF2 containing 500 mg tepotinib
- 2 film-coated tablets TF3 containing 250 mg tepotinib each, total dose 500 mg tepotinib.

TF2 and TF3 will be administered in the fasted state (at least 10 h fasting) together with 240 mL of water.

Parts B and C - Food Effect

Part B (Tepotinib TF2):

Subjects of Part B will receive the following single doses of tepotinib in randomized order:

- 1 film-coated tablet TF2 containing 500 mg tepotinib, administered in the fasted state (at least 10 h fasting) together with 240 mL of water
- 1 film-coated tablet TF2 containing 500 mg tepotinib, administered 30 min after start of a high-fat, high-calorie breakfast which must be consumed completely within 25 min. The tablet will be administered together with 240 mL of water.

Part C (Tepotinib TF3):

Subjects of Part C will receive the following single doses of tepotinib in randomized order:

- 2 film-coated tablets TF3 containing 250 mg tepotinib each, total dose 500 mg tepotinib, administered in the fasted state (at least 10 h fasting) together with 240 mL of water
- 2 film-coated tablets TF3 containing 250 mg tepotinib each, total dose 500 mg tepotinib, administered 30 min after start of a high-fat, high-calorie breakfast which must be consumed completely within 25 min. The tablets will be administered together with 240 mL of water.

The high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) breakfast consists of: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces (1 ounces = 28.35 g) of hash brown potatoes (approximately 120 g) and 8 ounces of whole milk (approximately 240 mL).

For all Parts (A, B and C):

The minimum washout period will be at least 21 days between Day 1 of each period to prevent any significant PK carryover effects between periods.

Subjects will be administered the tablet formulations in upright position.

In all periods 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.

Food intake is not allowed for 4 h after IMP administration. Further drinking is not allowed from 1 h before to 1 h after IMP administration.

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

6.3 Assignment to Treatment Groups

Only subjects who comply with all selection criteria will be included into the trial. The subjects will be enrolled into either Part A, B or C, and will be recruited separately for each of the study

parts. Prior to the first administration, the subjects enrolled into the respective Part A, B, or C will be randomly assigned to 1 of 2 treatment sequences, via the random number on Day 1 (see Section 8.3).

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

The Investigator will keep a record relating the subjects' random numbers and the names of all subjects (including screening number and the Nuvisan GmbH ID number) who have given their informed consent, to allow easy checking of data in subject files, when required. This record will also include the date of subject's enrolment and completion, as well as subjects who could not be randomized for whatever reason.

6.4 Non-investigational Medicinal Products to be Used

Not applicable.

6.5 Concomitant Medications and Therapies

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

6.5.1 Permitted Medicines

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

Any medications that are considered necessary to protect subject welfare and that will not interfere with the IMP may be given at the Investigator's discretion. The potential drug-drug interactions 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 study from the date of signature of informed consent.

6.5.2 Prohibited Medicines

The subjects are prohibited from using prescription or over-the-counter medications (apart from paracetamol up to 1500 mg per day, as judged appropriate by the Investigator) within 14 days or 5 half-lives, whichever is longer, prior to the first 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 (as provided by the site) and will be reminded regularly.

Throughout the PK profiling day, the following restrictions must be met:

- Subjects will be in the fasted state for at least 10 h before administration of tepotinib (except for the breakfast)
- Drinking is not allowed 1 h before and after administration of tepotinib (except for the breakfast and administration)
- 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 trial site during the in-patient period
- No intake of caffeine- and xanthine-containing food and beverages (eg coffee, black or green tea, cola, cocoa, chocolate or chocolate-containing food or beverages) from 48 h before administration of tepotinib in each period until collection of last PK blood sampling of each period
- No intake of herbs or fruits that can have an influence on the PK (eg St. John's wort, Seville oranges, grapefruits, cranberry or the juice of these fruits), from 14 days prior to Day -1 of Period 1 until final examination
- No intake of poppy seeds (eg poppy seed rolls, poppy seed cake, yoghurt containing poppy seed etc.) from 72 h before first administration of study drug until completion of final examination
- No intake of concomitant medication within 14 days or 5 half-lives, whatever is longer, before first administration of 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 or 5 half-lives, whatever is longer, 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 study site for all AEs occurring during the study.

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.

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

The IMP supplies will be recorded in an IMP inventory.

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

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

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

6.8 Investigational Medicinal Product Accountability

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

- Upon receipt of IMPs, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File
- IMP dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit.
- Trial site IMP accountability records will include the following:
 - Confirmation of IMP receipt, in good condition 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, vial 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. No IMP that is dispensed to a subject may be redispensed to a different subject.

A Trial Monitor will periodically collect the IMP accountability forms.

