Clinical Study Protocol

Clinical Study Protocol Number	MS200095-0028
Title	Open-Label, Parallel-Group Phase 1 Study to Investigate the Effect of Various Degrees of Hepatic Impairment on the Pharmacokinetics, Safety and Tolerability of the c-Met Kinase Inhibitor Tepotinib
Phase	I
IND Number	106103
EudraCT Number	Not applicable
Principal Investigators	PI Orlando Clinical Research Center 5055 S. Orange Ave Orlando, FL 32809, USA Phone: PI Email: PI PI QPS MRA, LLC 6280 Sunset Drive, Suite 600 Miami, FL., 33143, USA Phone: PI Email: PI
Sponsor	EMD Serono Research & Development Institute, Inc, 45A Middlesex Turnpike, Billerica, MA 01821, USA. Medical Responsible: PI PI Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany Phone: PI Mobile: PI Email: PI
Sponsor Legal Representative in the European Union	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
Clinical Study Protocol Version	24 April 2018 / Version 2.0
Replaces Version	15 March 2017 / Version 1.0

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List of Abbreviations

AE	Adverse event
ALBI	Albumin-Bilirubin
ANOVA	Analysis of variance
AUC	Area under the plasma concentration-time curve
$AUC_{extra\%}$	Area under the plasma concentration-time curve extrapolated from time t to infinity as a percentage of $AUC_{0-\infty}$
AUC_{0-240h}	Area under the plasma concentration-time curve from time zero to 240 hours postdose
AUC_{0-t}	Area under the plasma concentration-time curve (AUC) from time zero to the last sampling time at which the concentration is at or above LLOQ
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
β-hCG	Beta-human chorionic gonadotropin
BLQ	Below the lower limit of quantitation
CI	Confidence interval
CL/f	Apparent total body clearance of drug from plasma following oral administration
C_{max}	Maximum plasma concentration observed
c-Met	Mesenchymal-epithelial transition factor gene
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HCC	Hepatocellular carcinoma
HGF	Hepatocyte growth factor
ICH	International Council for Harmonization
IMP	Investigational medicinal product

IRB	Institutional Review Board
λ_Z	Apparent terminal rate constant
LLOQ	Lower limit of quantitation
$MRAUC_{0-\infty}$	Metabolite (MSC2571109 or MSC2571107) $AUC_{0-\infty}$ to tepotinib $AUC_{0-\infty}$ ratio
MRC_{max}	Metabolite (MSC2571109 or MSC2571107) C_{max} to tepotinib C_{max} ratio
NCI	National Cancer Institute
NSCLC	Non-small cell lung carcinoma
ODWG	Organ Dysfunction Working Group
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
QTcF	Corrected QT intervals using Fridericia's formula
SAE	Serious adverse event
SMC	Safety Monitoring Committee
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Apparent terminal half-life
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TPR	Translocated promoter region
t_{max}	Time to reach the maximum plasma concentration
V_Z/f	Apparent volume of distribution during the terminal phase following extravascular administration
WOCBP	Woman of childbearing potential

1 Synopsis

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Sponsor Legal Representative in the European Union	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany

Study centers/countries	2 study centers in the USA: [PI] and [PI].
Planned study period (first subject in-last subject out)	May 2018 (first subject screened) to September 2018 (last subject last visit)
Trial Registry	Not applicable

Objectives:

Primary objective

- To assess the pharmacokinetics (PK) of tepotinib (MSC2156119J) in subjects with various degrees of impaired hepatic function (in comparison to healthy subjects).

Secondary objectives

- To further investigate the PK of tepotinib and its metabolites MSC2571109 and MSC2571107 in subjects with various degrees of impaired hepatic function (in comparison to healthy subjects)
- To assess safety and tolerability of tepotinib in subjects with various degrees of impaired hepatic function (in comparison to healthy subjects).

Methodology: This is a Phase 1, two-staged, open-label study to investigate the effect of various degrees of hepatic impairment on the PK, safety and tolerability of the mesenchymal-epithelial transition factor gene (c-Met) kinase inhibitor, tepotinib.

Part 1 will include subjects with hepatic impairment (Child-Pugh class A [6 subjects] and Child-Pugh class B [6 subjects]) and a control group (6 healthy subjects matched 1:1 to 6 subjects with Child-Pugh class B with regard to age ± 10 years, weight ± 10 kg, and same gender). All subjects will receive a single dose of 500 mg tepotinib.

Part 2 of the study is optional and, if conducted, will evaluate doses above 500 mg up to 1000 mg in 6 subjects with hepatic impairment of either Child-Pugh class A or B.

A Safety Monitoring Committee (SMC) may be established to evaluate the safety and PK results of Part 1 if the overall development program of tepotinib decides to use higher doses than 500 mg (up to 1000 mg) in the Phase 2 or Phase 3 studies. The SMC will then make a recommendation on the tepotinib dose and which population (Child-Pugh class A or B) to be enrolled in Part 2 based on the safety and PK results of Part 1.

Subjects will be screened from Day -28 to Day -2. Subjects will be admitted to the study center on Day -1 and will remain inpatient at the study center under medical supervision until discharge on the morning of Day 4.

The treatment consists of a single-dose administration of 500 mg tepotinib on Day 1 in Part 1. The dose to be investigated in Part 2 will be determined by the SMC after evaluation of the safety and PK results of Part 1.

Serial blood samples (PK and clinical laboratory assessments) and urine samples (clinical laboratory assessments) will be collected at specified timepoints. There is a PK sampling period of 2 weeks for healthy subjects and 3 weeks for hepatic impaired subjects.

The End of Study visit is planned on Day 15 for healthy subjects and on Day 22 for hepatic impaired subjects. An Early Termination visit will be conducted for subjects who withdraw prematurely. The same assessments as for the End of Study visit will be conducted at the Early Termination visit.

Planned number of subjects: Eighteen subjects in Part 1 and 6 subjects in Part 2.

Primary endpoints:

- PK profile of tepotinib (plasma) in terms of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} at Day 1 to Day 15 (healthy subjects) or Day 22 (hepatic impaired subjects) calculated by noncompartmental analyses.

Secondary endpoints:

- PK profile of tepotinib (plasma) in terms of t_{max}, $t_{1/2}$, CL/f, V_Z/f, $AUC_{extra\%}$ at Day 1 to Day 15 (healthy subjects) or Day 22 (hepatic impaired subjects) calculated by noncompartmental analyses

  PK profile of the major tepotinib metabolites MSC2571109 and MSC2571107 (plasma) in terms of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, $AUC_{extra\%}$ at Day 1 to Day 15 (healthy subjects) or Day 22 (hepatic impaired subjects) calculated by noncompartmental analyses, and $MRAUC_{0-\infty}$ and MRC_{max}

- Occurrence of treatment-emergent adverse events, changes from baseline in laboratory safety tests, 12-lead electrocardiograms (ECG) morphology and time intervals (PR, QRS, RR, QT and corrected QT intervals using Fridericia's formula [QTcF]), and vital signs.

Pharmacokinetics: Blood samples for PK analysis will be collected on Day 1 predose and 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, and 16.0 hours postdose, Day 2 at 24, 30, and 36 hours postdose, Day 3 at 48, 54, and 60 hours postdose, Day 4 (72 hours), Day 5 (96 hours), Day 6 (120 hours), Day 7 (144 hours), Day 8 (168 hours), Day 10 (216 hours), Day 13 (288 hours), Day 15 (336 hours), and Day 22 (504 hours postdose; hepatic impaired subjects only).

Other assessments: Throughout the study at specified timepoints treatment-emergent adverse events, changes from baseline in laboratory safety tests, 12-lead ECG morphology and time intervals (PR, QRS, RR, QT and QTcF), and vital signs will be assessed.

Diagnosis and key inclusion and exclusion criteria: Men and women (of nonchildbearing potential), 18 to 75 years (inclusive) of age, with a body mass index of 18 to 36 kg/m^2 (inclusive) and a body weight $\geq$ 50 kg at Screening, with the absence of acute hepatitis or HIV 1 and 2, who have given informed consent and are willing and able to comply with study procedures will be eligible for enrollment. Subjects with impaired hepatic function (Child-Pugh class A or Child-Pugh class B) and subjects with normal hepatic function will be eligible to enroll in the study. Healthy subjects will be excluded if they have hepatitis B or C or had a previous infection with hepatitis C treated with Sofosbuvir or other antiviral compounds, or any other clinically relevant disease, as considered by the Investigator. Subjects with impaired hepatic function will be excluded if they have primary biliary liver cirrhosis, nonstabilized chronic heart failure, hepatocarcinoma, hepatic encephalopathy (Grade III or IV), sepsis or gastrointestinal bleeding, or any other clinically relevant disease, as considered by the Investigator.
Investigational Medicinal Product: dose/mode of administration/ dosing schedule: One single oral dose of 500 mg tepotinib tablets (Tablet Formulation 2) will be administered in Part 1 and up to 1000 mg in Part 2 after the subject has completed a standard breakfast.
Reference therapy: dose/mode of administration/dosing schedule: Not applicable
Planned study and treatment duration per subject: Each subject will receive a single administration of the investigational medicinal product (IMP) on Day 1. In both Part 1 and Part 2, the planned study duration per subject from Screening until the End of Study visit is approximately 6 weeks for healthy subjects and approximately 7 weeks for hepatic impaired subjects.

Statistical methods:

Sample size:

Pharmacokinetic studies, including subjects with impaired liver function, are usually exploratory by nature. Considering the CVs for the primary endpoints AUC_{0-t} and C_{max} of tepotinib, 20.4% and 22.8% respectively, 6 evaluable subjects per group will provide 80% power at alpha level of 0.05 for detecting a group difference of 44% (AUC_{0-t}) and 50% (C_{max}), which is considered sufficient to meet the study objectives. Therefore, 18 subjects (3 groups x 6 subjects) should be included in Part 1 and 6 subjects in Part 2.

Analysis of primary endpoints:

As the primary analysis, an analysis of variance (ANOVA) model including hepatic function group as a fixed effect will be applied to log-transformed tepotinib PK parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. Differences between the hepatic impairment groups and matched control will be estimated together with their 90% CIs then back-transformed to the original scale for presentation.

Additionally, a generalized linear model including hepatic function group and sex (gender) as fixed effects, age and weight as covariates, will be applied to the same primary PK parameters. A further covariate log(dose) will be introduced when Part 2 data is included.

All endpoints will be descriptively analyzed using summary statistics by hepatic function group. Graphical displays will be given, where appropriate.

Analysis of secondary endpoints:

For the secondary PK parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of the tepotinib metabolites, the same analyses as defined for the primary endpoints will be performed.

Analysis of safety:

Safety data will be listed and descriptively summarized as appropriate.

Table 1 Schedule of Assessments: Part 1 and Part 2

[illegible]		[illegible]																		
[illegible]	[illegible]	1																		
[illegible]	[illegible]		1															2		
[illegible]	0	1	2															3		
[illegible]			[illegible]	[illegible]																
[illegible]	X																			
[illegible]	X	X																		
[illegible]	X	X[j]																		
[illegible][a]	X																			
[illegible][b]				X																
[illegible][c]			X		X	X X	X	X	X X	X	X	X X	X	X	X	X	X			
[illegible][d]												X		X		X	X			
[illegible] X			X																	
[illegible][c] [e] [e]	X	X	X									X		X				X		
[illegible][c]	X		X									X		X				X		
[illegible][f]	X		X															X		
[illegible][g]	X	X																		
[illegible][h],	X	X																		
[illegible][i]		X	X	X X	X	X	X X	X	X	X X	X	X	X	X	X X	X				
[illegible]	X	X	X X	X	X	X X	X	X	X X	X	X	X	X X	X	X	X				
[illegible]	X	X	X X	X	X	X X	X	X	X X	X	X	X	X X	X	X	X				

Activity/Assessment	On Treatment										End of Study for Healthy Subjects / Treatment visit for Hepatic Impaired Subjects	End of Study for Hepatic Impaired Subjects
Study Week	**1**							**2**			**3**	**4**
Study Day	**3**			**4**	**5**	**6**	**7**	**8**	**10**	**13**	**15**	**22**
Visit Number	**4**			**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Time (hh:mm)	**48:00**	**54:00**	**60:00**	**72:00**	**96:00**	**120:00**	**144:00**	**168:00**	**216:00**	**288:00**	**336:00**	**504:00**
PK blood sampling [c]	X	X	X	X	X	X	X	X	X	X	X [k]	X [l]
Vital signs [c], height [e] and weight [e]	X			X				X			X [k]	X [l]
12-lead ECG [c]	X			X				X			X [k]	X [l]
Clinical laboratory tests [f]				X				X			X [k]	X [l]
Physical examination				X							X [k]	X [l]
Subject confinement [i]	X	X	X	X								
AE monitoring	X	X	X	X	X	X	X	X	X	X	X [k]	X [l]
Previous/concomitant medication and nondrug therapy/intervention monitoring	X	X	X	X	X	X	X	X	X	X	X [k]	X [l]

AE = adverse event; β-hCG = Beta-human chorionic gonadotropin; ECG = electrocardiogram; FSH = follicle-stimulating hormone; IMP = investigational medicinal product; PK = pharmacokinetic.

a For hepatic insufficiency assessment in subjects with hepatic impairment only.

b Drug administration will occur 30 minutes after start of the intake of a standard breakfast with 240 mL of water. Subjects should eat this meal within 25 minutes or less. The subject will remain fasting for 4 hours after the breakfast, after which a standardized lunch will be served.

