Clinical Trial Protocol

Clinical Trial Protocol Number	MS100015-0019
Title	An Open-label, Phase I, Dose Escalation Trial of Methionine Aminopeptidase 2 Inhibitor M8891 in Subjects with Advanced Solid Tumors
Phase	I/Ib
IND Number	PPD
EudraCT Number	Not applicable
Coordinating Investigator	PPD PPD PPD PPD PPD Phone: PPD Email: PPD
Sponsor	**For all countries except USA and Japan:** Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany **In the USA:** EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821, USA **Medical Responsible:** PPD Merck Healthcare KGaA. Frankfurter Str. 250, 64293 Darmstadt, Germany Phone: PPD Fax: PPD email: PPD
Clinical Trial Protocol Version	11 March 2020 / Version 4.0, including amendment 3.0

Replaces Version 27 August 2019 / Version 3.0

[redacted]

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
4.0	Global substantial amendment	11-Mar-2020
3.0[a]	Global substantial amendment	27-Aug-2019
2.0	Global substantial amendment	02-Jan-2018
1.0	Original Protocol	28-Mar-2017

a: No subjects were enrolled under Version 3.0.

Protocol Version 4.0 (11 March 2020)

Overall Rationale for the Amendment

This amendment provides some minor clarifications to protocol Version 3.0 prior to the actual implementation of Version 3.0 at sites.

Section # and Name	Description of Change	Brief Rationale
Tables 2 and 3, Schedules of Assessment for Part 2	Change in frequency of assessment following Cycle 5 and alignment of tumor assessments with other assessments.	Decreased burden on subjects, while maintaining appropriate monitoring.
Tables 2 and 3, Schedules of Assessment for Part 2A and Part 2B	Reduced blood volume for plasma marker samples and specified more clearly sample acquisition timing schedules in footnotes.	Decreases burden on subjects and clearer sample acquisition timing information.
Table 3, Schedule of Assessments	Remove a sample for M8891 PK.	Decrease burden on subjects.
Tables 4 and 5. Schedule of Assessments	Clarification and alignment of timings with Tables 2 and 3.	Clarification
5.1.4, Follow-up	Clarification of EOT visit timepoint for Part 1 and Part 2.	Clarification
5.1.3.4 Maximum tolerated dose … 8.1.2.1, [Sample size] Part 2A]	Clarify that minimum number of treated subjects on maximum tolerated dose applies to Part 1 not Part 2.	Clarify that minimum of 6 subjects treated for maximum tolerated dose continues for Part 1 but is not necessary for Part 2.
5.1.3.2.2 [Treatment period] Part 2B	Add a potential meeting of the Safety Monitoring Committee at the start of Part 2B.	Additional evaluation of safety and tolerability.

Section # and Name	Description of Change	Brief Rationale
CCI [redacted]		
Sponsor Signature	Update of address.	Clarification
Sponsor Responsible Persons	Updated to changes in personnel.	Clarification
Throughout	Minor edits	Correct formatting, English usage, etc.

This Version 4.0 is identical to Version 3.0, except for clarifications as noted above. No patient has been enrolled in Version 3.0 of the protocol.

(The revisions made in Version 3.0, which are retained in this Version 4.0, are summarized in Appendix IV.)

Protocol Table of Contents

Table of In-Text Tables

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List of Abbreviations

AE	Adverse Event
CCI	[redacted]
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the curve
BED	Biologically effective dose
BOR	Best overall response
BUN	Blood urea nitrogen
CR	Complete response
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DDI	Drug-drug interaction
DLT	Dose limiting toxicity
DoR	Duration of response
DVT	Deep vein thrombosis
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EOT	End of treatment
FBE	Free-Base Equivalent
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICB	Immune Checkpoint Blockade
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
LMWH	Low-molecular-weight heparin

LSFD	Last Subject First Dose
LLOQ	Lower limit of quantification
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
CCI [redacted]	
CCI [redacted]	
MoA	Mode of Action
mRCC	Metastatic renal cell carcinoma
MRI	Magnetic resonance imaging
ms	milliseconds
mTOR	mammalian target of rapamycin
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for AEs
NOAEL	No observed adverse effect levels
ORR	Objective response rate
CCI [redacted]	
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
CCI [redacted]	
PK	Pharmacokinetic
PR	Partial response
QD	Once daily
QTcF	QT interval corrected for heart rate according to Fridericia
RECIST	Response Evaluation Criteria in Solid Tumors
RDE	Recommended dose for expansion
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SD	Stable disease
SMC	Safety Monitoring Committee
SoA	Schedule of Assessments
SOC	System Organ Class

SoC	Standard of care
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
CCI [redacted]	
ULN	Upper limit of normal
USPI	US-Prescribing Information
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
CCI [redacted]	
VTE	Venous thromboembolism
WBC	White blood cells
WOCBP	Woman of childbearing potential

