# Appendix 16.1.1 List of Protocols and Protocol Amendments

Protocol Version 1.0, 05 September 2019

# Clinical Trial Protocol

| | |
|---|---|
| **Clinical Trial Protocol Number** | MS200095_0038 |
| **Title** | An open-label, single-dose, randomized, 2-period, 2-sequence cross-over, single-center Phase I trial in healthy subjects to assess the bioequivalence of tepotinib tablet formulation 3 administered as 5 tablets of 100 mg versus 2 tablets of 250 mg dose strength. |
| **Phase** | 1 |
| **IND Number** | Not applicable |
| **EudraCT Number** | 2019-003578-13 |
| **Principal Investigator** | PI<br>PI<br>Germany |
| **Sponsor** | Merck Healthcare KGaA<br>an affiliate of Merck KGaA, Darmstadt, Germany<br>Frankfurter Str. 250<br>Darmstadt, Germany<br>Medical Responsible:<br>PI<br>Merck Healthcare KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany<br>Phone: PI<br>Mobile: PI |
| **Clinical Trial Protocol Date / Version** | 05-Sep-2019 / Version 1.0 |
| **Replaces Version** | Not applicable |

- Confidential -

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## Table of In-Text Tables



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# 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 |
| $AUC_{0-\infty}$ | Area under the plasma concentration-time curve from time zero (= dosing time) extrapolated to infinity |
| $AUC_{0-t}$ | Area under the plasma concentration-time curve from time zero (= dosing time) to the last sampling time ($t_{last}$) at which the concentration is at or above the lower limit of quantification. |
| $AUC_{extra}$ | The AUC from time $t_{last}$ extrapolated to infinity |
| $AUC_{extra\%}$ | $AUC_{extra}$ / $AUC_{0-\infty}$ 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_0038 |
| **Title** | An open-label, single-dose, randomized, 2 period, 2-sequence cross-over, single-center Phase I trial in healthy subjects to assess the bioequivalence of tepotinib tablet formulation 3 administered as 5 tablets of 100 mg versus 2 tablets of 250 mg dose strength. |
| **Trial Phase** | 1 |
| **IND Number** | Not applicable |
| **FDA covered trial** | No |
| **EudraCT Number** | 2019-003578-13 |
| **Principal Investigator** | PI [redacted] Germany |
| **Sponsor** | Merck Healthcare KGaA, an affiliate of Merck KGaA, Darmstadt, Germany, Frankfurter Strasse 250, 64293 Darmstadt, Germany |
| **Trial center** | PI [redacted] Germany |
| **Planned trial period (first subject in-last subject out)** | October to December 2019 |
| **Trial Registry** | ClinicalTrial.gov, EU Clinical Trials Register |

**Primary Objectives:**

- To demonstrate bioequivalence between 5 tablets of the 100 mg dose strength of tepotinib tablet formulation 3 (TF3, test treatment) and 2 tablets of the 250 mg dose strength of TF3 (reference treatment) after single dose administration in healthy subjects under fasting conditions

**Secondary Objectives:**

- To further investigate the PK of tepotinib

- To further assess the safety and tolerability of tepotinib TF3 under fasting conditions

**Exploratory Objectives:**

- To investigate the PK of tepotinib metabolites
- To explore the effect of pharmacogenetics (PGx) and variations of associated genes on the PK profile of tepotinib (if applicable).

**Methodology:** This is an open-label, single-dose, randomized, 2-period, 2-sequence cross-over, single-center trial to investigate the bioequivalence of the 100 mg and 250 mg dose strengths of tepotinib tablet formulation 3 under fasted condition.

For each subject, the study consists of a screening period (Day -21 to Day -2) and 2 treatment periods including a washout of 21-days in each period. 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 of 2 treatment sequences 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:**

18 subjects.

**Primary Endpoints:**

- 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.

**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) $\geq 18.5$ and $\leq 29.9$ 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 TF3 containing 100 mg of drug substance for oral administration (test treatment)
- Tepotinib film-coated tablet TF3 containing 250 mg of drug substance for oral administration (reference treatment)

Administration of single doses of 500 mg tepotinib per treatment period, administered as 2 tablets of 250 mg, and 5 tablets of 100 mg, after overnight fasting.