The standard breakfast will contain approximately 500 calories and will be balanced in macronutrients (approximately 50% carbohydrates, 25% protein, and 25% fat). The menu must be approved by the Sponsor. The subject will be expected to eat the entire meal. The percentage consumed will be recorded for all subjects. A deviation will be recorded if the subject eats less than 90% of the meal. Subjects will not be excluded from dosing if they are unable to complete the meal in full.

c When several procedures are scheduled at the same theoretical time, the following sequence should be followed: 12-lead ECG followed by vital signs before the specified timepoint, preceding the PK sampling which will be performed at the specified timepoint.

d The Tepotinib Free Fraction (TFF) sample will not be drawn separately; TFF will be analyzed from the PK back up sample.

e Height will be measured at Screening only. Body weight will be measured at Screening and at Day -1 only.

f Clinical laboratory tests comprise of clinical chemistry, hematological parameters, coagulation (at Screening and Day 1 only), urinalysis, and other tests (at Screening and Day 1 only) as specified in Table 4. Subjects should fast for 8 hours prior to clinical laboratory blood sample collection.

g A β-hCG test will be done at Screening and on the day of admission to exclude pregnancy. If necessary to confirm postmenopausal status, FSH samples will be drawn at Screening.

h For all subjects, a negative cannabinoid (THC) result on drugs of abuse screening is required to participate in the study. If the result is positive, the Principal Investigator may request to repeat the test. For subjects with hepatic impairment, a positive cannabinoid (THC) result on drugs of abuse screening will not be exclusionary (at Screening or Day -1) if the subject uses cannabinoids on medical recommendation. In subjects with hepatic impairment, positive test for drugs used on medical recommendation will be not exclusionary.

i Subjects will be admitted in the morning of Day -1 as indicated. Subjects will leave the study center in the morning of Day 4, after all assessments have been performed.

j An update of medical history will be performed at admission to the study center on Day -1.

k Day 15 is considered End of Study visit for healthy subjects only. Subjects with hepatic impairment are expected to have a follow-up visit on Day 15, with the following assessments: PK sampling, monitoring of AEs and previous/concomitant medication and nondrug therapy/intervention.

l Hepatic impaired subjects only.

2 Sponsor, Investigators and Study Administrative Structure

This clinical study will be sponsored by: EMD Serono Research & Development Institute, Inc, 45A Middlesex Turnpike, Billerica, MA 01821, USA. The Sponsor's legal representative in the EU/EEA is Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany.

The study will be conducted at 2 study centers (hospital-based, inpatient, Phase 1 research centers) in the USA:

- PI , USA
- PI , USA

The Principal Investigators, PI (Orlando Clinical Research Center), and PI (QPS MRA, LLC) will provide expert medical input and advice relating to study design and execution and are responsible for the review and signoff of the clinical study report (CSR).

Signature pages for the Protocol Lead and the Principal Investigators as well as a list of Sponsor responsible persons are in Appendix II.

A Safety Monitoring Committee (SMC) may be established. If an SMC is established it will consist of, but may not be limited to, the following members: the Clinical Pharmacologist, Principal Investigators, Sponsor's Medical Responsible, and the Sponsor's Global Drug Safety Product Lead. Ad hoc members will be consulted as needed and may include, but is not restricted to, the Biostatistician. Details regarding the SMC responsibilities are provided in Section 5.1.

The Sponsor's Global Drug Safety department or its designated representative will supervise drug safety and the timeline for reporting of adverse events (AEs) and serious adverse events (SAEs) to all concerned parties in accordance with the applicable guidelines, laws, and regulations.

The Sponsor will partner with a contract research organization (CRO), to conduct the clinical part of the study including study set-up, coordination, monitoring, data capture, data management, statistical analysis, and CSR preparation. A central laboratory will be used for clinical laboratory analysis. A testing laboratory will be responsible for analysis of the pharmacokinetic (PK) samples. The Sponsor will supervise all outsourced activities.

The Sponsor will arrange delivery of the investigational medicinal product (IMP) to the study centers.

Laboratory sample processing, handling, and storage instructions as well as dose preparation and dispensing details will be presented in separate manuals which will be prepared by the CRO in coordination with the Sponsor.

3 Background Information

3.1 General Information

The mesenchymal-epithelial transition factor (c-Met) receptor tyrosine kinase is a cell surface receptor, capable of mediating pleiotropic effects, including cell migration, survival, and proliferation. Its ligand is the hepatocyte growth factor (HGF), also known as scatter factor (1). Under physiological conditions, c-Met regulates invasive growth and morphogenesis in multiple embryonic tissues, such as muscles, the nervous system, bones, and vascular system and is essential for development. c-Met/HGF have been implicated in carcinogenesis and metastatic tumor progression by enhancing angiogenesis, cancer cell proliferation, migration, invasion, and conferring resistance to apoptosis. Activating c-Met point mutations and amplification as well as c-Met/HGF co-expression have been observed in a number of human tumors. Pharmacological interference with the HGF/c-Met axis is considered with increasing interest as a promising strategy to inhibit primary tumor growth and metastasis.

The resistance of advanced epithelial tumors to conventional standard chemotherapies have been linked to their genetic complexity; however recent findings indicate that many solid tumors are "addicted" to particular activated kinases.

Targeting such kinases with selective inhibitors represents a promising anticancer approach. The role of c-Met in tumor progression and metastatic dissemination makes it a privileged candidate for therapeutic intervention.

Given the important role of aberrant HGF/c-Met signaling in cancer, several different therapeutic strategies, aimed at inhibiting HGF/c-Met signaling, have been developed and are currently being evaluated in clinical studies. These include agents that directly inhibit HGF and/or its binding to c-Met, antibodies targeted at c-Met, and small-molecule c-Met tyrosine kinase inhibitors (1 - 6).

Proof of concept has been shown in Phase 2 studies with onartuzumab (a monoclonal antibody against the c-Met receptor) in combination with erlotinib in subjects with stage IIIB/IV non-small cell lung carcinoma (NSCLC) with c-Met overexpressing tumors (7), and with rilotumumab (a monoclonal antibody against HGF) in combination with chemotherapy in advanced/metastatic gastro-esophageal cancer with c-Met overexpressing tumors (8).

The free base form of tepotinib (EMD 1160879) has an identical structure to tepotinib (MSC2156119J). Both compounds have been used in a number of pharmacological studies, yielding comparable results. Competition experiments and crystallographic studies indicate that tepotinib is a reversible adenosine triphosphate-competitive kinase inhibitor. The biochemical activity of tepotinib, measured with the recombinant human c-Met kinase domain and a peptide substrate, resulted in an average half maximal inhibitory concentration of 1.7 nM. Tepotinib (free base form) displayed high selectivity towards c-Met using in vitro kinase reactions. Using a panel of more than 100 different kinases, high doses of the free base form of tepotinib (10 micromolar [µM]) inhibited only the oncogenic kinases ALK, Axl, Blk, Ron, and TrkB by > 50%, and blockade of these kinases is suggested to further support the antitumor activity of the free base form of tepotinib through c-Met kinase.

In vivo, the activity of both tepotinib and the free base form of tepotinib was demonstrated in tumor models with ligand independent c-Met activation (Gastric Hs746T, gastric MKN-45, NSCLC NCI-H441, NSCLC EBC-1) and in tumor models co-expressing HGF and c-Met (Glioblastoma U87MG, pancreatic carcinoma KP-4, liver cancer MHCC97H) as well as in translocated promoter region (TPR)-Met transformed murine fibroblasts. Tepotinib and the free base form of tepotinib significantly inhibited tumor growth and induced partial or complete regression of established EBC-1, Hs746T, MKN-45, NCI-H441, U87MG, KP-4, MHCC97H, and TPR-Met NIH3T3 tumors. The antitumor efficacy of the combination of tepotinib with cetuximab, erlotinib, sorafenib, and temozolomide was demonstrated in mouse xenograft models of NSCLC, glioblastoma, and hepatocellular carcinoma (HCC).The mechanism of action of tepotinib was investigated in vivo in a PK/pharmacodynamic (PD) study, conducted on Hs746T gastric cancer xenografts and the finding indicate that treatment with tepotinib induces cell cycle arrest and inhibition of tumor cell proliferation.

In primary PD studies, tepotinib 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, TPR-Met. Serum proteins only moderately interfered with the inhibitory activity of tepotinib, which persisted over a prolonged period of time. Tepotinib treatment of susceptible tumor cells inhibited cell survival and HGF-dependent cell migration in a dose-dependent manner. Both effects were associated with inhibition of c-Met activation.

As of 30 September 2017, about 452 subjects had been exposed to tepotinib in 5 completed studies, in healthy volunteers (EMR200095-002, EMR200095-007, and MS200095-0012; n=79 subjects), and in subjects with different solid tumors (EMR200095-001 and EMR200095-003; n=161), and 4 ongoing studies in subjects with HCC, or epidermal growth factor receptor mutated or c-Met mutated NSCLC (EMR200095-004, EMR200095-005, EMR200095-006, and MS200095-0022). In the ongoing studies, subjects with HCC have received tepotinib as monotherapy and subjects with NSCLC received either tepotinib monotherapy or a combination with gefitinib in Phase 1 or Phase 1b/2 studies thus far. Doses of tepotinib up to 1400 mg daily and 1000 mg daily have been explored in patients with solid tumors in Study EMR200095-001 and in patients with HCC in Study EMR200095-004, respectively.

Investigations in clinical pharmacology studies are often done in healthy volunteers. Based on the currently available nonclinical as well as clinical safety data there is no objection against administration of single doses of tepotinib to healthy volunteers. Accordingly, healthy volunteer studies have already been performed administering single tepotinib doses of up to 500 mg. It is recognized that healthy volunteers will not benefit by participating in this study. However, this study will generate mandatory human data about the administration of tepotinib to subjects with hepatic impairment. This is basic information to safeguard the further clinical development of tepotinib in patients suffering from malignancies such as HCC. During the development of tepotinib 3 healthy volunteer studies have been performed in 79 healthy volunteers. Healthy volunteers tolerated a single or 3 doses of tepotinib (different dose levels) well. All treatment-emergent adverse events (TEAEs) were mild to moderate, except for one Grade 3 asymptomatic lipase elevation in 1 subject. Across all 3 studies, the TEAEs did not show a pattern.

No SAEs were reported and no subject died. No clinically significant findings with regard to laboratory parameters, vital signs, and electrocardiograms (ECGs) including corrected QT intervals using Fridericia's formula (QTcF) values were noted.

Volunteers enrolled in this study might be exposed to a potential risk, including pancreatic enzyme elevation. However, inclusion of healthy volunteers 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.

Asymptomatic elevations in serum lipase and amylase are considered as important potential risk for subjects administered tepotinib. These elevations were observed in 5 out of 78 healthy volunteers exposed to tepotinib and were mild to moderate in severity (exception: one Grade 3 lipase elevation). The asymptomatic increase of serum amylase/lipase was not associated with a pancreatitis.