1 Synopsis

Clinical Trial Protocol Number	MS100015-0019
Title	An Open-label, Phase I, Dose Escalation Trial of Methionine Aminopeptidase 2 Inhibitor M8891 in Subjects with Advanced Solid Tumors
Trial Phase	I/Ib
IND Number	PPD
FDA covered trial	Yes
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Coordinating Investigator	PPD PPD PPD PPD PPD Phone: PPD Email: PPD
Sponsor	For all countries except USA and Japan: Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany In the USA: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821, USA
Trial centers/countries	Part 1: Approximately 5 sites / USA Part 2: Approximately 7 sites / USA
Planned trial period (first subject in-last subject out)	April 2017 – March 2022
Trial Registry	ClinicalTrials.gov and all other required registries

Objectives:

Part 1, M8891 Single Agent, Solid Tumors

Primary:

- To determine the maximum tolerated dose (MTD) of M8891 as a single agent in subjects with solid tumors.

Secondary:

- To evaluate the safety profile and tolerability of M8891 as a single agent
- To investigate the pharmacokinetic (PK) profile of M8891 as single agent
- To assess the antitumor activity of M8891 as single agent according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- To determine the recommended Phase II dose (RP2D) as single agent.

CCI [redacted]

Part 2, M8891 Combined with Cabozantinib, Metastatic Renal Cell Carcinoma (mRCC)

Part 2A, Dose Escalation

Primary:

- To determine the recommended dose for expansion (RDE) (MTD, if reached) of M8891 combined with cabozantinib in subjects with mRCC, based on safety, tolerability, and antitumor activity

Secondary:

- To characterize the PK profile of M8891 (single and multiple dose exposure) combined with cabozantinib in subjects with mRCC
- To further assess antitumor activity of M8891 combined with cabozantinib in subjects with mRCC

CCI [redacted]

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Part 2B, Expansion Cohort

Primary:

- To determine recommended Phase II dose (RP2D) of M8891 combined with cabozantinib in subjects with mRCC based on antitumor activity and safety.

Secondary:

- To assess other measures of antitumor activity of M8891 combined with cabozantinib in subjects with mRCC.
- To characterize the PK profile of M8891 (single and multiple dose exposure) in subjects with mRCC.

CCI

Methodology:

This is a 2-part, Phase I/Ib, first in human, multicenter, open-label trial of M8891 administered daily.

Part 1 is a dose-escalation study designed to explore the safety, tolerability, PK and CCI profiles, and clinical activity of M8891 as a single agent across cycles of 21-day treatment, in subjects with advanced solid tumors with no surgical, radiation, or systemic anticancer therapies available.

Part 2 is designed to determine the safety, tolerability, and anti-tumor activity of M8891 combined with cabozantinib in subjects with mRCC. In Part 2A, a dose escalation (Part 2A) and an expansion cohort (Part 2B) design are planned.

In Part 2A, escalating doses of M8891 will be combined with cabozantinib in subjects with mRCC who have progressed to 1 or more previous lines of systemic anticancer therapy, excluding treatment with cabozantinib. The Part 2A of the study allows subjects accrual in a

staggered manner. Thus, enrollment in Part 2A can occur while Part 1 is still ongoing; however, enrollment will only be at a dose level of M8891 that has already been determined safe in Part 1 of the study. CCI [redacted]

In the expansion Part 2B, M8891 at the RDE/MTD defined in Part 2A will be combined with cabozantinib in subjects with mRCC who have progressed to 1 or 2 previous lines of systemic anticancer therapy, excluding treatment with cabozantinib. In Part 2B, subjects should have failed to only 1 previous antiangiogenic tyrosine kinase inhibitor (TKI) for metastatic disease. Adjuvant therapy with sunitinib will be considered as 1 line of therapy for metastatic disease in the case that disease progression occurs during or within 3 months of the completion of the treatment.

Planned number of subjects: Part 1: 36-42 subjects. Part 2A: 6-15 subjects. Part 2B: 30-40 subjects.

Part 1, M8891 Single Agent, Solid Tumors

Primary endpoints:

- Dose limiting toxicities (DLTs) during the first 21-day treatment cycle, based on a pre-defined set of adverse events (AEs), to determine the MTD.

Secondary endpoints:

- Occurrence and severity of treatment-emergent adverse events (TEAEs), and deaths, including cause of death, from screening up to the End of Treatment visit (EOT)
- Changes in clinical laboratory measures, electrocardiogram (ECG) measures, vital signs, Eastern Cooperative Oncology Group Performance status (ECOG PS)
- Best overall response (BOR: complete response [CR], partial response [PR], stable disease [SD] or progressive disease [PD]) according to RECIST v1.1. criteria as assessed by Investigators
- Clinical benefit defined as CR, PR, and SD for $\geq$ 12 weeks
- PFS (progression-free survival) time.