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

6.9 Assessment of Investigational Medicinal Product Compliance

During the treatment periods, drug administrations will be performed by a Nuvisan GmbH staff member in accordance with the specifications of the Investigator. This includes checking the oral and buccal cavity with the aid of a flashlight and tongue depressor. The proper administration of the trial medication will be documented on the individual eCRF.

6.10 Blinding

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

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol or planned for an individual subject enrolled in the trial. Even if it does not meet other criteria for an SAE, any overdose must be recorded in the trial medication section of the eCRF and reported to Drug 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.

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

Study procedures are the same for all periods in all parts except for the food intake on Day 1. A detailed schedule of trial procedures/assessments is provided in Table 1.

Prior to performing any trial assessments that are not part of routine medical care for the subject, 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. The Screening examination will be conducted not more than 21 days prior to the planned first drug administration, ie between Day -21 to Day -2 before commencing to first study period. Only subjects who meet the inclusion criteria and none of the exclusion criteria will be admitted to the trial.

Prior to Screening examination, the subjects will receive a screening number for identification. Eligible subjects will receive a random number upon enrolment into the study.

There is a notification on the subject's card as well as in the electronic subjects' 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 (ICF).

At Screening (Days -21 to -2), the following assessments will be performed (Table 1):

- Recording of demographic information including body height, body weight and BMI
- Recording of medical history

- Physical examination
- Measurement of vital signs
- 12-lead safety ECG recording (as triplicate)
- Blood and urine sampling for safety laboratory assessments
- Serological tests for hepatitis B, C, and HIV1/HIV2
- Serum Pregnancy test (for females)
- Urine drug screen (including test for cotinine)
- Alcohol breath test
- Assessments of AEs
- Documentation of prior and concomitant medication
- Preliminary evaluation of inclusion and exclusion criteria.

7.1.2 Treatment Periods

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

For time points and assessments please refer to [Table 1](#) (Parts A, B and C).

Day -1 (Admission)

Subjects will be admitted to the clinic in the morning of Day -1 until completion of the 72 h assessments in the morning of Day 4 of each period.

In each period, the following assessments will be performed:

- Physical examination
- Measurement of vital signs
- 12-lead safety ECG recording
- Blood and urine sampling for safety laboratory assessments
- Pregnancy test (in urine)
- Urine drug screen (including test for cotinine)
- Alcohol breath test
- Assessment of AEs
- Documentation of concomitant medication
- Evaluation of inclusion and exclusion criteria (Period 1 only)

- Blood sampling for PGx (Period 1 only).

Days 1 to 4 (inpatient)

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

- Measurement of vital signs
- 12-lead safety ECG recording
- Blood and urine sampling for safety laboratory assessments
- Pre-dose PK blood sample for determination of tepotinib and its metabolites.

After completion of pre-dose assessments study drug will be administered in the morning of Day 1 of each period as the following:

Part A: Study drug will be administered in both periods in the fasted state together with 240 mL of water.

Parts B and C: Study drug will be administered in one period in a fasted state and in the other period 30 min after start of a standardized high fat, high calorie breakfast, which must be consumed completely within 25 min. The study drug will be administered together with 240 mL of water.

A detailed guidance on dosage and administration is provided in Section [6.2](#).

After dosing the following assessments will be performed at the time points given in the Schedule of Assessments ([Table 1](#)):

- PK blood samples for determination of tepotinib and its metabolites will be taken regularly until 72 h (Day 4) post-dose before discharge (for time points please refer to Table 1)
- Measurement of vital signs and 12-lead safety ECG recordings on Day 1 (2 h and 8 h post-dose), Day 2 and Day 4 before discharge
- Blood and urine sampling for safety laboratory assessments on Day 2 and Day 4 before discharge
- Physical examination (only on Day 2 and Day 4 before discharge)
- Regular assessment of AEs and concomitant medication.

After completion of the Day 4 assessments (72 h measurements) subjects will be discharged.

Days 5 to 8 (ambulatory)

Subjects will return to the clinic for daily blood sampling to determine the PK of tepotinib. Additionally, AEs will be monitored and concomitant medications will be recorded.

The washout period will be at least 21 days between Day 1 of each period (see [Figure 2](#)).

Restrictions:

A detailed listing of restrictions during the trial is provided in Section [6.5](#).

7.1.3 End of Trial Visit

The End of Trial examination has to verify that all values tested in the Screening have remained within a clinically acceptable range. The assessments will be performed 21 days (± 1 day) after tepotinib administration in the second period. 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 following assessments will be performed:

- Physical examination
- Measurement of vital signs
- 12-lead ECG recording
- Blood and urine sampling for safety laboratory assessments
- Serum Pregnancy test (for females)
- Assessment of AEs
- Documentation of concomitant medication.

No medical treatment is planned after the End of Trial.

The End of 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: date of birth, sex (gender), race, ethnicity, height, weight, and BMI.

Furthermore, the following will be documented:

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

7.3 Efficacy Assessments

Not applicable.