Knowing that the inhibition of c-Met shows teratogenic effects in knockout mice, stringent criteria are applied to ensure exclusion of women of childbearing potential in this study. Only healthy women that are known to be postmenopausal or surgically sterile (ie, hysterectomy and oophorectomy) will be enrolled in this study (for details see Appendix I).

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

Based on previous studies, the 500 mg once daily dose achieves c-Met inhibition ≥ 90% and results in sufficiently high steady state (trough) exposure levels in ≥ 90% of subjects to induce activity in tumors with varying degrees of sensitivity to c-Met inhibition. The 500 mg once daily dose is, therefore, considered to be safe and in the biologically active range.

Refer to the Investigator's Brochure for further information about the nonclinical and clinical programs and Guidance for the Investigator.

3.2 Study Rationale

In a mass balance trial, ^{14}C-MSC2156119 was moderately metabolized in human subjects and a total of 10 different Phase 1 and Phase 2 metabolites were found. Total radioactivity was also mainly eliminated via feces (~78%) while only about 14% was recovered in urine. In feces, roughly 45% of the administered dose could be related to parent drug. This indicates a high extent of active secretion (likely via bile), but unabsorbed drug as well as reduction of N-oxides and hydrolysis of the glucuronide to parent drug may have also contributed to this high recovery. Based on AUC_{all} (which corresponds to the $AUC_{0\text{-}240h}$ within the observation period), the M506 could be identified as major metabolite both with respect to European Medicines Agency (EMA) Guidance ICH M3(2) EMA/CPMP/ICH/286/1995 (4) and the draft Food and Drug Administration (FDA) Guidance for Industry – Drug Interaction Studies (5). Ratios of geometric mean values of AUC_{all}

of M506 to total radioactivity and to parent MSC2156119J compound were about 40.4% and 74.9%, respectively. M506 is formed from MSC2156119J with a median t_{max} of 24 hours ranging from 24 to 60 hours and showed an apparent geometric mean half-life of 93 hours ranging from 66 to 145 hours estimated on concentration data from 4 subjects. Urinary excretion was identified as minor route of excretion with an average recovery in urine of only 13.6% (range 8.8% to 17.7%).

According to the hepatic impairment guidances (FDA Guidance for Industry 2003 (9), EMA Guideline CPMP/EWP/2339/02 2005) it should be determined if alterations of excretory and metabolic activities by hepatic impairment can lead to drug accumulation.

Currently, enrolment of subjects into tepotinib HCC studies is restricted to subjects with mild hepatic impairment, ie, Child-Pugh class A.

This study will evaluate the PK and safety of tepotinib in subjects with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment.

In most cases, HCC develops within an established background of chronic liver disease (70 to 90% of all patients) (10) and patients with cirrhosis have the highest risk of developing HCC (90 to 95% of subjects who develop HCC have underlying cirrhosis) (11). It is therefore assumed that the results of this study in subjects with hepatic impairment are also applicable to patients with HCC, especially patients with Child-Pugh class B.

In Part 1 of the study, PK and safety of a single dose of 500 mg tepotinib will be assessed in subjects with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment in comparison to healthy subjects. A higher dose than 500 mg may be evaluated in Part 2 of the study in subjects with hepatic impairment if deemed necessary by the project team. In this case, the SMC will assess the results of Part 1 and make a recommendation on the tepotinib dose and which population (Child-Pugh class A or B) to be enrolled in Part 2. Healthy subjects will not be enrolled in Part 2 of the study.

This clinical study will be conducted in compliance with the clinical study protocol, ICH GCP, the Declaration of Helsinki, and any additional applicable regulatory requirements.

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

4 Study Objectives

4.1 Primary Objective

- To assess the PK of tepotinib in subjects with various degrees of impaired hepatic function (in comparison to healthy subjects).

4.2 Secondary Objectives

- To further investigate the pharmacokinetics of tepotinib and its metabolites MSC2571109 and MSC2571107 in subjects with various degrees of impaired hepatic function (in comparison to healthy subjects)
- To assess safety and tolerability of tepotinib in subjects with various degrees of impaired hepatic function (in comparison to healthy subjects).

4.3 Other Objectives

Not applicable

5 Investigational Plan

5.1 Overall Study Design and Plan

This is a Phase 1, two-staged, open-label study to investigate the effect of various degrees of hepatic impairment on the PK, safety and tolerability of the c-Met kinase inhibitor, tepotinib.

Part 1 will include subjects with hepatic impairment (Child-Pugh class A [6 subjects] and Child-Pugh class B [6 subjects]) and a control group (6 healthy subjects matched 1:1 to 6 subjects with Child-Pugh class B with regard to age ± 10 years, weight ± 10 kg, and same gender). All subjects will receive a single dose of 500 mg tepotinib.

Part 2 of the study is optional and, if conducted, will evaluate doses above 500 mg up to 1000 mg in 6 subjects with hepatic impairment of either Child-Pugh class A or B.

An SMC may be established to evaluate the safety- and PK results of Part 1 if the overall development program of tepotinib decides to use higher doses than 500 mg (up to 1000 mg) in the Phase 2 or Phase 3 studies. The SMC will then make a recommendation on the tepotinib dose and which population (Child-Pugh class A or B) to be enrolled in Part 2 based on the safety- and PK results of Part 1. See Figure 1 for a diagram of the study design.

Subjects will be screened from Day -28 to Day -2. Subjects will be admitted to the study center on Day -1 and will remain inpatient at the study center under medical supervision until discharge on the morning of Day 4.

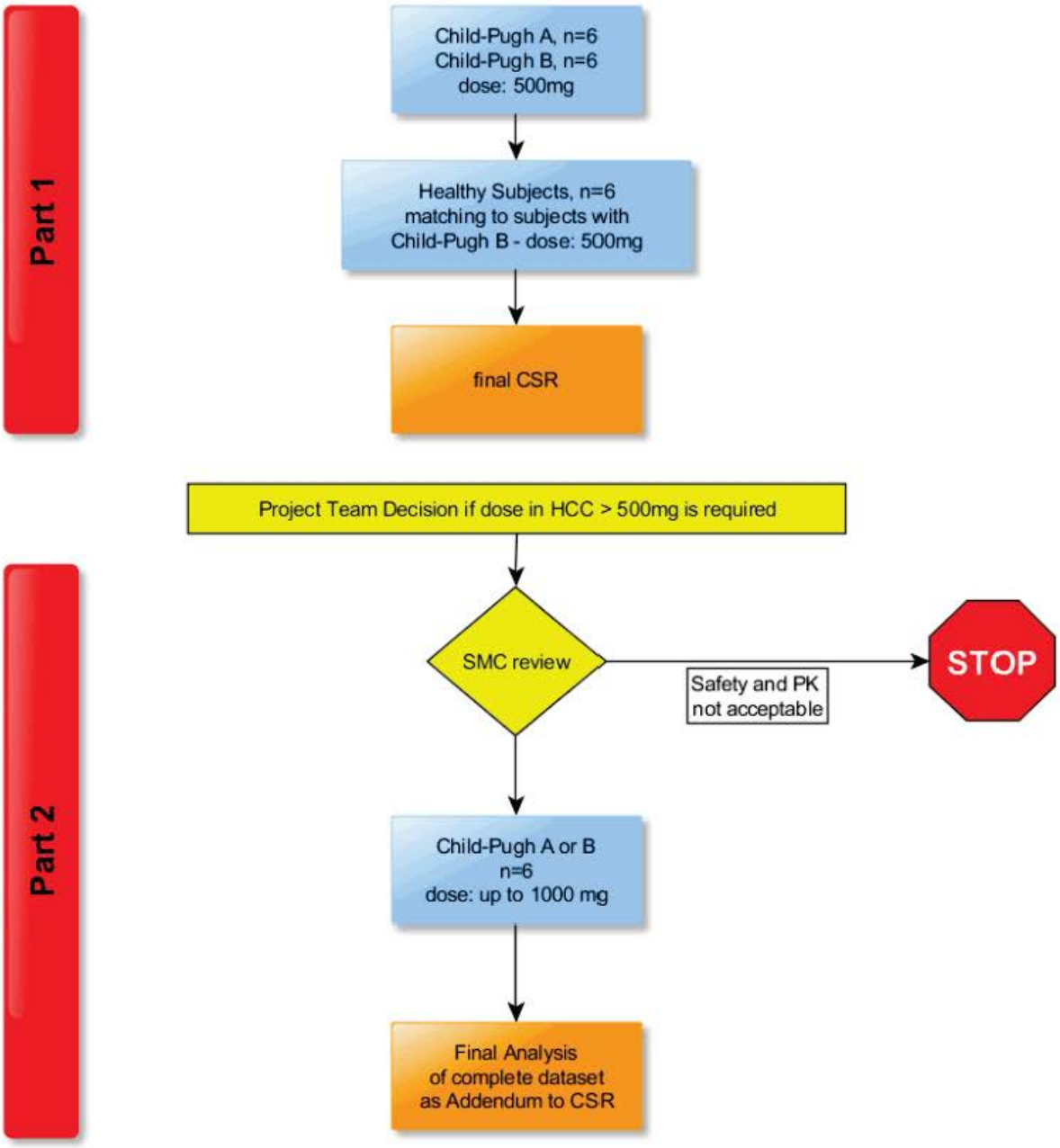
The treatment consists of a single-dose administration of 500 mg tepotinib on Day 1 in Part 1. The dose to be investigated in Part 2 will be determined by the SMC after evaluation of the safety- and PK results of Part 1.

Serial blood samples (PK and clinical laboratory assessments) and urine samples (clinical laboratory assessments) will be collected at the timepoints provided in Table 1. There is a PK sampling period of 2 weeks for healthy subjects and 3 weeks for hepatic impaired subjects.

The End of Study visit is planned on Day 15 for healthy subjects and on Day 22 for hepatic impaired subjects. An Early Termination visit will be conducted for subjects who withdraw

prematurely. The same assessments as for the End of Study visit will be conducted at the Early Termination visit.

Figure 1 Design Diagram



Part 2 of the study is optional.

CSR = Clinical study report; HCC = Hepatocellular carcinoma; PK = Pharmacokinetic, SMC = Safety Monitoring Committee.

5.2 Discussion of Study Design

A parallel design with a small number of hepatic impaired subjects and controls with normal hepatic function is the standard design for hepatic impairment studies, in line with the FDA and EMA guidances/guidelines. According to the hepatic impairment guidances (FDA Guidance for Industry 2003, EMA Guideline CPMP/EWP/2339/02 2005), 6 evaluable subjects should be enrolled per group. The control group will consist of 6 healthy subjects with normal hepatic function, matched 1:1 to the subjects with moderate (Child-Pugh class B) impaired hepatic function with regard to age ± 10 years, weight ± 10 kg, and same gender.

Subjects with hepatic impairment will be assigned to a group of mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment at Screening by use of the Child-Pugh system. See Table 2 and Table 3.

Table 2 Child-Pugh Grades/Class of Hepatic Impairment

Child-Pugh Score	Child-Pugh Grade/Class	Severity of Hepatic Impairment
5-6	A	Mild
7-9	B	Moderate
10-15	C	Severe[a]

a Subjects with severe hepatic impairment will not be included in this study

Grading of hepatic impairment by use of the Child-Pugh system, including ultrasound examination for detection and classification of ascites as well as assessment of hepatic encephalopathy, will only be performed in subjects with hepatic impairment.

Table 3 Child-Pugh Criteria

	Points Scored for Observed Findings (14, 15, 16)		
	1	**2**	**3**
Encephalopathy grade[a]	none	1 or 2 or medically controlled [c]	3 or 4 or medically controlled [c]
Ascites[b]	absent	slight or medically controlled [c]	Moderate or medically controlled [c]
Serum bilirubin (mg/dL)	< 2	2 to 3	> 3
Serum albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
International Normalized Ratio (INR)	< 1.70	1.70 to 2.20	> 2.20

a Encephalopathy will be assessed by an experienced physician at Screening using the following criteria:
Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2 to 3 cycles per second delta activity.

b Ascites will be assessed by an experienced physician by physical examination as well as ultrasound examination at Screening using the following criteria:
Absent: No ascites is detectable by manual and also not by ultrasound investigation.
Slight: Ascites palpitation doubtful, but ascites measurable by ultrasound investigation.
Moderate: Ascites detectable by palpitation and by ultrasound investigation.

c Diagnosis and treatment of medically controlled subjects must be confirmed by the subject's medical records.