Part 2, M8891 Combined with Cabozantinib, mRCC

Part 2A, Dose Escalation

Primary endpoints:

- Occurrence of DLTs in subjects with mRCC receiving M8891 combined with cabozantinib during the first 22-day treatment cycle (21 days of M8891 combined with cabozantinib, preceded by 1 day of M8891 alone) based on predefined set of AEs
- Occurrence of TEAEs (including TEAEs leading to death or discontinuation of treatment) in subjects with mRCC receiving M8891 combined with cabozantinib. Any AEs that occur

or worsen between start of study intervention and 30 days after end of study intervention will be considered TEAEs

- Study clinically relevant abnormal changes in clinical laboratory measures from baseline, vital signs, ECOG performance status, and ECGs from start of study intervention to 30 days after end of study intervention
- Objective Response according to RECIST v1.1 as assessed by Investigators

Secondary endpoints:

- Duration of Response (DoR) according to RECIST v1.1 criteria as assessed by Investigators
- PFS time according to RECIST v1.1 criteria as assessed by Investigators

Part 2B, Expansion Cohort

Primary endpoints:

- Occurrence of study serious AEs including deaths from first dose of study intervention to 30 days after end of study intervention
- Study clinically relevant abnormal changes in clinical laboratory measures from baseline, vital signs, ECOG PS, and ECGs from start of study intervention to 30 days after end of study intervention
- Occurrence of TEAEs (including deaths) from start of the study intervention to 30 days after end of the study intervention
- Objective response according to RECIST v1.1 criteria as assessed by Investigators

Secondary endpoints:

- DoR according to RECIST v1.1 criteria as assessed by Investigators
- PFS time according to RECIST v1.1 criteria as assessed by Investigators

Pharmacokinetics

Part 1, M8891 Single Agent, Solid Tumors

- PK parameters of M8891 after QD dosing, as applicable: C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{0-\tau}$, $t_{1/2}$, λ_z, CL/F, CL_{ss}/F, V_z/F, Racc(AUC_τ) and Racc(C_{max})

Part 2, M8891 Combined with Cabozantinib, mRCC

Part 2A, Dose Escalation

- PK parameters of M8891 in terms of C_{max}, t_{max}, AUC_{0-t} on Day 1 Cycle 1, (combined with cabozantinib, single dose)
- PK parameters of M8891 in terms of C_{max}, t_{max}, AUC_{0-t} on Day 8 and Day 15 Cycle 1, and Day 1 Cycle 2 (combined with cabozantinib, multiple dose)

- PK parameters of M8891 in terms of C_{max}, AUC_{0-t}, t_{max}, t_{lag}, $t_{1/2}$, $AUC_{0-\infty}$, CL/F, V_z/F on Day -1 Cycle 1 (M8891, single dose). CCI [redacted]
- PK parameters of cabozantinib in terms of C_{max}, t_{max}, AUC_{0-t} on Day 1 Cycle 1 (combined with M8891, single dose)
- PK parameters of cabozantinib in terms of C_{max}, t_{max}, AUC_{0-t} on Day 8 and Day 15 Cycle 1, and Day 1 Cycle 2 (combined with M8891, multiple dose)

Part 2B Dose Expansion

- Plasma concentrations of M8891 on Day 1, Day 8 and Day 15 Cycle 1 (combined with cabozantinib, multiple dose)
- Plasma concentrations of cabozantinib on Day 1, Day 8 and Day 15 Cycle 1 (combined with M8891, multiple dose)

CCI [redacted]

Diagnosis and key inclusion and exclusion criteria:

Part 1, M8891 Single Agent, Solid Tumors

Key inclusion:

- Subjects must be refractory to or intolerant of existing cancer therapy(ies) known to provide clinical benefit

- Histologically confirmed advanced solid tumors with no clear curative treatment options available after at least 1 prior systemic anticancer therapy
- Tumor accessible for biopsies and agreement to conduct pre-dose and post-dose fresh tumor biopsies
- Male or female subjects at least 18 years of age.

Key exclusion:

- ECOG PS ≥ 2
- Extensive prior radiotherapy on more than 30% of bone marrow reserves, or prior bone marrow/stem cell transplantation within 5 years of study start
- Severe bone marrow, renal or liver impairment

Part 2, M8891 Combined with Cabozantinib, mRCC

Key inclusion:

- Histologic or cytologic evidence/proven of mRCC with clear cell component
- Previous treatments:
    a. **Part 2A**: Subjects should have progressed to 1 or more previous lines of systemic anticancer therapy, excluding treatment with cabozantinib
    b. **Part 2B**: Subjects should have progressed to 1 or 2 previous lines of systemic anticancer therapy, excluding treatment with cabozantinib. Subjects should have failed to only 1 previous TKI for metastatic disease. Adjuvant therapy with sunitinib will be considered as 1 line of therapy for metastatic disease in the case that disease progression occurs during or within 3 months of the completion of the treatment.
- At least 1 lesion that is measurable using RECIST v1.1.
- Adequate organ function (i.e. liver, kidney, bone marrow), as evidenced by multiple laboratory value results within specific parameters