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings including vital signs 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 (NCI) - Common Terminology Criteria for AEs (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 of a particular AE is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following 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.

According to Sponsor convention, 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 described 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 the IMP (including any other non-IMPs, or medical procedures, as applicable, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP, known side effects of the IMP, medical history, concomitant medication, course of the underlying disease, trial procedures.

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

Related: Reasonably related to the IMP. AE could medically (pharmacologically/clinically) be attributed to the IMP/study treatment 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 hydration therapy application) 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 and all non-serious AEs of special interest 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 IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of the IMP.

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 h** 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, 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 AE 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 [7], 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 particular and 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” [SUSARs]). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

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

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

7.4.1.6 Monitoring of Subjects with Adverse Events

AEs are recorded and assessed continuously throughout the trial (see Section 7.4.1.3) and are assessed for final outcome at the End of Trial Visit. All 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 and urine samples will be collected for the clinical laboratory tests (hematology, biochemistry, virology, drugs of abuse, hormones, and urinalysis) following the timing noted in the Schedule of Assessments ([Table 1](#)). Additional laboratory safety examinations during the course of the trial are at the discretion of the Investigator.

All blood and urine samples must be clearly identified and 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.

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

All safety laboratory examinations will be carried out under fasting conditions. Some additional parameters may be routinely analyzed by the laboratory after abnormal findings, or requested by the Investigator, including but not limited to eg microscopic differential blood count, direct bilirubin and creatine phosphokinase myocardium/brain type.

In case of positive findings of blood, protein, nitrite or leucocytes in the urinalysis, a subsidiary microscopic examination of the sediment will be performed.

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

The following parameters will be determined as summarized in [Table 2](#).

The amount of blood sampled in this trial is specified in [Appendix II](#).

Table 2 Clinical Laboratory Evaluations

Biochemistry	Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase γ-Glutamyl-transferase Lactate dehydrogenase Creatine phosphokinase ^b Amylase Lipase	Bilirubin (total) ^a Cholesterol Triglycerides Uric acid	Sodium Potassium Creatinine Urea Glucose Cystatin C (if applicable)
Hematology	Hematocrit Hemoglobin Red blood cell count Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration	Platelet count White blood cell count	White blood cell differentials and absolute counts ^c : Basophils Eosinophils Lymphocytes Monocytes Neutrophils
Urinalysis	pH Nitrite Protein Glucose	Ketone bodies Urobilinogen Bilirubin	Leucocytes Blood Microscopic examination ^d
		Urine pregnancy test, females only	
Urine drug screen	Cocaine Amphetamines Methamphetamines Opiates	Barbiturates Benzodiazepine 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), females only eGFR ^e Alcohol breath test		

eGFR = estimated glomerular filtration rate, HIV = human immunodeficiency virus, beta-HCG = beta-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 leukocytes are positive on the dipstick.

^e Estimated glomerular filtration rate calculated using the Cockcroft-Gault equation.

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 per the oscillometric method using an automated device, which also indicates the corresponding pulse rate. Blood pressure and pulse rate will be measured after at least 5 min in a supine position, according to the Schedule of Assessments (see [Table 1](#)).

Body temperature will be measured auricular.

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

7.4.4.2 Physical Examination

A standard examination will be performed including general appearance, skin, head, neck (including thyroid), eyes, ears, nose, throat, abdomen, as well as neurological, peripheral vascular, musculoskeletal, cardiovascular and pulmonary system.

Physical examination will be scheduled according to the Schedule of Assessments (see Table 1). Further physical examinations during the trial are at the discretion of the Investigator. Any relevant findings are to be recorded on the Medical History form in the eCRF (for findings from the past that occurred prior to ICF signature) or on the AE form in the eCRF (for findings presently occurring; events existing but unresolved prior to drug administration).

7.4.4.3 Electrocardiogram

12-lead ECGs will be recorded according to the Schedule of Assessments (see Table 1) using the ECG system Cardio Perfect®, Welch Allyn. The ECGs will be recorded in a supine position after at least 5 min rest.

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

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

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

7.4.4.4 Alcohol Breath Test

A commercially available breath analyzer (Alcotest 6510, Draeger Safety GmbH) will be used to determine the concentration of alcohol in the subject's breath according to the Schedule of Assessments (see Table 1).

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

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.

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.

Plasma concentrations of tepotinib and its metabolites MSC2571109A and MSC2571107A will be determined in each period according to the sampling schedule outlined in the Schedule of Assessments (see [Table 1](#)). 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 3 need an explanation and will be considered as protocol violation.