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:**

About 9 weeks each from Screening to End of Trial Visit, including 2 treatment periods of 21 days each.

**Statistical methods:**

**Primary Endpoints:**

An analysis of variance (ANOVA) model will be fitted to 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 as fixed effects and subject within sequence as random effect.

Treatment differences on the log scale of tepotinib will be estimated for $C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$ together with their 90% CIs.

The null hypothesis of non-bioequivalence will be rejected if the 90% CI for the ratio of the geometric mean lies within the bioequivalence acceptance interval of 0.8000 to 1.2500 for all primary PK parameters.

**Secondary and exploratory endpoints** will be analyzed with summary statistics.

## Table 1 Schedule of Assessments

| Assessment/ Activity | Screening | All periods | | | | End of Trial Visit |
|---|---|---|---|---|---|---|
| **Day** | **-21 to -2** | **-1** | **1** | **2 - 4** | **5 - 8** | **21 (± 1) after dosing in Period 2** |
| Written informed consent [a] | | | | | | |
| Hospitalization | | X ---------- X | | | | |
| Ambulatory visits | X | | | | X | X |
| In-/exclusion criteria | X | X (Period 1 only) | | | | |
| Randomization | | | X (predose, 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 | X | pre-dose [b], 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 |
| Coagulation | 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 pre-dose will be recorded in triplicate

[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 Healthcare KGaA an affiliate of Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany.

Single trial site at [PI], Germany.

The Principal Investigator ([PI], [PI], 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 19-July-2019, 715 subjects have been exposed to tepotinib at doses up to 1400 mg, including 195 healthy participants, and 12 subjects with Child-Pugh class A or B hepatic impairment in 8 Clinical Pharmacology studies.

Four of the Clinical Pharmacology studies in healthy subjects (EMR200095-007, n = 27; EMR200095-0012, n = 24; MS200095-0039, n = 12 and MS200095-0044, n = 66) were conducted as single-dose studies with 500 mg tepotinib, in one study (EMR200095-002, n = 28), single doses of 30 mg tepotinib were administered to healthy subjects. In two further studies, healthy subjects received multiple doses of 500 mg tepotinib over 11 days (MS200095-0030, n = 12) or 8 days (MS200095-0032, n = 20).

In all 7 studies performed in healthy subjects, the subjects well tolerated single doses of 30 mg or 500 mg tepotinib, or multiple doses of 500 mg tepotinib. All treatment-emergent adverse events (TEAEs) were mild to moderate, except 2 Grade 3 asymptomatic lipase elevations in 2 subjects, and 2 Grade 3 TEAE (back pain and collum femoris fracture) that were not considered related to treatment. TEAEs did not show a pattern across the trials. No drug-related 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) were noted.

In a further Clinical Pharmacology trial (MS200095-0028), 6 subjects with Child-Pugh Class A, 6 subjects with Class B hepatic impairment, and 6 healthy subjects received single doses of 500 mg tepotinib. No subject had serious adverse events, Grade ≥ 3 TEAEs, or discontinued due to a TEAE, or died during the study

In 2 clinical studies (EMR200095-001 and EMR200095-003), 161 patients with different solid tumors received multiple doses up to 1400 mg tepotinib. In 2 studies, 138 patients with hepatocellular cancer (EMR200095-004 and EMR200095-005) received multiple doses of 300 mg, 500 mg or 1000 mg tepotinib. In a clinical study in patients with MET-positive, non-small-cell lung cancer (NSCLC) harboring epidermal growth factor receptor mutations (EMR200095-006), 64 patients received multiple doses of 300 mg or 500 mg tepotinib.

Until 19-July-2019, 145 patients with NSCLC in the ongoing VISION trial (MS200095-0022) have received multiple doses of 500 mg tepotinib.

Elevations in serum lipase and amylase are identified risks for tepotinib and were observed in healthy subjects and patients exposed to tepotinib. These increases 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.

This study will investigate the bioequivalence of tepotinib tablet formulation 3 (TF3) administered as 5 tablets of 100 mg versus 2 tablets of 250 mg dose strength. 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.