The majority of healthy volunteers are not expected to have measurable concentrations after Day 15; therefore sampling until Day 15 is sufficient. Sampling for one additional week for the subjects with hepatic impairment to cover a possibly longer half-life appears appropriate. This was confirmed with a compound model developed in Simcyp, which allowed to simulate the impact of change in active liver size in subjects with hepatic impairment. Simulations using the population representatives indicate that the concentration reached after 21 days decline is attained in subjects with hepatic impairment about 1 to 2 days later, ie, the predicted difference between the healthy and subjects with moderate hepatic impairment.

Model limitations include non-consideration of possibly reduced metabolic enzyme expression. Of the number of physiological changes known to occur in subjects with hepatic impairment (size of active liver, plasma protein binding, blood flow, metabolizing enzymes), only the reduction of active hepatocytes could be implemented in the model. Thus the effect of hepatic impairment could be stronger than predicted.

5.2.1 Scientific Rationale for Study Design

The study design includes matched pairs of patients with hepatic impairment and healthy volunteers and is the recommended design to characterize the effects of impaired hepatic function on the PK of a drug. Part 2 is required if within the total tepotinib program, a higher therapeutic dose than 500 mg once daily will be used.

5.2.2 Justification for Dose

In clinical studies in healthy subjects, good safety and tolerability was observed after administration of single doses of 30 mg to 500 mg.

From patients with solid tumors, safety data is available for a dose regimen of 1400 mg tepotinib once daily. Even in case of a significant delay in elimination in patients with hepatic impairment, exposure in this study with single dose administration is expected to be less.

For Part 1 of this study, the recommended Phase 2 dose of 500 mg has been selected.

Tepotinib will be administered in the fed state, which is also the recommended mode of administration in clinical studies with tepotinib performed thus far.

Part 2 of the study is optional and will be conducted if the overall development program of tepotinib decides to use higher doses than the 500 mg in Phase 2 and Phase 3 studies. An SMC will make a recommendation on the tepotinib dose and which population to be enrolled in Part 2. Further details are provided in Section 5.1.

5.2.3 Rationale for Endpoints

The primary and secondary endpoints are relevant exposure parameters that are required to assess the impact of hepatic impairment on the exposure of tepotinib.

The rationale for including metabolites as secondary endpoints are as follows:

M506 was identified as the only major circulating metabolite and contributes with a low extent to the overall activity. Its contribution to safety and tolerability is not evaluated by nonclinical safety, as tepotinib is developed under the ICH S9 guidance.

M506 is formed from MSC2156119J with a median t_{max} of 24 hours, ranging from 24 to 60 hours, and showed an apparent geometric mean half-life of 93 hours, ranging from 66 to 145 hours, estimated on concentration data from 4 subjects. M506 consists of 2 enantiomers, the S-enantiomer, MSC2571107, and the R-enantiomer, MSC2571109, which have been included as secondary endpoints. MSC2571109 represents the major human plasma metabolite of tepotinib (64.6% of parent AUC_{0-240h}), while MSC2571107 is a metabolite of less significance (4.54% of parent AUC_{0-240h}). A bioanalytical assay is available, which analyzes tepotinib and the enantiomers.

5.2.4 Risks

On the basis of available clinical data, asymptomatic increase of lipase and amylase are considered as an identified risk of tepotinib. Such elevations have been reported for a number of other tyrosine kinase inhibitors with molecular targets other than c-Met (eg, sunitinib, imatinib, sorafenib) and can therefore be regarded as a class effect. The underlying mechanism that causes the enzyme elevation is unknown. The pancreas was not identified as a potential target organ in animal toxicology studies. No pancreatitis has been reported so far.

Tepotinib was identified as a P-glycoprotein (P-gp) substrate, as well as an inhibitor of P-gp, BCRP, OCT1, OCT2, MATE1, and MATE2. Intestinal and systemic drug-drug interactions on the transporter level with relevance cannot be ruled out. In vitro drug transporter interaction studies revealed a pronounced inhibition of OCT1, OCT2, and MATE2 by the major metabolite MSC257119A with the potential for clinically relevant drug-drug interactions considering its current mean exposure at steady state in clinical studies.

5.2.5 Inclusion of Special Populations

Standard inclusion and exclusion criteria have been selected for the inclusion of healthy subjects and subjects with mild (Child-Pugh class A) and moderate (Child-Pugh class B) impaired hepatic function. Women of childbearing potential are excluded from participation in the study.

5.3 Selection of Study Population

Only volunteers meeting all of the inclusion criteria and none of the exclusion criteria may be enrolled into the study. Prior to performing any study assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

All subjects:

1. Men and women (of nonchildbearing potential), 18 to 75 years (inclusive) of age at Screening

2. Body mass index of 18 to 36 kg/m^2 (inclusive) with a body weight ≥ 50 kg at Screening

3. Women must be postmenopausal for at least 1 year, as confirmed by follicle stimulating hormone (FSH) assessments performed at Screening, or surgically sterile (ie, documented hysterectomy, documented bilateral salpingectomy, or documented bilateral oophorectomy). Pregnancy assessments will also be performed on female subjects at Screening and at admission to the study center

4. A male participant must agree to use a barrier method, and to have their female partners use highly effective, medically acceptable methods of contraception (ie, methods with a failure rate of less than 1 % per year) as detailed in Appendix I of this protocol during participation in

the study and for at least 90 days after the last dose of IMP. Men must refrain from donating sperm during the same period

5. Heart rate in the range of 50 to 99 beats per minute after 10 minutes rest in the semi-supine position at Screening

6. Negative drug-screening results and a negative alcohol breathalyzer test at Screening and Day -1. For all subjects, a negative cannabinoid (THC) result on drugs of abuse screening is required to participate in the study. If the result is positive, the Principal Investigator may request to repeat the test. For subjects with hepatic impairment, a positive cannabinoid (THC) result on drugs of abuse screening will not be exclusionary (at Screening or Day -1) if the subject uses cannabinoids on medical recommendation. In subjects with hepatic impairment, positive test for drugs used on medical recommendation will be not exclusionary.

7. Negative human immunodeficiency virus 1 and 2 antibodies at Screening

8. 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

9. Absence of acute hepatitis.

Subjects with normal hepatic function:

10. Healthy volunteers, as judged by the Investigator

11. Medical history without any ongoing clinically relevant findings as judged by the Investigator

12. Physical examinations without any clinically relevant findings as judged by the Investigator.

Subjects with impaired hepatic function:

13. Subjects with mild (Child-Pugh class A) and moderate (Child-Pugh class B) impaired hepatic function at Screening

14. Subjects with confirmed cirrhosis (excluding primary biliary liver cirrhosis)

15. Systolic blood pressure in the range of 80 to 180 mmHg and diastolic blood pressure in the range of 45 to 95 mmHg at the Screening visit after 10 minutes rest in the semi-supine position

16. A 12-lead ECG recording that is normal, or with abnormalities which are not hazardous to the subject in the opinion of the Investigator at Screening.

5.3.2 Exclusion Criteria

All subjects:

1. Subject has taken an investigative medication within 30 days prior to administration of IMP
2. Subject has donated blood within 60 days or plasma within 14 days prior to Screening
3. Subject is lactating
4. Diseases or surgeries of the gastrointestinal tract, which could influence the gastrointestinal absorption or motility
5. A history of epilepsy
6. A history of malignant diseases other than basalioma
7. Clinically relevant allergies that require medical treatment, as judged by the Investigator
8. Inability to refrain from alcohol intake during confinement. Subjects should not consume more than 14 (women) or 21 (men) units of alcohol a week (unit = 1 glass of wine (125 mL) = 1 measure of spirits = ½ pint of beer)
9. Any other clinically relevant disease, which in the Investigator's opinion would exclude the subject from the study
10. Inability to communicate or cooperate with the Investigator (eg, language problem, illiterate, poor mental status) or to comply with the requirements of the entire study, including dietary restrictions
11. Smoking > 10 cigarettes per day, or equivalent use of other forms of nicotine (ie, patches, gum, chewing tobacco, vaping) for the duration of the study
12. Antacid drugs, H2-blocker and proton pump inhibitors might affect the absorption of tepotinib. H2-blocker or proton pump inhibitors should be stopped 5 days prior to Day 1 until Day 2. Antacids should not be taken 1 hour before the IMP administration until 2 hours after the IMP administration.
13. Renal dysfunction (defined as creatinine clearance < 60 mL/minute, calculated by use of the Cockcroft-Gault formula)

Healthy Subjects:

14. Presence of hepatitis B or hepatitis C or previous infection with hepatitis C, treated with Sofosbuvir or other antiviral compounds
15. Use of any medication, including multivitamin preparations, received within 10 days prior Day 1 or 6 times the elimination half-life, whichever is the longest, until the End of Study visit,

except the occasional use of paracetamol/acetaminophen or ibuprofen (not > 500 mg per day) within 7 days before Day 1 until the End of Study visit.

Subjects with impaired hepatic function:

16. Primary biliary liver cirrhosis

17. Nonstabilized chronic heart failure (New York Heart Association Class III and IV)

18. Hepatocarcinoma

19. Hepatic encephalopathy Grade III and IV

20. Sepsis or spontaneous bacterial peritonitis within the last 2 years prior to Screening

21. Gastrointestinal bleeding within 30 days prior to or during Screening

22. Esophageal varices > Grade II at Screening

23. Acute hepatic failure of any etiology (including viral, toxic, or drug induced)

24. Portosystemic shunt

25. Current intake of any drug with dose dependent hepatotoxicity, such as paracetamol/acetaminophen (> 500 mg per day)

26. Change in used medication (prescribed by a physician or over-the-counter medication) other than for hepatic insufficiency within 7 days prior to Day 1

27. Co-medication inducing or inhibiting P-gp, BCRP, OCT1, OCT2, MATE1, or MATE2 should be stopped from 5 days prior to Day 1 until the End of Study visit

28. Clinical evidence of severe ascites

29. Ascites requiring paracentesis within 21 days prior to Day 1.

5.4 Criteria for Initiation of Study Treatment

Inclusion and exclusion criteria will be checked within the Screening period and at Day -1. Subjects meeting all of the inclusion and none of the exclusion criteria will be enrolled to Part 1 or Part 2 of the study, as appropriate, and admitted to the study center on Day -1 for IMP administration on Day 1.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Investigational Medicinal Product Administration

Not applicable since the IMP is administered only once in the study.

5.5.2 Withdrawal from the Study

Subjects may withdraw from the study at any time without giving a reason.

A subject must be withdrawn from the study if any of the following occur during the study:

- Subject withdrew consent
- Participation in another clinical study during the duration of this study
- Use of nonpermitted concomitant medications, as defined in Section 6.5. However, any medications that are considered necessary for the subject's wellbeing may be given at the discretion of the Investigator
- Protocol noncompliance judged as significant by the Investigator, including noncompliance to the required study considerations (eg, food/diet requirements)
- Subject lost to PK sampling
- Any event that unacceptably endangers the safety of the subject.

If there is a medical reason for the withdrawal, the subject will remain under the supervision of the Investigator until satisfactory health has returned or care has been transferred to the subject's general practitioner or to a hospital consultant.

In case of premature withdrawal from the study, the assessments scheduled for the End of Study visit should be performed, if possible, with the focus on the most relevant assessments (see Table 1). Regardless, the appropriate electronic case report form (eCRF) section should be completed.

Subjects who are withdrawn after IMP administration and are not evaluable will be replaced, as discussed by the Investigator and Medical Responsible of the Sponsor.

5.6 Premature Termination of the Study

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

The Health Authorities and Institutional Review Boards (IRBs) will be informed about the discontinuation of the study in accordance with applicable regulations.

5.7 Definition of End of Study

The end of the study is defined as the completion of the last visit of the last subject.