Key exclusion:

- Previous use of cabozantinib or a MetAP2 inhibitor
- Thromboembolic events requiring therapeutic anticoagulation. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (i.e., warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (i.e., clopidogrel) started within the last 6 months of screening

  Note: Low dose aspirin for cardio-protection and low dose low-molecular-weight heparin (LMWH) are permitted (in subjects who are on a stable dose of LMWH for at least 6 weeks

before the first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor)

- Current significant cardiac conduction abnormalities, QT corrected for heart rate according to Fridericia (QTcF) interval prolongation of > 450 ms for males and > 470 ms for females or cardiovascular disorders, including symptomatic congestive heart failure, unstable angina pectoris, and serious cardiac arrhythmias.

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

Part 1, M8891 Single Agent, Solid Tumors

M8891 in capsule form will be administered orally QD, according to the dose escalation schedule and as determined by the safety monitoring committee (SMC). The starting dose of initial dose escalation cohort will be 7 mg QD. A Bayesian two-parameter logistic regression model with overdose control will be used to assist the SMC with dose selection during the dose escalation part. The model incorporates nonclinical toxicity and observed DLT information from all previously completed dose escalation cohorts to provide a recommended dose for the next cohort.

Part 2, M8891 Combined with Cabozantinib, mRCC

Part 2A, Dose Escalation

M8891 in capsule form combined with cabozantinib will be administered orally QD in the morning in fasted conditions. Three pre-specified dose levels of M8891 are planned (20 mg, 35 mg and 60 mg) combined with 60 mg of cabozantinib.

A Bayesian two-parameter logistic regression model with overdose control will be used to assist the SMC with dose selection for the next cohort and to determine the MTD/RDE of M8891 combined with cabozantinib 60 mg QD for Part 2B. Dose levels may be added or skipped for others that are not part of the pre-specified but they will never exceed the dose level of M8891 that has already been declared to be safe in Part 1.

Cabozantinib will be used at the approved 60 mg-free-base equivalent (FBE) daily dosage with dosage adjustments to 40 mg FBE or 20 mg FBE permitted to manage AEs.

Part 2B, Dose Expansion

In Part 2B, subjects will receive M8891 at the dose level defined in the Part 2A and cabozantinib at 60 mg QD in 21-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, or any criterion for withdrawal from the study.

In part 2B, the SMC will continue to monitor the safety of M8891 combined with cabozantinib and may recommend on continuation on the same dose, change in dose (not higher than MTD defined in Part 2A), or stop of the expansion cohort. Unacceptable toxicity for the expansion (Part 2B) cohort will be AEs that fulfill the DLT criteria. The SMC will evaluate the safety and cumulated toxicity of the combination therapy after 10 and after 20 subjects, who have finished

their DLT period or dropped out. The SMC decisions in the expansion cohort will also be supported by a two-parameter Bayesian logistic regression model. Enrollment of subjects will not be suspended between SMCs.

Reference therapy: dose/mode of administration/dosing schedule:

Not applicable.

Planned trial and treatment duration per subject:

Study duration per subject is approximately 8 months for Part 1, and 12 months for Part 2 including screening, treatment and follow up. Treatment is administered in consecutive 21-day cycles of continuous treatment. Subjects will receive study drug at the pre-specified dose level until disease progression, unacceptable toxicity, withdrawal of consent, or any criterion for withdrawal from the trial.

Statistical methods:

Part 1, M8891 Single Agent, Solid Tumors

Analyses will be prepared by dose level. There is no formal significance level for this trial and all analyses are considered descriptive.

Dose escalation will be aided by a Bayesian two-parameter logistic regression model. The SMC dedicated to dose escalation decisions will receive results of a Bayesian two-parameter logistic model with overdose control updated with the observed DLT data. Recommendation will be based on a loss function.

Part 2, M8891 Combined with Cabozantinib, mRCC

Part 2A, Dose escalation

A Bayesian two-parameter logistic regression model with overdose control will be used to assist the SMC to select the next dose of M8891 from 3 pre-specified dose levels (20 mg, 35 mg, and 60 mg QD). The SMC may add or skip a dose, as long as it does not exceed the dose level of M8891 that has already been declared to be safe in Part 1.

CCI [redacted]

Part 2B, Expansion cohort

A 2-stage design with an interim analysis for futility will be used to evaluate response.