For the PK of tepotinib refer to the IB.

## 3.1 Trial Rationale

This trial will investigate the bioequivalence of the 100 mg dose strength (test treatment) of the envisioned market formulation, TF3, compared to the 250 mg dose strength of the same formulation (reference treatment), both given at a single dose of 500 mg. The 250 mg dose strength of TF3 had been shown to be bioequivalent to the 500 mg dose strength of TF2, used in the Phase 2 studies, and in a previous bioequivalence study (MS200095-0044).

While the recommended clinical dose of 500 mg for the treatment of patients with NSCLC can be administered using the 250 mg dose strength, the lower TF3 dose strength of 100 mg will be made available for individual dose adaptation and future development options.

The tablet cores of both TF3 dose strengths are identical. The tablet film-coating is a non-functional coating that differs only marginally in composition between both dose strengths. However, owing to the different tablet sizes, the difference of coating material per surface area formally exceeds regulatory thresholds in certain regulatory regions. Clinical investigation of bioequivalence between the TF3 strengths will therefore be performed.

The trial design using an open-label 2-period, 2-sequence cross-over design under fasted conditions follows the regulatory guidelines of the Food and Drug Administration (FDA) [1, 2], the European Medicines Agency (EMA) [3] and the Pharmaceuticals and Medical Devices Agency (PMDA) [4, 5].

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.

## 3.2 Risk/Benefit Assessment

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. 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 embryo-fetal 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.

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

# 4 Trial Objectives

## 4.1 Primary Objectives

- To demonstrate bioequivalence between 5 tablets of the 100 mg dose strength of tepotinib TF3 (test treatment) and 2 tablets of the 250 mg dose strength of TF3 (reference treatment) after single dose administration in healthy subjects under fasting conditions.

## 4.2 Secondary Objectives

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

## 4.3 Exploratory Objectives

- To investigate the PK of tepotinib metabolites
- 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 an open-label, single-dose, randomized, 2-period, 2-sequence cross-over, single-center trial to investigate the bioequivalence of the 100 mg and 250 mg dose strengths of tepotinib TF3 when administered at the same dose under fasted condition.

For each subject, the study consists of a screening period (Day -21 to Day -2) and 2 treatment periods, including a 21-days washout in each period. 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 of 2 treatment sequences 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).

More details are given in Section 7.1.

**Common Visit Schedule**

Trial procedures are the same for both periods.

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.

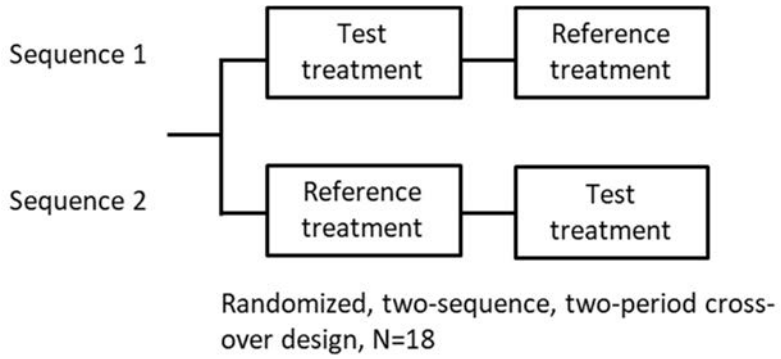
Subjects will be admitted to the study site on Day -1 of each period and will be resident at the study site under medical supervision from Days -1 to 4. They must visit the site on the morning of Days 5 to 8 for further blood sampling.

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 (± 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**




Test treatment: 5 tablets 100 mg tepotinib TF3, Reference treatment: 2 tablets 250 mg tepotinib TF3

**Figure 2** **Design of the Trial**

| | Each Period | | | | |
|---|---|---|---|---|---|
| | Day | | | | |
| **Procedure** | **-1** | **1** | **2 to 4** | **5 to 8** | **21** |
| Hospitalization | ← | ——— | ——— | → | |
| Tepotinib administration | | ↑ | | | |
| PK blood sampling | | ← | ——— | → | |
| Safety assessments[a] | ← | ——— | ——— | ——— | → |
| AE monitoring | ← | ——— | ——— | ——— | → |

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 and at the End of Trial Visit.