Table 3 Time Windows

Planned Blood Sampling	Time Windows (min)
Pre-dose	- 60
0.25 - 1 h post-dose	± 2
> 1 h - 12 h post-dose	± 5
> 12 h - 48 h post-dose	± 15
> 48 h - 168 h post-dose	± 30

Concentrations of tepotinib and its metabolites MSC2571109A and MSC2571107A will be measured using validated liquid chromatography-tandem mass spectrometry methods at Nuvisan. The assays will be carried out in accordance with Good Laboratory Practice regulations and the EMA reflection paper. A separate bioanalytical protocol will be provided before the start of the analytical part of the trial. Full details of the bioanalytical method used will be described in a separate bioanalytical report.

7.5.2 Calculation of Pharmacokinetic Variables

Noncompartmental computation of PK parameters will be performed using the software Phoenix® WinNonlin® 6.4 or higher (Certara, L.P., Princeton, New Jersey). For definitions of PK parameters, see [Table 4](#).

Table 4 **Definition of PK Parameters for Tepotinib and its Metabolites 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-∞}	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 $AUC_{0-∞}$ calculated by $C_{last,pred}/\lambda_z$, where $C_{last,pred}$ is the predicted plasma concentration at the last sampling time point, calculated from the log-linear regression line for λ_z determination at which the measured plasma concentration is at or above LLOQ
C _{max}	Maximum plasma concentration observed
t _{last}	The last sampling time at which the concentration is at or above the lower limit of quantification
t _{max}	Time to reach the maximum plasma concentration
t _{1/2}	Terminal half-life, calculated as $\ln 2/\lambda_z$
λ_z	Terminal rate constant determined from the terminal slope of the log-transformed plasma concentration curve using linear regression on terminal data points of the curve
CL/f	Apparent total body clearance of drug from plasma following oral/extravascular administration, calculated as dose/AUC _{0-∞} , only parent drug, will not be calculated for the metabolites
V _{z/f}	Apparent volume of distribution during the terminal phase following oral/extravascular administration, will not be calculated for the metabolites
AUC _{extra}	The AUC from time t_{last} extrapolated to infinity
AUC _{extra%}	$AUC_{extra\%} = (AUC_{extra} / AUC_{0-∞}) \times 100$

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

Concentrations below the lower limit of quantification (< LLOQ), which are before the last quantifiable data point, will be taken as zero for calculating the AUC.

7.6 Biomarkers

Biomarkers are not determined in this trial.

7.7 Pharmacogenetics

Pharmacogenetic sampling is mandatory for trial participation. An additional separate ICF will be used. One blood sample should be collected in duplicate on Day -1 of the first treatment period prior to administration. The pharmacogenetic samples will be analyzed conditionally in case of unexpected PK profiles. The results of the PGx analysis, as applicable, will be described in a separate report.

Storage and analyses of samples will be handled according to the specifications described in the ICF.

7.8 Other Assessments

Not applicable.

8 Statistics

8.1 Statistical Hypotheses

Part A

The following null hypothesis for the ratio of the geometric means (GeoMean) will be used to assess bioequivalence

$H_0: \mu_T/\mu_R \leq 0.8000$ or $1.2500 \leq \mu_T/\mu_R$ for at least one parameter (AUC_{0-t} or AUC_{0-∞} or C_{max})

$H_1: 0.8000 < \mu_T/\mu_R < 1.2500$ for all parameters (AUC_{0-t} and AUC_{0-∞} and C_{max})

where μ_T and μ_R are the geometric means for the test and reference treatment respectively.

The test treatment is the new tablet formulation (TF3) and reference is the tablet formulation used in clinical studies (TF2) both under fasting condition.

The null hypothesis will be tested using a two-stage adaptive design.

Parts B and C

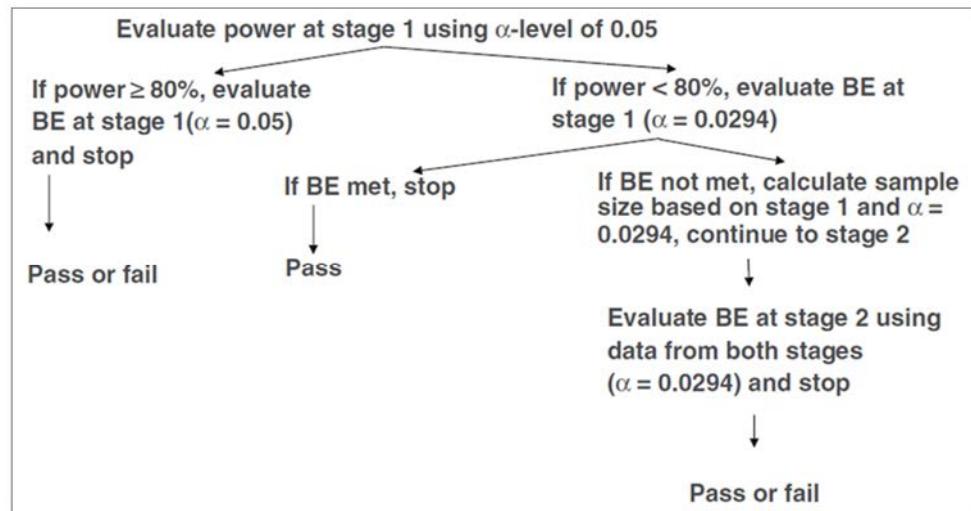
The statistical analysis of study data will be descriptive; no hypothesis tests will be performed.