Table 1 Schedule of Assessments for Part 1, M8891 Single Agent, Solid Tumors

Activity / Assessment	Screening	On Treatment Visits										EOT	Safety F/U [a]
	–28 to -1	Cycle 1						Cycle 2			Cycle 3 and following		
Cycle Day		1	2	4	8	15	16	1	8[b]	15[b]	1	30	
Visit Window					±1	±1		±2	±2	±2	±2	±3	
Written informed consent	X												
Demography	X												
Medical history[c]	X												
Serum pregnancy test (beta hCG)[d]	X	X											
Physical examination	X [e]	X		X	X	X		X			X	X	
Vital signs[f], weight, height (height at screening only)	X	X		X	X	X		X			X	X	
12-lead ECG[g]	X	X	X		X	X	X	X			X	X	
ECOG PS	X	X						X			X	X	
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology, biochemistry, coagulation[h]	X[e]	X		X	X	X		X			X	X	
Urine dipstick and pregnancy test[i]	X	X		X	X	X		X			X		
CCI													
Urine - PK urine samples[l]		X				X							
Blood - PK blood samples[m]		X	X		X	X	X	X			X		
CCI													
CCI													
CCI													
CCI													
Tumor assessment (RECIST v1.1)	X[r]	X									X[s]	X	
Drug administration and dispensing[t]		X	X	X	X	X	X	X	X	X	X	X	

AE: Adverse event; ALT: Alanine aminotransferase; AP: Alkaline phosphatase; aPTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CT: Computed tomography; ECG: Electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EOT: End of treatment; F/U: Follow up; FSH: Follicle-stimulating hormone; GGT: Gamma-glutamyl transferase; hCG: Human chorionic gonadotropin; MRI: Magnetic resonance imaging; INR: International Normalized Ratio; CCI ; CCI PK: Pharmacokinetic; PT: Prothrombin time; QD: Once daily; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: Serious adverse event; SMC: Safety Monitoring Committee; WBC: White blood cells.

a. Safety follow up will be performed if SAE is not recovered at the EOT, and may be done by phone interview if clinical visit is not feasible.
b. In Cycle 2 and subsequent cycles AE and concomitant medication assessment should be performed at clinic, but phone interview is acceptable if subjects have conflict schedule and can't visit clinic.
c. The tumor diagnosis must be proved by pathology report.
d. If applicable additional assessments should be performed as required and if clinically indicated. FSH measured if needed to confirm postmenopausal status.
e. Physical exam, hematology, biochemistry, and coagulation do not have to be repeated on Day 1 if performed within 48 hours as a screening/baseline assessment.
f. Heart rate, diastolic and systolic blood pressure, respiratory rate, body temperature.
g. 12-lead triplicate digital ECG will be performed with 2-minute intervals after at least 10 minutes rest in supine position. On Cycle 1 Day 1 and Day 15 at pre-dose and 1, 2, 4, 5, 6, 8, 12 hours and 24 hours post-dose (± 15 minutes) and on pre-dose on Day 8. The SMC may decide that the Day 15/Day 16 assessment can be waived in case no relevant drug accumulation is being observed. ECG assessments at subsequent cycles will be performed pre-dose at time points as indicated in the table. ECGs should be performed directly before PK sampling time points on days where both assessments are performed.
h. Hemoglobin, white blood cell count, differential, platelet count, creatinine, creatinine clearance AST, ALT, GGT, AP, lipase, amylase, BUN, total bilirubin, total protein, albumin, uric acid, sodium, chloride, bicarbonate, potassium, calcium, phosphorus, magnesium and glucose, PT, aPTT and INR.
i. Standard urine test, and pregnancy test will be done at each visit after Cycle 2 (corresponds to women of childbearing potential).

CCI [redacted]

CCI [redacted]

CCI [redacted]

m. PK time points: 3 mL (2 aliquots of 1.5 mL) blood each at following time points: QD dosing: Cycle 1 Day 1: 0 hour (pre-dose within 60 minutes prior to each treatment administration) and 1 (± 10 minutes), 2 (± 10 minutes), 3 (± 10 minutes), 4 (± 20 minutes), 5 (± 20 minutes), 6 (± 30 minutes), 8 (± 30 minutes), 12 hours post-dose (± 60 minutes), on Day 2 at 24 hours post-dose (before next drug administration) (± 60 minutes). Cycle 1 Day 8: 0 hour (pre-dose within 60 minutes prior to treatment administration), Cycle 1 Day 15: 0 hour (pre-dose within 60 minutes prior to each treatment administration) and 1 (± 10 minutes), 2 (± 10 minutes), 3 (± 10 minutes), 4 (± 20 minutes), 5 (± 20 minutes), 6 (± 30 minutes), 8 (± 30 minutes), 12 hours post-dose (± 120 minutes), on Day 16 at 24 hours post-dose (before next drug administration) (± 60 minutes), 63 mL blood in Cycle 1. Cycle ≥2 Day 1: 0 hour (pre-dose within 60 minutes prior to each treatment administration).

CCI [redacted]

CCI [redacted]

p. Pre-dose; optional blood sample: collection will only be performed after an Informed Consent Form has been signed.