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

## 5.2 Discussion of Trial Design

The primary objective is to demonstrate bioequivalence between 5 tablets of the 100 mg dose strength of TF3 (test treatment) and 2 tablets of the 250 mg dose strength of TF3 (reference treatment) after single dose administration in healthy subjects under fasting conditions.

The general trial design is strictly based on the regulatory guidelines of the FDA [1, 2], EMA [3] and PMDA [4, 5].

### 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 studies of this type. The single dose design under fasted conditions is more sensitive in showing changes in the PK as compared to multiple dose designs and is generally recommended by the relevant guidelines [1-5].

As illustrated in Figure 1, the study will utilize a randomized open-label, 2-period, 2-sequence cross-over design to minimize the influence of covariates.

In a recent clinical study with PK sampling up to 504 h after administration (MS200095-012), terminal elimination half-lives ($t_{1/2}$) of about 30 h for the parent compound tepotinib and about 45 h for the main metabolites MSC2571109A and MSC2571107A were observed (Study MS200095-0012). Due to the very sensitive bioanalytical method, very low concentrations (< 5% of the maximum plasma concentration [$C_{max}$]) were observed after 14 days in study MS200095-0012. No (or only negligible) concentrations above the detection limit are expected after 21 days following dosing. Accordingly, the washout period will be at least 21 days between Day 1 (study drug administration) of each treatment period to further minimize potential carry-over.

In a previous clinical study with single-dose administrations of 500 mg tepotinib as TF3 under fasted conditions (EMR200095-0044, Part A), the median time to reach the maximum plasma concentration ($t_{max}$) was 12 h (ranging from 8 h to 36 h), and the mean apparent half-life was 30.9 h (95% confidence interval: 29.4 h to 32.5 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 ($AUC_{0-\infty}$).

This trial will be performed in healthy volunteers to standardize the trial population and minimize inter-subject variability.

### 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 recommended Phase 2 dose (RP2D) 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 [$AUC_{0-t}$ and $AUC_{0-\infty}$]) of exposure after single dose administration are considered adequate endpoints to evaluate the bioequivalence. These endpoints are in line with the regulatory guidance of the FDA, EMA and PMDA (see Section 3.1).

## 5.3 Selection of Trial Population

Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments 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 ≤ 29.9 kg/m$^2$ and body weight between 50 and 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 (Appendix III Contraception Guidance):

    - Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL)
    - Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy

4. A male participant must agree to use and to have his female 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 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

## 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).

Subjects who dropped out will not be replaced as per design specificity. A drop-out compensation of 2 subjects has been added.

### 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 white-pink, oval, biconvex tablet with embossment "M" on one side TF3 for oral administration (reference treatment)

  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.

- 100 mg white-yellow, round, biconvex tablets with embossment "M" on one side TF3 for oral administration (test treatment).

  Tepotinib 100 mg film-coated tablets (TF3) have a drug load of approximately 30% 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

In the two treatment periods, the subjects will receive the following single administrations of tepotinib in randomized order:

- 5 film-coated tablets TF3 containing 100 mg tepotinib, with a total dose of 500 mg (test treatment)
- 2 film-coated tablets TF3 containing 250 mg tepotinib, with a total dose of 500 mg (reference treatment)

Both treatments will be administered in the fasted state (after at least 10 h fasting) together with 200 mL of water.

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 formulation in upright position.

In both 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 approximately 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. Prior to the first administration, the subjects enrolled into the trial will be randomly assigned to 1 of 2 treatment sequences, via the random number on Day 1 of Period 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
- Drinking is not allowed 1 h before and after administration of tepotinib (except for the 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 both periods. 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
- Blood and urine sampling for safety laboratory assessments
- Serological tests for hepatitis B, C, and HIV1/HIV2 and coagulation tests
- 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.

**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 (as triplicate)
- 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:

Study drug will be administered in both periods in the fasted state together with 200 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 and its metabolites. 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.

**Events Not to Be Considered as AEs/SAEs**

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions, and are not to be considered AEs.