8.2 Sample Size

8.2.1 Part A (Bioequivalence)

Part A of the study is planned as a two-stage adaptive design (see [Figure 3](#)) due to the residual risk with respect to the unknown PK-variability of tepotinib in the fasted state. The procedure will follow the method C described by Montague [\[4\]](#) and Potvin [\[5\]](#). For the first stage, the trial will be sufficiently powered to show bioequivalence based on an assumption for PK-variability in the fasted state (reliable data not available).

Figure 3 **Diagram of Two-Stage Adaptive Design**



Source: (Montague et al [4]) [Figure 2](#); BE: Bioequivalence

The total and mixed intrasubject variabilities CVs (%) observed most recently for AUC_{0-t} and C_{max} of tepotinib are summarized in Table 5.

Table 5 **Overview of the PK-Variability Observed in the Previous Tepotinib Studies**

Study	Formulation Dose (Condition)	Arm	AUC_{0-t}		C_{max}	
			Total Geometric CV%	Mixed intra- individual CV%	Total Geometric CV%	Mixed intra- individual CV%
EMR200095-002	TF1 - 30 mg (fed vs. fasted)	TF1 Fed	12.9%		14.8%	
		TF1 Fasted	18.3%	11.1%	28.2%	23.7%
EMR200095-007	CF2 vs. TF1 30 mg (fed)	CF2	28.7%		30.4%	
		TF1	21.4%	12.2%	26.3%	12.8%
EMR200095-0012	TF1 vs. TF1* 100 mg (fed)	TF1	20.4%		22.8%	
		TF1*	24.8%	10.0%	29.5%	12.7%
EMR200095-0012	TF1 vs. TF2 500 mg (fed)	TF1	24.0%		19.8%	
		TF2	27.0%	10.1%	26.2%	12.6%

AUC_{0-t} = area under the plasma concentration-time curve from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification, CF2 = Capsule Formulation 2; C_{max} = maximum plasma concentration, CV = coefficient of variation, PK = pharmacokinetics, TF1 = Tablet Formulation 1; TF1* = Tablet Formulation 1 with finely micronized active pharmaceutical ingredient; TF2 = Tablet Formulation 2.

Overall, the total variability in AUC and C_{max} in the fed state was between 12.9% and 26.3% for the formulation TF1. The mixed intrasubject variabilities of AUC and C_{max} were largely dose-independent ranged between 10.0% and 12.8% in the fed state across all the investigated doses.

AUC total variability was similar between TF1 and TF2 at the dose of 500 mg but C_{max} variability was somewhat higher for TF2.

Only one study (EMR200095-002) investigated tepotinib under fasted condition. The maximum value for the mixed intrasubject variability was observed for C_{max} (CV of 23.7%). As no data is available for the 500 mg dose level under fasted conditions, the CV value is assumed to be around 24% for C_{max} and slightly lower for AUC in this study.

With these assumptions, an assumed geometric mean ratio Test/Reference (GMR T/R) of 0.95, a one-sided alpha level of 0.05, 36 evaluable subjects will be needed to provide approximatively 90% power to show bioequivalence already in the first stage. A drop-out compensation of 4 subjects will be added.

With a CV of 29%, the sample size of 36 evaluable subjects would still result in approximately 80% power to show bioequivalence in the first stage.

The second stage will be performed only, if after Stage 1 the PK-variability turns out to be larger than initially assumed as specified in [Figure 3](#) (if power is less than 80% and bioequivalence criteria are not met in Stage 1 with an alpha of 0.0294). For Stage 2, the sample size will be adjusted based on the newly estimated PK-variability (maximum CV (%) value of the 3 PK primary endpoints), a targeted power of 80% and an adjusted alpha of 0.0294. The GMR T/R will be assumed to be 0.95 and will **not** be adjusted for the second stage.

As reported in Potvin [\[5\]](#) Table I and Table II for method C, with a first stage sample size of 36 subjects under the assumptions of a CV value of 20% (lower than the assumed CV of 24%), and a GMR of 0.95, the power to show bioequivalence will be approximately 98% and the probability of proceeding to Stage 2 will be 0.0%. With a first stage sample size of 36 subjects under the assumptions of a CV value of 30% (higher than the assumed CV of 24%), and a GMR of 0.95, the power to show bioequivalence will be less than 90% and the probability of proceeding to Stage 2 will be 22.7%. Table 6 summarizes the probability, mean total sample size (n) to proceed to Stage 2 for CV values up to 50% and the estimated overall power for both stages when considering a first stage sample size of 36 subjects.