CCI [redacted]

r. Imaging (e.g. CT scan) do not have to be repeated on Day 1 if performed within 28 days as a screening/baseline assessment.
s. Imaging analysis must be done with consistent modalities. ± 1 week time window is permitted. Tumor response will be assessed on Day 1 of Cycles 3, 5 and 7, and every 18 weeks (6 Cycles) thereafter. Subjects who discontinue treatment will undergo EOT visit procedures.
t. Subjects will receive M8891 once a day, at same time in the morning, in fasted condition for at least 2 hours prior and 1 hour post dosing, M8891 will be dispensed on Day 1 of each Cycle. Subjects should be asked to return all of the unused trial medication, including the packaging (even if empty), at every dispensing visit.

Note: At visits where assessment time points coincide with each other, the following procedure should be followed:

- Perform vital signs assessments slightly before the specific time point
- Perform ECG assessments on time
- PK blood sampling should be done directly after the ECG (e.g. within 10 minutes)
- CCI
- Use of agreed upon time windows will be allowed.

Table 2 Schedule of Assessments for Part 2A, M8891 Combined with Cabozantinib, mRCC, Dose Escalation

Activity / Assessment	Screening	On Treatment Visits								EOT[a]	Safety F/U[b]	Notes
		M8891	M8891 + Cabozantinib									
		Cycle 1				Cycle 2-4		Cycle 5	Cycle 7 and on			After Cycle 7, visits on Day 1 of every third cycle
Cycle Day	-28 to -2	-1 (-24h)[c]	1	8	15	1	15	1	1 of every third cycle	Within 7 days of last intervention	30 days after last dose	For rescreening see **Section 5.1.1** CCI [redacted]
Visit Window				±1	±1	±2	±2	±3	±3	+7	±7	
Written informed consent	X											
Demography	X											
Medical history	X											
Serum pregnancy test (beta hCG)[d]	X											
Physical examination	X[e]	X	X	X	X	X	X	X	X	X		
Vital signs, weight, height (height at screening only)	X	X	X	X	X	X	X	X	X	X		Heart rate, diastolic and systolic blood pressure, respiratory rate, body temperature
12-lead ECG	X	X	X	X	X	X		X	X	X		**Table 4**
ECOG PS	X	X	X	X	X	X	X	X	X	X		
AE assessment	X	X	X	X	X	X	X	X	X	X	X	AE and concomitant medication assessment should be performed at every visit
Concomitant medication	X	X		X	X	X	X	X	X	X		
Hematology, biochemistry, coagulation, thyroid function[f], urine chemistry, serology[g]	X[e]	X	X	X	X	X	X	X	X	X		**Appendix III**
Urine pregnancy test		X				X		X	X			**Appendix III**
Archival tumor biopsy (if available)[h]	X											
Blood – PK blood sample/s M8891		X	X	X	X	X						**Table 4** PK samples will be collected only until Day 1 Cycle 2

Activity / Assessment	Screening	On Treatment Visits								EOT[a]	Safety F/U[b]	Notes
		M8891	M8891 + Cabozantinib									
		Cycle 1				Cycle 2-4		Cycle 5	Cycle 7 and on			After Cycle 7, visits on Day 1 of every third cycle
Cycle Day	-28 to -2	-1 (-24h)[c]	1	8	15	1	15	1	1 of every third cycle	Within 7 days of last intervention	30 days after last dose	For rescreening see **Section 5.1.1** CCI [redacted]
Visit Window				±1	±1	±2	±2	±3	±3	+7	±7	
Blood – PK blood sample/s cabozantinib			X	X	X	X						**Table 4** PK samples will be collected only until Day 1 Cycle 2
CCI [redacted]												
CCI [redacted]												
Blood – ctDNA[j]			X		X	X		X	X	X		
Tumor assessment (RECIST v1.1)	X[k]	X[k]				X[l]		X[l]	X[l]	X		
Drug administration												
		Dispensing every Day 1 of each cycle until Cycle 5 and then on Cycle 7 and afterwards every third cycle										
M8891 Administration		X	M8891 given in clinic on C1D1 and taken once daily at home thereafter until study treatment is discontinued									**Section 5.1.3.2**
Cabozantinib Administration			Cabozantinib given in clinic on C1D1 and taken once daily at home thereafter until study treatment is discontinued									**Section 5.1.3.2**

AE: Adverse event; ctDNA: circulating tumor DNA; CT: Computed tomography; ECG: Electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance status; EOT: End of treatment; MRI: Magnetic resonance imaging; mRCC: Metastatic renal cell carcinoma; PK: Pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: Serious adverse event.

a. Subjects who discontinue treatment will undergo EOT visit procedures.

b. Safety follow up will be performed if SAE is not recovered at the EOT.

CCI [redacted]

d. For Contraception and postmenopausal status see Appendix 1.

e. Physical exam, hematology, biochemistry, and coagulation do not have to be repeated on Day -1, Cycle 1 (predose) if performed within 48 hours as a screening/baseline assessment.

f. Free T4 and TSH must be performed at screening, until Cycle 7 on Day 1 of each odd cycle (C1, 3, 5 , 7), after Cycle 7 on Day 1 of every third cycle (7,10, 13, etc), and at EOT (if not performed within the last 8 weeks). Thyroid Function test may be performed more frequently if clinically indicated.

g. Serology should be done only at screening and do not have to be repeated on Day -1, Cycle 1 if performed within 28 days as a screening/baseline assessment.