### 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

**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.

In the event of a non-serious AESI, the Investigator will complete the AESI Report Form and send it to the sponsor/designee within 24 h after becoming aware of the event. Serious AESIs must be reported in an expedited manner as SAEs as outlined above.

#### 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. This study does not allow inclusion of females of child-bearing potential under hormonal contraception. 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 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, coagulation, 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.

Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at Screening, on Day -1 and at the end of relevant systemic exposure of the study intervention to confirm non-pregnant status of female participants as per Inclusion Criteria (Section 5.3.1) the study.

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

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

[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 a validated liquid chromatography-tandem mass spectrometry method at Nuvisan. The assays will be carried out in accordance with the applicable Good Clinical Practice and 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) |
| $AUC_{0-\infty}$ | Area under the plasma concentration-time curve from time zero (= dosing time) extrapolated to infinity, calculated as $AUC_{0-t}$ + $AUC_{extra}$. $AUC_{extra}$ represents the extrapolated part of $AUC_{0-\infty}$ calculated by $C_{lastpred}/\lambda_z$, where $C_{lastpred}$ is the predicted plasma concentration at the last sampling time point, calculated from the log-linear regression line for $\lambda_z$ 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 $\ln 2/\lambda_z$ |
| $\lambda_z$ | 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/$AUC_{0-\infty}$, 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 |
| $AUC_{extra\%}$ | $AUC_{extra\%}$ = ($AUC_{extra}$ / $AUC_{0-\infty}$) x 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

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 $AUC_{0-\infty}$ or $C_{max}$)

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

where $\mu_T$ and $\mu_R$ are the geometric means for the test and reference treatment respectively.

The test treatment is 5 tablets of the 100 mg dose strength of TF3 and reference treatment is 2 tablets of the 250 mg dose strength of TF3, both under fasting condition.

## 8.2 Sample Size

The total and mixed intrasubject variability CVs (%) observed in study MS200095-0044 for $AUC_{0-t}$ and $C_{max}$ of tepotinib are summarized in Table 5 (total and mixed intra-individual CV for $AUC_{0-\infty}$ was very similar to that of $AUC_{0-t}$ and is not listed separately).

**Table 5 Overview of the PK-Variability Observed in Tepotinib Study MS200095-0044**

| | | | $AUC_{0-t}$ | | $C_{max}$ | |
|---|---|---|---|---|---|---|
| **Study Part** | **Formulation (Condition)** | **Arm** | **Total Geometric CV%** | **Mixed intra-individual CV%** | **Total Geometric CV%** | **Mixed intra-individual CV%** |
| Part A | TF3 vs TF2 (fasted) | TF3 (fasted) | 21.0 | | 22.5 | |
| | | TF2 (fasted) | 23.4 | 15.77 | 20.6 | 13.94 |
| Part B | TF2 (fed versus fasted) | TF2 (fed) | 25.1 | | 19.6 | |
| | | TF2 (fasted) | 38.1 | 17.96 | 29.5 | 12.67 |
| Part C | TF3 (fed versus fasted) | TF3 (fed) | 25.0 | | 17.0 | |
| | | TF3 (fasted) | 19.8 | 14.93 | 15.3 | 16.79 |

$AUC_{0-t}$ = 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, TF2/3 = tablet formulation 2/3; $C_{max}$ = maximum plasma concentration, CV = coefficient of variation.

Overall, the total variability in AUC and $C_{max}$ was between 15.3% and 25.0% for TF3. The mixed intrasubject variabilities of AUC and $C_{max}$ ranged between 12.67% and 17.96% across all investigated combinations of formulation and condition.

Assuming that the within-subject variability for the comparison between the test and reference treatment will be similar to that of Part A in MS200095-0044 (i.e., CV% = 15.77), and with an assumed geometric mean ratio Test/Reference (GMR T/R) of 0.95, a one-sided alpha level of 0.05, 16 evaluable subjects will be needed to provide approximatively 90% power to show bioequivalence. A drop-out compensation of 2 subjects will be added. In total, 18 subjects will be randomized. If the actual CV is up to 18.4%, the sample size of 16 evaluable subjects would still result in approximately 80% power to show bioequivalence.