Table 6 Power and Mean n for Declaring Bioequivalence for Individual PK Parameters

Sample size Stage 1 (n_1)	CV (%)	% Studies in Stage 2	Mean n	Power (%)
36	20	0.0	36.0	98
36	30	22.7	40.5	85
36	40	65.9	67.3	82
36	50	90.8	112.6	81

CV = coefficient of variation, n = total number of subjects, PK = pharmacokinetics

8.2.2 Parts B and C (Food Effect)

A total of 12 subjects will be randomized into Part B and Part C each. To obtain at least 12 evaluable subjects per group for the primary endpoint analysis, every drop-out with incomplete data must be replaced.

The half-width of the 90% confidence interval (CI) will be taken as a measure of precision.

The precision for the T/R ratios to be estimated for AUC and C_{max} for a series of CVs and a fixed sample size of 12 subjects per group is shown in Table 7.

A 2-sided alpha = 0.10 was used in the calculations, and the probability of achieving a pre-defined half-width (precision) was set to 0.80.

Based on these assumptions, the CI half-width for the estimated T/R ratios will be between 9% and 18% for both AUC and C_{max} . Considering the envisaged therapeutic window of tepotinib, this precision is sufficient to meet the study objectives.

Table 7 90% Confidence Intervals for Estimated Test/Reference Ratios, n = 12 per Group

CV	Half-width 90% CI	T/R Ratio	90% LCL	90% UCL
10%	8.8%	0.50	0.46	0.54
		0.75	0.69	0.82
		1.25	1.15	1.36
		1.50	1.38	1.63
15%	13.4%	0.50	0.44	0.57
		0.75	0.66	0.85
		1.25	1.10	1.42
		1.50	1.32	1.70
20%	18.2%	0.50	0.42	0.59
		0.75	0.63	0.89
		1.25	1.06	1.48
		1.50	1.27	1.77

SAS software version 9.4 was used to perform the calculations.

CI = Confidence Interval, CV = Coefficient of variation, LCL = Lower Confidence Limit, R = reference, T = test, UCL = Upper Confidence Limit

8.3 Randomization

Refer to Section 6.3 for the technical and logistical aspects of treatment allocation.

A total of 40 subjects will be randomized to Part A and 12 subjects each will be randomized to Parts B and C. In each study part, the subjects will be randomized to 1 of 2 sequences at a ratio of 1:1:

- Part A:

Sequence 1: TF3 - TF2

Sequence 2: TF2 - TF3

- Part B:

Sequence 1: TF2 fasted - TF2 fed

Sequence 2: TF2 fed - TF2 fasted

- Part C:

Sequence 1: TF3 fasted - TF3 fed

Sequence 2: TF3 fed - TF3 fasted.

If the PK-variability in Stage 1 of Part A is larger than assumed, additional subjects will be randomized to Part A as required.

A computer-generated randomization scheme will be provided by Nuvisan GmbH CTS Department.

8.4 Endpoints

8.4.1 Primary Endpoints

- Part A: AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} of tepotinib observed from time zero to 168 h post-dose of each period
- Parts B and C: AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} of tepotinib observed from time zero to 168 h post-dose of each period.

8.4.2 Secondary Endpoints

- t_{max} , $t_{1/2}$, apparent total body clearance considering the fraction of dose absorbed (CL/f), and apparent volume of distribution during terminal phase (V_z/f) of tepotinib observed from time zero to 168 h post-dose of each period
- Occurrence of TEAEs (incidence, frequency, intensity and causality), occurrence of changes in safety laboratory assessments, 12-lead ECGs and vital signs.

8.4.3 Exploratory Endpoints

- PK profiles of tepotinib metabolites:

AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , t_{max} , $t_{1/2}$ of tepotinib metabolites observed from time zero to 168 h post-dose of each period

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

8.5 Analysis Sets

8.5.1 Safety Analysis Set

The Safety analysis set will be defined for each part and will include all subjects who have received at least 1 dose of planned IMP and have had 1 subsequent safety assessment.

8.5.2 Definition of Pharmacokinetic Analysis Set

Part A (Bioequivalence)

The PK Analysis Set for Part A will include all subjects without any relevant protocol deviations with respect to PK and absence of factors likely to affect the comparability of PK results, with adequate trial medication compliance, and who have valid primary endpoints for both treatments.

All PK analyses for Part A will be based on this analysis set.

Parts B and C (Food Effect)

The PK Analysis Set for each Part B and C, will include all subjects without any relevant protocol deviations with respect to PK and absence of factors likely to affect the comparability of PK results, with adequate trial medication compliance, and who have at least 3 post-dose concentration measurements.

All PK analyses for Parts B and C will be based on the respective PK analysis set.