CCI [redacted]

CCI [redacted]

j. Blood – ctDNA: at Day 1 pre-dose and during treatment pre-dose within 60 minutes prior to M8891 combined with cabozantinib treatment administration mandatory blood sampling (20 mL each) to assess mutant allele frequency of tumor-derived cell-free DNA.

k. Imaging (e.g. CT scan) do not have to be repeated on Day -1, Cycle 1 if performed within 28 days as a screening/baseline assessment.

l. Imaging analysis must be using the same technique during the study, e.g. it's not allowed to use CT scan at baseline then change to MRI during the study. Tumor response will be assessed within 1 week prior to Day 1 of Cycles 3, 5, and 7, and every third cycle thereafter. Subjects who discontinue treatment will undergo EOT visit procedures.

Table 3 Schedule of Assessments for Part 2B, M8891 Combined with Cabozantinib, mRCC, Dose Expansion

Activity / Assessment	Screening	On Treatment Visits							EOT[a]	Safety F/U[b]	Notes
		M8891 + Cabozantinib									
		Cycle 1			Cycle 2-4		Cycle 5	Cycle 7 and on			After Cycle 7, visits on Day 1 of every third cycle
Cycle Day	-28 to -1	1	8	15	1	15	1	1 of every third cycle	Within 7 days of last intervention	30 days after last dose	For rescreening see **Section 5.1.1**
Visit Window			±1	±1	±2	±2	±3	±3	+7	±7	
Written informed consent	X										
Demography	X										
Medical history	X										
Serum pregnancy test (beta hCG)[c]	X										
Physical examination	X[d]	X	X	X	X	X	X	X	X		
Vital signs, weight, height (height at screening only)	X	X	X	X	X		X	X	X		Heart rate, diastolic and systolic blood pressure, respiratory rate, body temperature
12-lead ECG	X	X	X	X	X		X	X	X		**Table 5**
ECOG PS	X	X	X	X	X	X	X	X	X		
AE assessment	X	X	X	X	X	X	X	X	X	X	AE and concomitant medication assessment should be performed at every visit
Concomitant medication	X		X	X	X	X	X	X	X		
Hematology, biochemistry, coagulation, thyroid function[e], urine chemistry, serology[f]	X[d]	X	X	X	X	X	X	X	X		Appendix III
Urine pregnancy test		X			X		X	X			Appendix III
Archival tumor biopsy (if available)[g]	X										
Blood – PK blood sample/s M8891		X	X	X							**Table 5** PK samples will be collected only until Day 15 Cycle 1
Blood – PK blood sample/s cabozantinib		X	X	X							**Table 5** PK samples will be collected only until Day 15 Cycle 1

Activity / Assessment	Screening	On Treatment Visits							EOT[a]	Safety F/U[b]	Notes
		M8891 + Cabozantinib									
		Cycle 1			Cycle 2-4		Cycle 5	Cycle 7 and on			After Cycle 7, visits on Day 1 of every third cycle
Cycle Day	-28 to -1	1	8	15	1	15	1	1 of every third cycle	Within 7 days of last intervention	30 days after last dose	For rescreening see **Section 5.1.1**
Visit Window			±1	±1	±2	±2	±3	±3	+7	±7	
CCI [redacted] CCI											
Tumor assessment (RECIST v1.1)	X	X[j]			X[k]		X[k]	X[k]	X		
Drug administration		Dispensing every Day 1 of each cycle until Cycle 5 and then on Cycle 7 and afterwards every third cycle									
M8891 Administration		M8891 given in clinic on C1D1 and taken once daily at home thereafter until study treatment is discontinued									**Section 5.1.3.2**
Cabozantinib Administration		Cabozantinib given in clinic on C1D1 and taken once daily at home thereafter until study treatment is discontinued									**Section 5.1.3.2**

AE: Adverse event; CCI [redacted]; CT: Computed tomography; ECG: Electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance status; EOT: End of treatment; mRCC: Metastatic renal cell carcinoma; MRI: Magnetic resonance imaging; PK: Pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: Serious adverse event.

a. Subjects who discontinue treatment will undergo EOT visit procedures.

b. Safety follow up will be performed if SAE is not recovered at the EOT.

c. For contraception and postmenopausal status see Appendix I.

d. Physical exam, hematology, biochemistry, and coagulation do not have to be repeated on Day 1 if performed within 48 hours as a screening/baseline assessment.

e. Free T4 and TSH must be performed at screening, until Cycle 7 on Day 1 of each odd cycle (C1, 3, 5), after Cycle 7 on Day 1 of every third cycle (Cycle 7, 10, 13 etc), and at EOT (if not performed within the last 8 weeks). Thyroid Function test may be performed more frequently if clinically indicated.

f. Serology should be done only at screening and do not have to be repeated on Day -1, Cycle 1 if performed within 28 days as a screening/baseline assessment.

g. Archival tumor tissue (paraffin block) or 15 tumor slides to explore alterations in MetAP2 expression and other biologically related markers in correlation with tumor response to M8891 treatment (optional, but strongly recommended).