6 Investigational Medicinal Product and Other Drugs Used in the Study

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

6.1 Description of the Investigational Medicinal Product

Tablet Formulation 2 (film-coated tablet formulation) of tepotinib will be used in this study. For Part 1, 500 mg tablets of Tablet Formulation 2 will be used. For Part 2, 100 mg tablets of Tablet Formulation 2 or a bioequivalent formulation may also be used for doses other than 500 mg or 1000 mg.

Tepotinib 100 mg and 500 mg film-coated tablets for Phase 1, 2 and 3 clinical studies contain the excipients D-mannitol, silica colloidal anhydrous, crospovidone, magnesium stearate, and Opadry® II pink (for 100 mg) or Opadry II yellow (for 500 mg). The film-coated tablets are intended for oral administration.

6.2 Dosage and Administration

All subjects will receive the IMP once only in the course of the study. A single oral dose of 500 mg in Part 1 and up to 1000 mg in Part 2 tepotinib tablets will be administered to subjects after they have completed a standard breakfast. The IMP administration will occur 30 minutes after the start of the intake of a standard meal. Subjects should eat this meal within 25 minutes or less. The IMP will be administered with 240 mL of water. The subject will remain fasting for 4 hours after the breakfast, after which a standardized lunch will be served. Further details on the standard breakfast are provided in Section 6.5.3.

6.3 Assignment to Treatment Groups

Part 1 will have 1 treatment group and 1 control group receiving a single dose of 500 mg tepotinib. Part 2 is optional, and if conducted, will have 1 treatment group receiving a single dose of between 500 mg up to 1000 mg, as per SMC decision.

6.4 Noninvestigational Medicinal Products to be Used

Not applicable

6.5 Concomitant Medications and Nondrug Therapies/Interventions

All concomitant medications taken by the subject during the study, from the date of signature of informed consent are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration 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

Any medications that are considered necessary to protect subject welfare and will not interfere with the study medication may be given at the Investigator's discretion.

Healthy Subjects

Occasional use of paracetamol/acetaminophen or ibuprofen (not > 500 mg per day) within 7 days before IMP administration is allowed.

Hepatic Impaired Subjects

A stable regimen of other prescribed drugs and vitamins is allowed.

6.5.2 Prohibited Medicines

All Subjects

Antacids, H2-blockers, and proton pump inhibitors might affect the absorption of tepotinib. H2-blockers or proton pump inhibitors should be stopped 5 days prior Day 1, until Day 2. Antacids should not be taken 1 hour before IMP administration until 2 hours after IMP administration.

Healthy Subjects

Use of any medication, including multi-vitamin preparations, received within 10 days prior to Day 1, or within 6 times the elimination half-life, whichever is the longest, except the occasional use of paracetamol/acetaminophen or ibuprofen (> 500 mg per day is prohibited) within 7 days before Day 1 until the End of Study visit.

Hepatic Impaired Subjects:

Concomitant medication inducing or inhibiting P-gp, BCRP, OCT1, OCT2, MATE1, or MATE2 should be stopped from 5 days prior to Day 1 until the End of Study visit.

Current intake of any drug with dose dependent hepatotoxicity, such as paracetamol/ acetaminophen > 500 mg per day is not allowed.

A change in the medication (prescribed by a physician or over-the-counter) used other than for hepatic insufficiency within 7 days prior to Day 1 is not allowed.

The use of nonpermitted concomitant medications for any reason during the study must result in withdrawal of the subject from the study. However, any medications that are considered necessary for the subject's wellbeing may be given at the discretion of the Investigator.

6.5.3 Other Interventions

All Subjects

Subjects are not allowed to smoke > 10 cigarettes per day, or equivalent use of other forms of nicotine (ie, patches, gum, chewing tobacco, vaping) for the duration of the study.

Subjects are required to refrain from alcohol intake during confinement. Subjects should not consume more than 14 (women) or 21 (men) units of alcohol a week (unit = 1 glass of wine (125 mL) = 1 measure of spirits = ½ pint of beer).

Subjects will receive the IMP after they have completed a standard breakfast. Drug administration is 30 minutes after start of the intake of a standard breakfast with 240 mL of water. Subjects should eat this meal within 25 minutes or less. The subject will remain fasting for 4 hours after the breakfast, after which a standardized lunch will be served. The standard breakfast will contain approximately 500 calories and will be balanced in macronutrients (approximately 50% carbohydrates, 25% protein, and 25% fat). The menu must be approved by the Sponsor. The subject will be expected to eat the entire meal. The percentage consumed will be recorded for all subjects. A deviation will be recorded if the subject eats less than 90% of the meal. Subjects will not be excluded from dosing if they are unable to complete the meal in full.

6.5.4 Special Precautions

This study will be performed at 2 hospital-based, inpatient, Phase 1 research centers with personnel trained in basic or immediate life support. Equipment and other agents (ie, epinephrine and prednisolone equivalents, etc.) will be available at the study center in case of allergic reactions.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

No specific measures for management of specific AEs or adverse drug reactions are proposed at this stage. Adverse drug reactions should be treated symptomatically. Standard medical care will be provided at the study center for all AEs encountered during the study.

For details on the management of AEs and adverse drug reactions, see Section 7.4.1.6.

6.6 Packaging and Labeling of the Investigational Medicinal Product

Packaging and labeling will be in accordance with Manufacture of Investigational Medicinal Products (Annex 13, Volume 4), applicable local regulatory requirements, and applicable Good Manufacturing Practice Guidelines.

Tepotinib tablets will be supplied in aluminum-aluminum blisters. The blisters will be packed in a suitable carton box labeled with (but not limited to) the following required information: study number, number of tablets per box, storage conditions, the words "Caution: New Drug – Limited by Federal (or United States) law to investigational use", batch number, and the Sponsor's name.

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

The pharmacy or designee will receive tepotinib labeled and packaged according to the local regulatory requirements and the storage requirements. Tepotinib is formulated as tablets, and is ready for use. The responsible pharmacist or designee will dispense a single dose of tepotinib for administration to the subject during the IMP administration visit. Detailed guidance will be provided in the pharmacy manual.

The IMP supplies will be recorded in a drug inventory and stored in a locked cabinet, protected from environmental extremes until used in the study. Tepotinib should be stored at or below 25°C. Any deviations from the recommended storage conditions should immediately be reported to the Sponsor specified in the pharmacy manual, and the medication should not be used until authorization has been received from the Sponsor.

6.8 Investigational Medicinal Product Accountability

The Investigator (or designee) is responsible for ensuring tepotinib (IMP) accountability, including reconciliation of drugs and maintenance of records.

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

The study center 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 study. No IMP that is dispensed to a subject may be redispensed to a different subject.

A Study 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

The IMP will be administered by the study center staff within the confines of the study center. A mouth and hand check will be performed after administration of the IMP to ensure that the dose has been swallowed.

6.10 Blinding

Blinding is not applicable. (Note: the bioanalytical assay will be performed without knowledge of hepatic function group information. Access to hepatic function group 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 study protocol or planned for an individual subject enrolled in the study. Even if it does not meet other criteria for an SAE, any overdose must be recorded in the study 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 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 judgement for the management of any clinical symptoms or evaluation results.

6.13 Medical Care of Subjects after End of Study

Since this is not an interventional study, medical care of subjects after the End of Study visit is not applicable. After a subject has completed the study or has withdrawn early, follow up treatment will only be administered if required due to an ongoing TEAE.

7 Study Procedures and Assessments

Prior to performing any study assessments, the Investigator will ensure that the subject has provided written informed consent according to the procedure described in Section 9.2.

A subject identifier (see Section 9.3) will be assigned for each subject for who provided written informed consent.

Subjects are not allowed to have participated in a clinical study within the 30 days prior to administration of IMP.

All efforts should be made to perform assessments as close as possible to the scheduled timepoints.

Subjects will be admitted to the study center on Day -1 and remain resident at the study center until the morning of Day 4, after completion of the Day 4 assessments.

When several procedures are scheduled at the same theoretical time, the following sequence should be followed: 12-lead ECG followed by vital signs before the specified timepoint, preceding the PK sampling which will be performed at the specified timepoint. Therefore, assessments not performed at the exact timepoint are not to be considered protocol deviations as long as the actual collection date and time is recorded. Every effort should be made to perform assessments at the appropriate timepoint.

7.1 Schedule of Assessments

The detailed Schedule of Assessments for Part 1 and Part 2 are provided in Table 1.

7.1.1 Screening Visit

Screening of the subjects will take place within 2 to 28 days prior to Day 1. At the start of Screening, candidates for the study will be fully informed about the nature of the study and the possible risks, and will receive a copy of the subject information and informed consent form for review.

After written informed consent is obtained for all procedures in the study, subjects will be evaluated for entry into the study according to the inclusion and exclusion criteria (Section 5.3). Screening procedures specified in the Schedule of Assessments for Part 1 and Part 2 (Table 1) must be performed and evaluated during Days -28 to -2.

If the subject meets all of the protocol inclusion criteria and none of the exclusion criteria, he/she will be considered as eligible and will be enrolled into the clinical study.

Subjects who fail to meet the protocol specified criteria for dosing, who withdraw from the study or who withdraw their consent in the Screening period are considered screening failures. The following data, as a minimum, should be recorded for these subjects: date of informed consent, inclusion/exclusion criteria, demographics (including age, sex (gender), weight, and height), AEs (if any) from the date of informed consent until the subject is considered a screen failure by the Investigator, reason for screening failure, and the Investigator's signature. Rescreening for eligibility of subjects who failed the initial screening will be allowed once per subject within the 28 day Screening period.

7.1.2 Treatment Period

A review and update of the subject's medical history, possible AEs, concomitant medication use and inclusion/exclusion criteria, to ensure the subject remains eligible for participation in the study,

should be performed prior to admission to the study center, on Day -1. Eligible subjects will participate in Part 1 of the study. Subjects will receive their respective IMP dose on Day 1. Subjects will be discharged from the study center on the morning of Day 4, after completion of the Day 4 assessments.

Part 2 of the study is optional. Details are provided in Section 5.1.

Specific assessments to be performed during the treatment periods are presented in the Schedule of Assessments (Table 1).

7.1.3 End of Study Visit/Early Termination Visit

Healthy subjects will partake in the End of Study visit on Day 15 and hepatic impaired subjects will partake in the End of Study visit on Day 22. Assessments at the End of Study visit are specified in the Schedule of Assessments for Part 1 and Part 2 (Table 1). Subjects who discontinue from the study for any reason prior to the End of Study visit must undergo an Early Termination visit immediately upon discontinuation. Assessments at the Early Termination visit are the same as for the End of Study visit.

7.2 Demographic and Other Baseline Characteristics

7.2.1 Demographics

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

Demographic data collected at Screening will be recorded in the eCRF.

7.2.2 Medical History

A complete review of the subject's medical history (including the hepatic insufficiency) should be performed at Screening to determine the subject's eligibility. An update of medical history will be performed at admission to the study center on Day -1. At Screening, subjects with hepatic impairment will be allocated to the mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment group according to the Child-Pugh classification as specified in Table 2 and Table 3.

7.2.3 Medication History

The medication history of subjects must be collected at Screening and updated at admission to the study center. See Section 6.5 for details regarding permitted and prohibited medications.

7.2.4 Other Baseline Assessments

All other baseline measurements, such as vital signs, height and weight, a complete physical examination, clinical laboratory parameters, alcohol breathalyzer test, cotinine test, drugs of abuse screen, pregnancy test in women, FSH levels in postmenopausal women, and 12-lead ECGs will

be assessed at timepoints as specified in the Schedule of Assessments for Part 1 and Part 2 (Table 1).

7.3 Efficacy Assessments

Not applicable

7.4 Assessment of Safety

Subjects will be admitted to the study center on Day -1 and closely monitored for AEs after administration of the IMP. The safety profile of tepotinib will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings including vital signs, 12-lead ECG recordings, and laboratory tests. Pre-existing conditions that are present before the IMP administration will be recorded as baseline conditions.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the study. 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 Investigators are required to grade the severity or toxicity of each AE.

Investigators will reference the most recent version of the National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE), a descriptive terminology that can be used for AE reporting when describing AEs.

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 a particular AE's severity 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 anemia or neutropenia, 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 (for example, 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 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, study procedures.