For all Parts (A, B and C)

Subjects in a particular period may be excluded after vomiting or with diarrhea 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. Relevant decisions will be made before database lock.

8.6 Description of Statistical Analyses

8.6.1 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, minimum, and maximum) and categorical data will be summarized by means of frequency tables (ie count and percentages), if not stated otherwise.

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

Graphical displays will be given, where appropriate. PK variables will be evaluated and listed for all subjects who provide sufficient concentration-time data. Invalid data will be flagged accordingly.

Missing values will be handled as such and not be replaced by estimates.

Details of the statistical analysis will be described in the statistical analysis plan.

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

8.6.2 Analysis of Primary Endpoints

Part A

An analysis of variance (ANOVA) model will be fitted for the log-transformed PK parameters C_{\max} , AUC_{0-t} , $AUC_{0-\infty}$ based on the PK analysis set. The model will include treatment, period, sequence and subject within sequence as fixed effects. If a Stage 2 is required and the number of subjects in Stage 2 is sufficiently large, stage will be included as additional effect in the ANOVA model for the analysis of the pooled data of both stages. More details will be given in the SAP.

Treatment differences on the log scale of tepotinib will be estimated for C_{\max} , AUC_{0-t} , $AUC_{0-\infty}$ together with their CIs with coverage probability according to the planned 2-stage procedure in [Figure 3](#). Point estimates and CIs will be back-transformed to the original scale for the comparisons. The variance estimate from Stage 1 will be used to evaluate the power at Stage 1.

The comparison will be the new tablet formulation (TF3) vs the tablet formulation used in clinical studies (TF2) under fasting condition.

Bioequivalence will be assessed after Stage 1 using Stage 1 data, or after Stage 2 using the pooled data of both stages.

The null hypothesis will be rejected if the CI corresponding to the α -level in the [Figure 3](#) (either 90% or 94.12%) for the ratio of the GeoMean lies within the interval 0.8000 to 1.2500.

Parts B and C

A mixed model with treatment, period and sequence as fixed effects and a random effect for subject within sequence will be applied to log-transformed PK parameters C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ based on the PK analysis set. Treatment differences on the log scale of tepotinib 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 for the comparisons:

- Part B: Tepotinib PK parameters after administration of the tablet formulation TF2 under fasting administration vs tepotinib TF2 after a high fat, high calorie breakfast
- Part C: Tepotinib PK parameters after administration of the tablet formulation TF3 under fasting administration vs tepotinib TF3 after a high fat, high calorie breakfast.

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

8.6.3 Analysis of Secondary Endpoints

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

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

8.6.4 Analysis of Safety and Exploratory Endpoints

Safety data analysis will be conducted on the Safety Analysis Set of each part. The number and percentage of subjects experiencing at least 1 TEAE will be summarized by treatment as will the number of events. Tables by relationship to study 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 clinically significant abnormalities/out of the normal range.

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

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

Exploratory endpoints will be analyzed with descriptive statistics.

8.7

Interim and Additional Planned Analyses

A two-stage design is used in Part A. Based on the measured variability, the corresponding power for the number of subjects in Stage 1 will be estimated. If the power is < 80%, an interim analysis will be performed. The significance level for both the interim analysis and the final analysis will then be set to 0.0294. For details refer to section 8.6.2.

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 [7], 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 or an appropriate designee (if local regulations permit) before informed consent is obtained.

A subject information sheet must be prepared in the local language in accordance with ICH GCP [7] and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or a designate will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

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

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

A separate subject information sheet will be prepared for the PGx testing. The subjects will be informed in the written form and verbally about pertinent aspects of the planned PGx testing including an explanation that this additional examination is mandatory for subjects' participation in this clinical trial. Only subjects who have signed and dated the ICF for PGx testing will be included in this clinical trial.

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 patient 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 information provided on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

The first point of contact for all emergencies will be the clinical 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/she will answer any questions. Any subsequent action will follow the standard process established for Investigators.

In cases where the Investigator is not available, the Phase 1 facility will provide the appropriate means to contact a physician. This includes the provision of a 24-hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage will be provided for this 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 at a given site, this clinical trial protocol will be submitted together with its associated documents (including but not limited to Subject Information and ICF, insurance certificate, Investigator's Brochure) 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 be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

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

9.7 Health Authorities

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

10 Trial Management

10.1 Case Report Form Handling

Refer to the Manual of Operations for eCRF handling guidelines.

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

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented appropriately on all applicable forms. 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 Sponsor or its designated organization contain no mention of any subject names.

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

10.2 Source Data and Subject Files

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

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

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

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

10.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines [\[7\]](#), 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 [\[7\]](#) 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 IMP 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. Substantial amendments will usually require submission to the Health Authorities and to the relevant IEC for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

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

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report will be written by Nuvisan GmbH following the guidance in ICH Topic E3 [\[8\]](#).