## 8.3 Randomization

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

A total of 18 subjects will be randomized. Subjects will be randomized to 1 of 2 sequences at a ratio of 1:1:

Sequence 1: 5 x 100 mg (Test) – 2 x 250mg (Reference)

Sequence 2: 2 x 250 mg (Reference) – 5 x 100 mg (Test)

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

## 8.4 Endpoints

### 8.4.1 Primary Endpoints

- $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ of tepotinib calculated from concentration data obtained 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

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

All PK analyses will be based on this analysis set.

## 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, $25^{th}$ and $75^{th}$ 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

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 as fixed effects and subject within sequence as a random effect.

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

The comparison will be the test treatment (5 x 100 mg TF3) vs the reference treatment (2 x 250 mg TF3) under fasting condition.

The null hypothesis for non-bioequivalence will be rejected if the 90% CI for the ratio of the GeoMean lies within the interval 0.8000 to 1.2500 for all primary pharmacokinetic parameters.

## 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 laboratory values/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

Not applicable.

# 9 Ethical and Regulatory Aspects

## 9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the site and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP [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. Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms, PMDA 2012.
5. Guideline for Bioequivalence Studies of Generic Products, PMDA 2012.
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.

# 12 Appendices

# Appendix I Signature Pages and Responsible Persons for the Trial

## Signature Page – Protocol Lead

| | |
|---|---|
| **Trial Title:** | An open-label, single-dose, randomized, 2-period, 2-sequence cross-over, single-center Phase I trial in healthy subjects to assess the bioequivalence of tepotinib tablet formulation 3 administered as 5 tablets of 100 mg versus 2 tablets of 250 mg dose strength. |
| **EudraCT Number:** | 2019-003578-13 |
| **Clinical Trial Protocol Date / Version:** | 05-Sep-2019 / Version 1.0 |

**Protocol Lead:**

I approve the design of the clinical trial:

PI

PI

Signature Date of Signature

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

## Signature Page – Principal Investigator

| | |
|---|---|
| **Trial Title** | An open-label, single-dose, randomized, 2-period, 2-sequence cross-over, single-center Phase I trial in healthy subjects to assess the bioequivalence of tepotinib tablet formulation 3 administered as 5 tablets of 100 mg versus 2 tablets of 250 mg dose strength. |
| **EudraCT Number** | 2019-003578-13 |
| **Clinical Trial Protocol Date / Version** | 05-Sep-2019 / 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

Function / Title: Principal Investigator

Institution: PI

Address: PI Germany

Telephone number: PI

Fax number:

E-mail address:

## Sponsor Responsible Persons not Named on the Cover Page

Name: PI

Function / Title: PI

Institution: Merck Healthcare KGaA

Address: Frankfurter Strasse 250, 64293 Darmstadt, Germany

Telephone number: PI

E-mail address:

Name: PI

Function / Title: PI

Institution: Merck Healthcare KGaA

Address: Frankfurter Strasse 250, 64293 Darmstadt, Germany

Telephone number: PI

E-mail address:

# 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** |
| Coagulation | 3.0 | 1 | | | | | **3.0** |
| PK | 2.0 | | 22 [b] | 2 | | 44 | **88.0** |
| PGx | 2.0 | | 2 [c] | | | 2 | **4.0** |
| Total | | 2 | 32 | | 2 | 66 | **169.0** |
| 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 (WOCBP)**

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

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

A WOCBP is **not**:

1. Premenarchal
2. A premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

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

   For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion applies to determine study entry.
3. A postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
   - A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

## Contraception Guidance:

**CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:**

**Highly Effective Methods That Have Low User Dependency**

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

**Highly Effective Methods That Are User Dependent**Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

- Oral
- Intravaginal
- Transdermal
- Injectable

- Progestogen-only hormone contraception associated with inhibition of ovulation
  - Oral
  - Injectable
- Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.

Notes:

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

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

Hormonal contraception may be susceptible to interaction with the study intervention(s), which may reduce the efficacy of the contraceptive method. As such, male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are **not** acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure with friction).