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

Related: Reasonably related to the IMP. The AE could medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical study 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 Investigators. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, or increased alanine aminotransferase) 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 study treatment or study 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 Screening 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.

Adverse Events of Special Interest

No AEs of special interest have been defined.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each study 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.

Subjects will be educated to inform the study staff of any AE they may be experiencing, as they occur. While the subjects are confined to the study center, study staff will solicit responses from subjects daily for any AEs or any changes to their health in general. Furthermore, any changes in safety monitoring (eg, vital signs, laboratory results, etc), notable as AEs through review by the Investigator/designee, will be recorded accordingly.

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

It is important that each AE report include a description of the event, its duration (onset and resolution dates (and times when it is important to assess the time of AE onset relative to the recorded treatment administration time), its severity, its causal relationship with the IMP, any other potential causal factors, any treatment given or other action taken, including 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 Guidelines provided by the CRO.

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 study (date of first signature of informed consent/) and continues until the End of Study 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

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee using the SAE Report Form following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an SAE Report Form must be provided immediately thereafter.

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.

7.4.1.5 Safety Reporting to Health Authorities, Institutional Review Boards and Investigators

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

The Investigators must comply with any applicable study center-specific requirements related to the reporting of SAEs (particularly deaths) involving study subjects to the IRB that approved the study.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IRB's approval/favorable opinion to continue the study." 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"). The Investigators 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 the appropriate Safety Reports directly to the concerned lead IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or study center-specific regulations, the Investigator will be responsible for promptly notifying the concerned IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/suspected unexpected serious adverse reactions/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 study (see Section 7.4.1.3) and are assessed for final outcome at the End of Study visit. All SAEs ongoing at the End of Study visit must be monitored and followed up by the Investigators 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 the IMP (for example, resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all

pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the eCRF. The 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 study.

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 female subject occurring during the course of the study, the subject must be discontinued from study medication immediately.

In the unlikely event of a pregnancy in a female partner of a male subject occurring during the course of the study, The Sponsor/designee must be notified without delay. The Investigator will attempt to collect pregnancy information on any female partner who becomes pregnant while her male partner is participating in the study. The Investigator will request the necessary signed informed consent from the female partner and if the consent is provided, the Investigator will record pregnancy information on the appropriate form for submission to the Sponsor. If consent is provided, follow up on the pregnancy will continue through the delivery date or termination of the pregnancy, and information regarding the pregnancy outcome and fetal/infant status at outcome (presence or absence of anomalies) will be documented.

7.4.3 Clinical Laboratory Assessments

Blood and urine samples will be collected for the following clinical laboratory tests, following the timing noted in the Schedule of Assessments for Part 1 and Part 2 (Table 1). All samples should be clearly identified.

The Sponsor should receive a list of laboratory normal ranges before shipment of the IMP. Any change in laboratory normal ranges during the study should be forwarded to the Sponsor or its designee.

The laboratory variables to be assessed for safety evaluations are provided in Table 4. Unscheduled retest of laboratory safety tests at the discretion of the investigator are permitted during screening and throughout the study.

Table 4 Clinical Laboratory Evaluations[a]

Biochemistry	Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase γ-Glutamyltransferase Lactate dehydrogenase Creatine phosphokinase	Bilirubin (total) Protein (total) Albumin α-1-acid glycoprotein Cholesterol Triglycerides Amylase Lipase Uric acid	Sodium Potassium Chloride Bicarbonate Calcium Magnesium Phosphate Creatinine Urea Glucose
Hematology	Hematocrit Hemoglobin Red blood cell count Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration	Platelet count White blood cell count	White blood cell differentials and absolute counts: Basophils Eosinophils Lymphocytes Monocytes Neutrophils
Coagulation	International Normalized Ratio (INR)		
Other Tests	Hepatitis B surface antigen Hepatitis B core antibody Hepatitis C antibody Human immunodeficiency virus I and II antibodies	Cotinine Alcohol (breathalyzer) Follicle-stimulating hormone (for postmenopausal women)	
Urinalysis	pH Nitrite Protein Glucose	Ketone bodies Urobilinogen Bilirubin Leukocyte esterase Blood	
Urine Microscopy[b]			
Urine Drug Screen[c]	Cocaine Amphetamines Methamphetamines Opiates	Barbiturates Ecstasy Benzodiazepine Methadone	Cannabinoids (THC) Phencyclidine Oxycodone Tricyclic antidepressants

a Subjects should fast for 8 hours prior to clinical laboratory blood sample collection.

b Only if blood, protein, nitrite, or white blood cell count is positive on the dipstick.

c For all subjects, a negative cannabinoid (THC) result on drugs of abuse screening is required to participate in the study. If the result is positive, the Principal Investigator may request to repeat the test. For subjects with hepatic impairment, a positive cannabinoid (THC) result on drugs of abuse screening will not be exclusionary (at Screening or Day -1) if the hepatic-impaired subject uses cannabinoids on medical recommendation. In subjects with hepatic impairment, positive test for drugs used on medical recommendation will be not exclusionary.

The total blood volume to be drawn from each subject for planned assessments during the study will not exceed the volume of a standard donation (approximately 450 mL) and will be specified in the laboratory manual.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

7.4.4.1 Vital Signs

Vital signs, including oral temperature, systolic and diastolic blood pressure, and pulse rate will be assessed as per the timepoints specified in the Schedule of Assessments for Part 1 and Part 2 (Table 1).

A semi-automated pulse rate and blood pressure recording device with an appropriate cuff size will be utilized. The pulse rate and blood pressure will be measured after 10 minutes rest in the semi-supine position (supine at timepoints where the assessment coincides with 12-lead ECG assessment) with the subject's arm unconstrained by clothing or other material. The blood pressure should be assessed on the same arm for each subject throughout the study.

7.4.4.2 Physical Examination

Complete physical examinations will be performed at the timepoints specified in the Schedule of Assessments for Part 1 and Part 2 (Table 1) and will include an assessment of: general appearance, skin, head and neck, lymph nodes, thyroid, abdomen, and musculoskeletal, cardiovascular, respiratory, and neurological systems.

Body weight will be measured at Screening and at Day -1. Height will be measured at Screening only.

All clinically significant abnormalities occurring before signature of informed consent should be recorded in the medical history and/or disease history section of the eCRF; all abnormalities occurring or worsening after the subject signed the Informed Consent Form should be recorded in the AE section of the eCRF.

7.4.4.3 Electrocardiograms

Standard 12-lead ECGs will be performed at the timepoints specified in the Schedule of Assessments for Part 1 and Part 2 (Table 1) after 10 minutes rest in the supine position. Only the overall evaluation (normal/abnormal) will be recorded in the eCRF, and if abnormal, the specific abnormality will be recorded. Abnormal evaluations will be judged as clinically significant or not clinically significant by the Investigator. The ECG recordings must be performed before PK sampling timepoints on days where both assessments are performed.

7.5 Pharmacokinetics

7.5.1 Body Fluids

Blood samples for the PK evaluation of tepotinib and its metabolites (MSC2571109 and MSC2571107) in plasma will be collected at the timepoints specified in the Schedule of Assessments for Part 1 and Part 2 (Table 1). The exact date and time of sample collection will be recorded in the eCRF. Samples not collected at the exact timepoint are not to be considered

protocol deviations as long as the actual collection date and time is recorded. Every effort should be made to collect samples at the appropriate timepoint.

Details of the sample collection, blood volume, labeling, storage and shipment requirements will be provided in a separate manual of operations or laboratory manual.

The PK sampling is planned differently for healthy subjects than for hepatic impaired subjects as a different half-life is expected. As the majority of healthy subjects do not have measureable concentrations after Day 15, PK sampling until Day 15 is considered sufficient. As the optimal sampling schemes of the hepatic impairment group is difficult to predict, an additional sampling time of 1 week (up to Day 22) is considered to be sufficient. The SMC may decide on a different sampling scheme for Part 2.

All sample analyses will be performed using a validated method measuring parent drug and metabolites.

The free fraction of tepotinib will be determined to assess a potential effect of low serum albumin concentration which might result in an increased free fraction of tepotinib in subjects with hepatic impairment.

7.5.2 Pharmacokinetic Calculations

The PK parameters (see Table 5) of tepotinib and its metabolites MSC2571109 and MSC2571107, if applicable, will be evaluated. Noncompartmental computation of PK parameters will be performed using the software Phoenix® WinNonlin® 6.4 or higher (Certara, L.P., Princeton, NJ, USA, SAS® System (Version 9.4 or later; SAS Institute, Cary, NC, USA) or equivalent software. Individual PK parameters will be calculated using actual sample collection times. The predose sample time will be considered as if it had been taken simultaneously with the IMP administration. Pharmacokinetic variables will be evaluated and listed for all subjects who provide sufficient concentration-time data.

If $AUC_{extra\%}$ is greater than 20%, λ_z and all derived parameters should be flagged as invalid.

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

Table 5 Definition of Pharmacokinetic Parameters

Tepotinib and its Metabolites	
Symbol	***Definition***
AUC_{0-t}	Area under the plasma concentration-time curve (AUC) from time zero to the last sampling time at which the concentration is at or above LLOQ, calculated according to the mixed log linear trapezoidal rule (ie, linear up/log down)
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity, calculated as AUC_{0-t} + $AUC_{extra\%}$, according to the mixed log linear trapezoidal rule (ie, linear up/log down). $AUC_{extra\%}$ represents the extrapolated part of $AUC_{0-\infty}$ calculated by $C_{lastcalc}/\lambda_Z$, where $C_{lastcalc}$ is the calculated plasma concentration at the last sampling timepoint at which the measured plasma concentration is at or above LLOQ
C_{max}	Maximum plasma concentration observed
t_{max}	Time to reach the maximum plasma concentration
$t_{1/2}$	Apparent terminal half-life, calculated as $\ln 2/\lambda_Z$
λ_Z	Apparent 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	Total body clearance of drug from plasma following oral administration, calculated as $Dose/AUC_{0-\infty}$ (for tepotinib only)
V_Z/f	Apparent volume of distribution during the terminal phase following extravascular administration, calculated as $Dose/(AUC_{0-\infty}*\lambda_z)$
$AUC_{extra\%}$	Area under the plasma concentration-time curve extrapolated from time t to infinity as a percentage of $AUC_{0-\infty}$
$MRAUC_{0-\infty}$	Metabolite (MSC2571109 or MSC2571107) $AUC_{0-\infty}$ to tepotinib $AUC_{0-\infty}$ ratio
MRC_{max}	Metabolite (MSC2571109 or MSC2571107) C_{max} to tepotinib C_{max} ratio

7.6 Biomarkers

No biomarker assessments are planned.

7.7 Other Assessments

No other assessments are planned.

8 Statistics

Details of the statistical analyses will be described in a separate statistical analysis plan.

8.1 Sample Size

Pharmacokinetic studies including subjects with impaired hepatic function are usually exploratory by nature. Considering the CVs for the primary endpoints AUC_{0-t} and C_{max} of tepotinib, 20.4% and 22.8% respectively (Study EMR200095-007), 6 evaluable subjects per group will provide 80% power for detecting a group difference of 44% (AUC_{0-t}) and 50% (C_{max}), which is considered

sufficient to meet the study objectives having the therapeutic window of tepotinib in mind. The significance level was set to 0.05 two-sided.

Therefore, 18 subjects (3 groups x 6 subjects) should be included in Part 1 and 6 subjects in Part 2. Drop-outs will be replaced only if they cannot provide an evaluable PK profile.

8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Primary Endpoints

- PK profile of tepotinib (plasma) in terms of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} at Day 1 to Day 15 (healthy subjects) or Day 22 (hepatic impaired subjects) calculated by noncompartmental analyses.

8.3.2 Secondary Endpoints

- PK profile of tepotinib (plasma) in terms of t_{max}, $t_{1/2}$, CL/f, V_Z/f, $AUC_{extra\%}$ at Day 1 to Day 15 (healthy subjects) or Day 22 (hepatic impaired subjects) calculated by noncompartmental analyses

  PK profile of the major tepotinib metabolites MSC2571109 and MSC2571107 (plasma) in terms of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, $AUC_{extra\%}$ at Day 1 to Day 15 (healthy subjects) or Day 22 (hepatic impaired subjects) calculated by noncompartmental analyses, and $MRAUC_{0-\infty}$ and MRC_{max}
- Occurrence of TEAEs, changes from baseline in laboratory safety tests, 12-lead ECG morphology and time intervals (PR, QRS, RR, QT and QTcF), and vital signs.