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. Guidance for Industry; Bioavailability and Bioequivalence Studies submitted for NDAs or INDs – General Considerations. FDA CDER Office of Clinical Pharmacology, Mar 2014.
2. Guideline for Industry: Food-Effect Bioavailability Fed Bioequivalence Studies. FDA CDER. Dec 2002.
3. EMA GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE. CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** London, 20 January 2010.
4. Montague TH, Potvin D, DiLiberti CE, et al. Additional results for ‘Sequential design approaches for bioequivalence studies with crossover designs. Pharmaceut Statist. 2012;11(1):8-13.
5. Potvin D, DiLiberti CE, Hauck WW, et al. Sequential design approaches for bioequivalence studies with crossover designs. Pharm Stat 2008 Oct-Dec;7(4):245-62.
6. 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.
7. ICH Topic E6(R2) Guideline for good clinical practice E6(R2). EMA/CHMP/ICH/135/1995. London, 1 December 2016. 1-70.
8. ICH Topic E3. Structure and Content of Clinical Study Reports. CPMP/ICH/137/95, London July 1996. 1-47.

Appendix I Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title: Phase 1, Open-label, 3-Parts Study with Crossover Design in each part to Investigate the Bioequivalence of the Tablet Formulation of Tepotinib TF3 compared to TF2 (Part A), and to Investigate the Influence of Food on the Pharmacokinetics of each Tablet Formulation TF2 (Part B) and TF3 (Part C) of Tepotinib in Healthy Subjects

EudraCT Number: 2017-005056-29

Clinical Trial Protocol Date / Version: 29 May 2018/ Version 1.0

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 1, Open-label, 3-Parts Study with Crossover Design in each part to Investigate the Bioequivalence of the Tablet Formulation of Tepotinib TF3 compared to TF2 (Part A), and to Investigate the Influence of Food on the Pharmacokinetics of each Tablet Formulation TF2 (Part B) and TF3 (Part C) of Tepotinib in Healthy Subjects

EudraCT Number 2017-005056-29

Clinical Trial Protocol Date / Version 29 May 2018/ Version 1.0

Center Number PI

Principal Investigator PI

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

PI

PI

Signature

Date of Signature

Name, academic degree: PI, PI

Function / Title: Principal Investigator

Institution: PI

Address: PI, Germany

Telephone number: PI

Fax number: PI

E-mail address: PI

Sponsor Responsible Persons not Named on the Cover Page

Name: PI [REDACTED]
Function / Title: PI [REDACTED] on behalf of PI [REDACTED]
Institution: Cytel France Sarl
Address: 63 Avenue des Champs Elysées, 75008 Paris, France
Telephone number: PI [REDACTED]
E-mail address: PI [REDACTED]

Name: PI [REDACTED]
Function / Title: PI [REDACTED]
Institution: Merck KGaA
Address: Frankfurter Strasse 250, 64293 Darmstadt, Germany
Telephone number: PI [REDACTED]
E-mail address: PI [REDACTED]

Appendix II Blood Volume Sampled in the Clinical Trial

Blood sample for	Amount per sample (mL)	Number of Scheduled Blood Samples per Subject					Total amount per Subject (mL)
		Screening	Per Period	No. of Periods per Part	End of Trial Visit	Total	
Clinical laboratory tests							
Biochemistry (incl. viral serology, TSH and FSH levels, if applicable)	4.7	1	4 ^a	2	1	10	47.0
Hematology	2.7	1	4 ^a	2	1	10	27.0
PK	2.0		22 ^b	2		44	88.0
PGx	2.0		2 ^c			2	4.0
Total		2	32		2	66	166.0

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: **200**

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

Clinical laboratory (biochemistry and hematology) blood samples:

^a Each period: on Day -1, pre-dose on Day 1, on Day 2 and before discharge on Day 4 = 4 samples;

PK blood samples for determination of tepotinib and its metabolites:

^b Each period: pre-dose, 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96, 120, 144 and 168 h post-dose = 22 samples;

PGx blood samples:

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

Appendix III Contraception Guidance

Definitions

Woman of Childbearing Potential

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

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

1. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

2. Premenarchal

3. Postmenopausal female

- Females who are postmenopausal (age-related amenorrhea \geq 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 enrolment.

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 .	
<ul style="list-style-type: none">• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation ^b<ul style="list-style-type: none">• oral• intravaginal• transdermal• Progestogen-only hormonal contraception associated with inhibition of ovulation ^b<ul style="list-style-type: none">• oral• injectable	
Highly Effective Methods That Are User Independent	
<ul style="list-style-type: none">• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation ^b• Intrauterine device (IUD)• Intrauterine hormone-releasing system (IUS)• Bilateral tubal occlusion	
<ul style="list-style-type: none">• Vasectomized partner <p>(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.)</p>	
NOTES:	
<p>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.</p>	
<p>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</p>	