8.3.3 Other Endpoints

Not applicable.

8.4 Analysis Sets

Screening Analysis Set

The Screening Analysis Set will include all subjects who provide signed informed consent, regardless of treatment status in the trial. This analysis set will be used for subject disposition.

Safety Analysis Set

The Safety Analysis Set will include all subjects who receive study treatment. All safety analyses will be based on this analysis set.

Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set will include all subjects who receive a single dose of the study treatment and have at least 1 postdose PK measurement without important protocol deviations/violations or events (such as vomiting within 2 times the median t_{max}, after dosing) that may affect the PK. All PK analyses will be based on this analysis set.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

Section 10.6.1 describes the process for performing analyses and reporting of results.

Statistical analysis will be performed using the computer program package SAS System (Version 9.4 or later; SAS Institute, Cary North Carolina, US).

Details on the statistical analysis will be presented in the statistical analysis plan that will be finalized prior to database lock.

The statistical analyses will not be started until all data for Part 1 have been corrected and checked for plausibility and until all necessary coding and assessments have been completed. Part 2 of the study is optional, and if conducted, the results will be provided in an addendum to the CSR.

All data recorded during the study will be presented in individual data listings performed on the Safety Analysis Set, as appropriate.

All data will be evaluated as observed; no imputation method for missing values will be used.

Plasma concentration data will be summarized descriptively for all PK analytes (tepotinib and its metabolites) by hepatic function group and scheduled timepoint using appropriate summary statistics. Any values BLQ will be taken as zero for descriptive statistics.

8.5.2 Analysis of Primary Endpoints

As the primary analysis, an analysis of variance (ANOVA) model including hepatic function group as a fixed effect will be applied to log-transformed tepotinib PK parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of the hepatic impairment groups (Child-Pugh class A and Child-Pugh class B) and matched control group (healthy subjects). Differences between the hepatic impairment groups and matched control will be estimated together with their 90% CIs on the log scale. Point estimates and CIs will be back-transformed to the original scale for presentation.

Additionally, a generalized linear model including hepatic function group and sex (gender) as fixed effects, age and weight as covariates, will be applied to the same primary PK parameters. A further covariate log(dose) will be introduced, when/if Part 2 data is included. The model may be reduced for the final estimates, if appropriate.

All endpoints will be descriptively analyzed using summary statistics by hepatic function group. Graphical displays will be presented, where appropriate.

8.5.3 Analysis of Secondary Endpoints

For the secondary PK parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of the tepotinib metabolites, the same analyses as defined for the primary endpoints will be performed.

In a further analysis, the subjects with liver impairment will be evaluated according to the Albumin-Bilirubin (ALBI) score and the Organ Dysfunction Working Group (ODWG) classification (12,13). Further details of the statistical analyses will be described in a statistical analysis plan.

8.5.4 Analysis of Safety and Other Endpoints

Safety data analysis will be conducted on the Safety Analysis Set. The number and percentage of subjects experiencing at least one or more AEs will be summarized by group, relationship to IMP, and severity. Adverse events will be coded using the latest version of the Medical Dictionary for Regulator Activities terminology. Severity of AEs will be graded using the most up-to-date version of the NCI-CTCAE toxicity grades.

Observed and change-from-baseline laboratory values will be summarized by hepatic function group using descriptive statistics, by postdose shifts relative to baseline and data listings of clinically significant abnormalities/outliers, as appropriate.

Clinically significant, abnormal findings from the physical examination are to be reported as AEs. Separate summaries of the physical examination will not be provided. Vital signs and 12-lead ECG data will be summarized for observed and change-from-baseline values by hepatic function group and timepoint using descriptive statistics. Clinically noteworthy 12-lead ECG findings for individual subjects will be listed and summarized as appropriate.

8.6 Interim and Additional Planned Analyses

An SMC may be established to evaluate the safety and PK results of Part 1 and provide recommendations on the tepotinib dose and population to be enrolled in Part 2 if the overall development program of tepotinib decides to use higher doses than 500 mg (up to 1000 mg) in the Phase 2 or Phase 3 studies. Details regarding the SMC responsibilities are provided in Section 5.1.

No additional planned analyses are scheduled.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigators are responsible for the conduct of the study at the study centers and will ensure that the study is performed in accordance with this protocol, the ethical principles outlined in the

Declaration of Helsinki, ICH GCP, and any other applicable regulations. The Investigators must ensure that only subjects who have given informed consent are included in the study.

According to United States Code of Federal Regulations Part 54.2 (e), for studies conducted in any country that could result in a product submission to the United States FDA for marketing approval and could contribute significantly to the demonstration of efficacy and safety of an IMP (which are considered "covered clinical trials" by the FDA), the Investigator and all subinvestigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the study and for 12 months following completion of the study.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the study is written informed consent, which must be given before any study-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 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 study, 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.

If permitted by national regulations, a person other than the Investigator may inform the subject about the study and sign the Informed Consent Form, as above.

After the information is provided by the Investigator, the Informed Consent Form must be signed and dated by the subject and the Investigator.

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

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IRB 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 study subject and obtain new written consent for continued participation in the study. 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.

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 study as well as in the clinical study database. All subject data collected in the study will be stored under the appropriate subject number. Only the Investigator will be able to link study data to an individual subject via an identification list kept at the study center. 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 the CRO for use during study participation in order to provide clinical study subjects with a way of identifying themselves as participating in a clinical study and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject.

The first point of contact for emergencies will be an emergency room, who should contact the clinical study Investigator caring for the affected subject for relevant information. 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, they will answer any questions. Any subsequent action will follow the standard process established for Investigators.

In cases where the Investigator is not available, the study centers 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 Study Insurance and Compensation to Subjects

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

9.6 Institutional Review Board

Prior to commencement of the study at a given center, this clinical study protocol will be submitted together with its associated documents (Subject Information, Informed Consent Form, Investigator's Brochure, subject card) to the responsible IRB 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 at the CRO.

The IRB 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 study, the clinical study protocol version and the Subject Information and Informed Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

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

9.7 Health Authorities

The clinical study protocol and any applicable documentation (ie, Investigational Medicinal Product Dossier, Subject Information and Informed Consent Form) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each study center.

10 Study 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 study 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 study 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 the Sponsor or its designated organization contain no mention of any subject names.

The data will be entered into a validated database. The Sponsor or its designee 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 study.

The eCRFs are essential study documents and must be suitable for regulatory inspections and submissions.

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 study. 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 (gender), height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the study)
- Study identification, that is, the Sponsor study number for this clinical study, and subject number
- Dates for entry into the study (informed consent) and visits to the study center
- Any medical examinations and clinical findings predefined in this clinical study protocol
- All AEs
- Date that the subject left the study including any reason for early study discontinuation or withdrawal from IMP (if applicable).

All documents containing source data must be filed, including, but not limited to computed tomography or magnetic resonance imaging scan images, 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.

The Monitor will be trained to use the electronic database / eCRF and will have read-only access to the study data in the eCRF for source data verification. Data reviewed can be signed off and queries issued directly in the eCRF.

10.3 Investigator Site File and Archiving

Upon initiation of the study, the Investigator will be provided with an Investigator Site File containing all necessary study documents, which will be completed throughout the study 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 study, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the study. The documents to be archived include the Subject Identification List and the signed subject Informed Consent Forms. If archiving of the Investigator Site File is no longer possible at the study center, the Investigator must notify the Sponsor/designee.

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

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This study will be monitored in accordance with the ICH GCP, and any other applicable regulations. The study center Monitor will perform visits to the study center at regular intervals.

The clinical study protocol, each step of the data capture procedure, and the handling of the data, including the final CSR, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study 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 study documents and other materials at the study center, 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 Study Protocol

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

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

10.6 Clinical Study Report and Publication Policy

10.6.1 Clinical Study Report

After completion of Part 1 of the study, the final CSR will be written by the CRO in consultation with the Sponsor and the Principal Investigators following the guidance in ICH Topic E3. Part 2 of the study is optional, and if conducted, the results will be provided in an addendum to the CSR.

10.6.2 Publication

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

11 References Cited in the Text

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12 Appendices

Appendix I: Contraceptive Guidance and Woman of Childbearing Potential

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

Contraceptive Guidance

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

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

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

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
• Vasectomized partner (A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 90 days after the last dose of study treatment

Appendix II: Signature Pages and Responsible Persons for the Study

Signature Page – Protocol Lead

Study Title:	Open-Label, Parallel-Group Phase 1 Study to Investigate the Effect of Various Degrees of Hepatic Impairment on the Pharmacokinetics, Safety and Tolerability of the c-Met Kinase Inhibitor Tepotinib
IND Number:	106103
Clinical Study Protocol Date / Version:	24 April 2018 / Version 2.0

Protocol Lead:

I approve the design of the clinical study:

PI _____ PI _____

Signature Date of Signature

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

Signature Page – Principal Investigators

Study Title	Open-Label, Parallel-Group Phase 1 Study to Investigate the Effect of Various Degrees of Hepatic Impairment on the Pharmacokinetics, Safety and Tolerability of the c-Met Kinase Inhibitor Tepotinib
IND Number	106103
Clinical Study Protocol Date / Version	24 April 2018 / Version 2.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the study at this study center and affirm that I understand and will conduct the study according to the clinical study protocol, any approved protocol amendments, International Council for Harmonization Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

PI PI

Signature Date of Signature

Name, academic degree:	PI
Function / Title:	Principal Investigator
Institution:	Orlando Clinical Research Center
Address:	5055 S. Orange Ave Orlando, FL 32809, USA
Telephone number:	PI
Fax number:	PI
E-mail address:	PI

Signature Page – Principal Investigators

Study Title	Open-Label, Parallel-Group Phase I Study to Investigate the Effect of Various Degrees of Hepatic Impairment on the Pharmacokinetics, Safety and Tolerability of the c-Met Kinase Inhibitor Tepotinib
IND Number	106103
Clinical Study Protocol Date / Version	24 April 2018 / Version 2.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the study at this study center and affirm that I understand and will conduct the study according to the clinical study protocol, any approved protocol amendments, International Council for Harmonization Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

PI _____ PI _____

Signature Date of Signature

Name, academic degree:	PI
Function / Title:	Principal Investigator
Institution:	QPS MRA, LLC
Address:	6280 Sunset Drive, Suite 600 Miami, FL., 33143, USA
Telephone number:	PI
Fax number:	PI
E-mail address:	PI

Sponsor Responsible Persons not Named on the Cover Page

Name, academic degree:	PI
Function / Title:	PI
Institution:	EMD Serono, Inc.
Address:	45A Middlesex Turnpike, Billerica, MA 01821, USA
Telephone number:	PI
Fax number:	-
E-mail address:	PI

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

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

Appendix III: Protocol Amendments and List of Changes

Table of Amendments

Amendment Number	Substantial (Y/N)	Date	Region or Country	Included in the current document (Y/N)
1	N	24 April 2018	Global	Y

Amendment #1

Effective date: 24 April 2018, applicable globally.

Rationale

Change in clinical sites for the study and few administrative changes.

Major Scientific Changes

None.

Administrative and Editorial Changes

Changes to the clinical trial protocol text are presented in the table below. Additions and amended text are shown in bold. If the original clinical trial protocol text was already bold, changes are shown in bold and underlined, deletions are marked using strike through.

Comparison with Clinical Trial Protocol Version 1.0, 15 March 2017

Change	Section	Page	Previous Wording	New Wording
Change in clinical sites and Sponsor Medical Responsible.	Title page, synopsis, Section 2, Appendix II	1, 18, 64, 65	PI DaVita Clinical Research – Minneapolis 825 South 8th Street, Suite 300 Minneapolis, MN 55404, USA Phone: PI Email: PI PI DaVita Clinical Research – Denver St. Anthony's Medical Plaza 1 11750 West 2nd Place, Suite 300 Lakewood, CO 80228, USA Phone: PI Email: Medical Responsible: PI PI Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany Phone: PI Mobile: PI Email: PI	PI ~~DaVita Clinical Research – Minneapolis~~ ~~825 South 8th Street, Suite 300~~ ~~Minneapolis, MN 55404, USA~~ ~~Phone:~~ PI ~~Email:~~ PI PI ~~DaVita Clinical Research – Denver~~ ~~St. Anthony's Medical Plaza 1~~ ~~11750 West 2nd Place, Suite 300~~ ~~Lakewood, CO 80228, USA~~ ~~Phone:~~ PI ~~Email:~~ PI **Orlando Clinical Research Center** **5055 S. Orange Ave** **Orlando, FL 32809, USA** **Phone:** PI **Email:** PI PI **QPS MRA, LLC** **6280 Sunset Drive, Suite 600** **Miami, FL., 33143, USA** **Phone:** PI **Email:** PI Medical Responsible: PI PI Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany Phone: PI Mobile: PI Email: PI

Change	Section	Page	Previous Wording	New Wording
Matching criteria was changed so that matches can be identified before the last moderate hepatic impairment subject is identified.	Synopsis	11	Part 1 will include subjects with hepatic impairment (Child-Pugh class A [6 subjects] and Child-Pugh class B [6 subjects]) and a control group (6 healthy subjects matched to 6 subjects with Child-Pugh class B). All subjects will receive a single dose of 500 mg tepotinib.	Part 1 will include subjects with hepatic impairment (Child-Pugh class A [6 subjects] and Child-Pugh class B [6 subjects]) and a control group (6 healthy subjects matched **1:1** to 6 subjects with Child-Pugh class B **with regard to age ± 10 years, weight ± 10 kg, and same gender**). All subjects will receive a single dose of 500 mg tepotinib.
Subject visits were clarified.	Table 1	15	-	Visit number was added.
Schedule of assessments clarified	Table 1	16	“x” was marked for "subject confinement" at EOS for healthy subjects	“x” marked for "subject confinement" at EOS for healthy subjects was removed. Row for Visit number was added.
Day 15 visit column was renamed.	Table 1 Day 15 visit column	16	End of Study for Healthy Subjects	End of Study for Healthy Subjects / **Treatment visit for Hepatic Impaired Subjects**
Drug screening instructions were clarified.	Table 1, footnote j	16	For healthy subjects, a positive cannabinoid (THC) result on drugs of abuse screening may be repeated and if negative on repeat, the subject will be allowed to participate in the study.	For ~~healthy~~ **all** subjects, a ~~positive~~ **negative** cannabinoid (THC) result on drugs of abuse screening ~~may be repeated and if negative on repeat, the subject will be allowed~~ **is required** to participate in the study. **If the result is positive, the Principal Investigator may request to repeat the test.**
New footnote added to clarify TFF sampling in Schedule of assessments and following footnotes were renumbered.	Table 1, footnote f	17		**The Tepotinib Free Fraction (TFF) sample will not be drawn separately; TFF will be analyzed from the PK back up sample.**
CRO name was removed	2 Sponsor, Investigators and Study Administrative Structure	18	The Sponsor will partner with QuintilesIMS, a contract research organization (CRO), to conduct the clinical part of the study including study set-up, coordination, monitoring, data capture, data management, statistical analysis, and CSR preparation.	The Sponsor will partner with ~~QuintilesIMS,~~ a contract research organization (CRO), to conduct the clinical part of the study including study set-up, coordination, monitoring, data capture, data management, statistical analysis, and CSR preparation.
"LabCorp" and “Nuvisan” names were removed	2 Sponsor, Investigators and Study Administrative Structure	18	LabCorp will serve as the central laboratory for clinical laboratory analysis. Nuvisan will be responsible for analysis of the pharmacokinetic (PK) samples.	~~LabCorp will serve as the~~ **A** central laboratory **will be used** for clinical laboratory analysis. **A testing laboratory** ~~Nuvisan~~ will be responsible for analysis of the pharmacokinetic (PK) samples.

Change	Section	Page	Previous Wording	New Wording
Text was made more generic.	2 Sponsor, Investigators and Study Administrative Structure	18	The Sponsor's Clinical Trial Supplies department will supply the investigational medicinal product (IMP) to the study centers.	~~The Sponsor's Clinical Trial Supplies department will supply~~ **The Sponsor will arrange delivery of** the investigational medicinal product (IMP) to the study centers.
Matching criteria was changed so that matches can be identified before the last moderate hepatic impairment subject is identified.	5.1 Overall Study Design and Plan	23	Part 1 will include subjects with hepatic impairment (Child-Pugh class A [6 subjects] and Child Pugh class B [6 subjects]) and a control group (6 healthy subjects matched to 6 subjects with Child-Pugh class B).	Part 1 will include subjects with hepatic impairment (Child-Pugh class A [6 subjects] and Child Pugh class B [6 subjects]) and a control group (6 healthy subjects matched **1:1** to 6 subjects with Child-Pugh class B **with regard to mean age ± 10 years, mean weight ± 10 kg, and same gender**).
Figure 1 Design Diagram was modified	Figure 1 Design Diagram	24		'One Protocol – One Report' box was deleted.
Matching criteria was changed so that matches can be identified before the last moderate hepatic impairment subject is identified.	5.2 Discussion of Study Design	25	The control group will consist of 6 subjects with normal hepatic function, matched to the subjects with moderate (Child-Pugh class B) impaired hepatic function with regard to mean age ± 10 years, mean weight ± 10 kg, and same gender.	The control group will consist of 6 **healthy** subjects with normal hepatic function, matched **1:1** to the subjects with moderate (Child-Pugh class B) impaired hepatic function with regard to ~~mean~~ age ± 10 years, ~~mean~~ weight ± 10 kg, and same gender.
Text was made more generic for the bioanalytical assay.	5.2.3 Rationale for Endpoints	28	An enantiomer selective bioanalytical assay is available, which analyzes tepotinib and the enantiomers in 1 run.	~~An enantiomer selective~~ **A** bioanalytical assay is available, which analyzes tepotinib and the enantiomers ~~in 1 run~~.
Drug screening instructions were clarified.	5.3.1 Inclusion Criterion 6	30	For healthy subjects, a positive cannabinoid (THC) result on drugs of abuse screening may be repeated and if negative on repeat, the subject will be allowed to participate in the study. For subjects with hepatic impairment, a positive cannabinoid (THC) result on drugs of abuse screening will not be exclusionary (at Screening or Day -1) if the subject uses cannabinoids on medical recommendation.	For ~~healthy~~ **all** subjects, a ~~positive~~ **negative** cannabinoid (THC) result on drugs of abuse screening ~~may be repeated and if negative on repeat, the subject will be allowed~~ **is required** to participate in the study. **If the result is positive, the Principal Investigator may request to repeat the test.** For subjects with hepatic impairment, a positive cannabinoid (THC) result on drugs of abuse screening will not be exclusionary (at Screening or Day -1) if the subject uses cannabinoids on medical recommendation. **In subjects with hepatic impairment, positive test for drugs used on medical recommendation will be not exclusionary.**

Change	Section	Page	Previous Wording	New Wording
Exclusion criterion 25 was moved to "all subjects" to ensure that liver impaired participants have sufficient renal function	5.3.2 Exclusion Criterion 13	30		**Renal dysfunction (defined as creatinine clearance < 60 mL/minute, calculated by use of the Cockcroft-Gault formula).**
Text was amended to make the study less restrictive for potential subjects.	5.3.2 Exclusion Criteria	31	Subject has taken an investigative medication within 30 days prior to Screening.	Subject has taken an investigative medication within 30 days prior to ~~Screening~~ **administration of IMP**.
It was documented that used and unused IMP kits will be destroyed at the trial site.	6.8 Investigational Medicinal Product Accountability	38	-	**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.**
Blinding procedure was clarified for bioanalytical assay.	6.10 Blinding	37	Not Applicable.	**Blinding is not applicable. (Note: the bioanalytical assay will be performed without knowledge of hepatic function group information. Access to hepatic function group information will be restricted and defined in a Data Access Plan).**~~Not applicable.~~
Unscheduled safety laboratory retest at the discretion of the investigator during screening was added to the protocol	7.4.3 Clinical Laboratory Assessments	46	-	**Unscheduled retest of laboratory safety tests at the discretion of the investigator are permitted during screening and throughout the study.**

Change	Section	Page	Previous Wording	New Wording
Drug screening instructions were clarified.	7.4.3 Clinical Laboratory Assessments, Table 4, footnote c	47	For healthy subjects, a positive cannabinoid (THC) result on drugs of abuse screening may be repeated and if negative on repeat, the subject will be allowed to participate in the study. For subjects with hepatic impairment, a positive cannabinoid (THC) result on drugs of abuse screening will not be exclusionary (at Screening or Day -1) if the subject uses cannabinoids on medical recommendation.	For ~~healthy~~ **all** subjects, a ~~positive~~ **negative** cannabinoid (THC) result on drugs of abuse screening ~~may be repeated and if negative on repeat, the subject will be allowed~~ **is required** to participate in the study. **If the result is positive, the Principal Investigator may request to repeat the test.** For subjects with hepatic impairment, a positive cannabinoid (THC) result on drugs of abuse screening will not be exclusionary (at Screening or Day -1) if the **hepatic-impaired** subject uses cannabinoids on medical recommendation. **In subjects with hepatic impairment, positive test for drugs used on medical recommendation will be not exclusionary.**
Text was made more generic for the bioanalytical assay.	7.5.1 Body Fluids	49	All sample analyses will be performed using a validated enantioselective ultra-performance liquid chromatography coupled to tandem high-definition mass spectrometry method measuring parent drug and metabolites in 1 run.	All sample analyses will be performed using a validated ~~enantioselective ultra-performance liquid chromatography coupled to tandem high-definition mass spectrometry~~ method measuring parent drug and metabolites ~~in 1 run~~.
ODWG classification was added to the analysis.	8.5.3 Analysis of Secondary Endpoints	53	In a further analysis, the subjects with liver impairment will be evaluated according to the Albumin Bilirubin (ALBI) score (12).	In a further analysis, the subjects with liver impairment will be evaluated according to the Albumin Bilirubin (ALBI) score **and the Organ Dysfunction Working Group (ODWG) classification** (12,**13**).
eCRF entry time was aligned within site CTA language	10.1 Case Report Form Handling	55	The main purpose of the eCRF is to obtain data required by the clinical study protocol in a complete, accurate, legible and timely.	The main purpose of the eCRF is to obtain data required by the clinical study protocol in a complete, accurate, legible and timely **manner**.
Text regarding withdrawal from the study or IMP was clarified	10.2 Source Data and Subject Files	57	Date that the subject left the study including any reason for early withdrawal from the study or IMP (if applicable).	• Date that the subject left the study including any reason for **early study discontinuation or withdrawal from IMP**~~early withdrawal from the study or IMP~~ (if applicable).
Text was made more generic.	10.2 Source Data and Subject Files	57	The Monitor will be trained in INFORM (electronic database) and will have read-only access to the study data in INFORM for source data verification. Data reviewed can be signed off and queries issued directly in INFORM.	The Monitor will be trained ~~in INFORM (electronic database)~~ **to use the electronic database / eCRF** and will have read-only access to the study data in ~~INFORM~~ **the eCRF** for source data verification. Data reviewed can be signed off and queries issued directly in ~~INFORM~~ **the eCRF**.

Change	Section	Page	Previous Wording	New Wording
Reference was added for ODWG classification	11 References Cited in the Text	59	-	**LoRusso PM, Venkatakrishnan K, Ramanathan RK, et al. Pharmacokinetics and safety of bortezomib in patients with advanced malignancies and varying degrees of liver dysfunction: Phase 1 NCI Organ Dysfunction Working Group study NCI-6432. Clin Cancer Res. 2012; 18(10), doi:10.1158/1078-0432.CCR-11-2873.**
Reference was added for Child-Pugh Criteria	Table 3 Child-Pugh Criteria, 11 References Cited in the Text	26, 58, 59	-	**Pugh RN, Murray-Lyon IM, Dawson JL, et. al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973; 60:646. PMID: 4541913** **Child CG, Turcotte JG. The Liver and Portal Hypertension. Philadelphia, WB Saunders Co. 1964. NLMN: 46218** **Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. NEJM. 1966; 274:473. PMID: 5904286**