CCI [redacted] CCI

j. Imaging (e.g. CT scan) do not have to be repeated on Day 1, Cycle 1 if performed within 28 days as a screening/baseline assessment.

k. Imaging analysis must be using the same technique during the study, e.g. it's not allowed to use CT scan at baseline then change to MRI during the study. Tumor response will be assessed, within 1 week prior to Day 1 of Cycles 3, 5, and 7, and every third cycle thereafter. Subjects who discontinue treatment will undergo EOT visit procedures.

Table 4 Schedule of Pharmacokinetic, Electrocardiogram Assessments and Food Guidance during Part 2A M8891 Combined with Cabozantinib, mRCC, Dose Escalation

Treatment Day	Time h (± min)[a,b]	ECG[c]	PK M8891	PK Cabozantinib
Day -1, C1	Pre-dose (-60 min)	X	X[d]	
	1 (± 5)		X[d]	
	2 (± 10)	X	X[d]	
	3 (± 15)		X[d]	
	4 (± 15)		X[d]	
	6 (± 15)	X	X[d]	
	8 (± 15)		X[d]	
D1 C1	Pre-dose (-60 min)	X	X	X
	1 (± 5)		X	
	2 (± 10)	X	X	X
	3 (± 15)		X	
	4 (± 15)		X	
	6 (± 15)	X	X	X
D8 C1	Pre-dose (-60 min)	X	X	X
	2 (± 5)	X	X	X
D15 C1	Pre-dose (-60 min)	X	X	X
	1 (± 5)		X	
	2 (± 10)	X	X	X
	3 (± 15)		X	
	4 (± 15)		X	
	6 (± 15)	X	X	X
D1C2	Pre-dose (-60 min)	X	X	X
	2 (± 10)	X	X	X
D1C3-5	Pre-dose (-60 min)	X		
	1 (± 5)	X		
D1C7 (and Day 1 of every third cycle)	Pre-dose (-60 min)	X		
	1 (± 5)	X		

C: Cycle; D: Day; ECG: Electrocardiogram; eCRF: Electronic case report form; mRCC: Metastatic renal cell carcinoma; PK: Pharmacokinetics.

a. At visits where assessment time points (ECG and PK) coincide with each other
   1) Perform vital signs assessments at first
   2) ECG assessments slightly before the specific collection time point
   3) PK assessments at scheduled collection time point.

b. Actual collection times should be documented in the eCRF.

c. Standard triplicate (within 2 min) 12-lead ECG will be obtained after the subject has been rested in semi-recumbent position for at least 5 min at the indicated times. ECGs will be also performed during the End of Treatment and Safety Follow-up Visit (30 ± 7 days). Triplicate ECGs will be read locally. The calculated QTcF interval average of the three 12-lead ECGs must be ≤ 450 ms for males and ≤ 470 ms for females for elig bility. Subjects, in which the calculated QTcF interval average increases to > 500 ms or > 60 ms change over baseline during treatment, must interrupt study treatment until further clinical evaluations (See Section 7.4.5).

d. All subjects in Part 2A will receive on Day -1, Cycle 1 a single dose of M8891 with a high calorie, high-fat breakfast. PK data collected at the indicated times will be compared with those obtained at the same dose-levels in Part 1 where subjects have received M8891 under fasted conditions.

Table 5 Schedule of Pharmacokinetic and Electrocardiogram Assessments during Part 2B M8891 Combined with Cabozantinib, mRCC, Expansion Cohort

Treatment Day	Time h (± min)[a,b]	ECG[c]	PK M8891	PK Cabozantinib
D1 C1	Pre-dose (-60 min)	X	X	X
	2 (± 10)	X	X	
	6 (± 15)	X	X	X
D8 C1	Pre-dose (-60 min)	X	X	X
	2 (± 5)	X	X	X
D15 C1	Pre-dose (-60 min)	X	X	X
	2 (± 10)	X	X	
	6 (± 15)	X	X	X
D1C2	Pre-dose (-60 min)	X		
	2 (± 5)	X		
D1C3-5	Pre-dose (-60 min)	X		
	1 (± 5)	X		
D1C7 (and Day 1 of every third cycle)	Pre-dose (-60 min)	X		
	1 (± 5)	X		

C: Cycle; D: Day; ECG: Electrocardiogram; eCRF: Electronic case report form; mRCC: Metastatic renal cell carcinoma; PK: Pharmacokinetics.

a. At visits where assessment time points (ECG, and PK) coincide with each other
   1) Perform vital signs assessments at first
   2) ECG assessments slightly before the specific collection time point
   3) PK assessments at scheduled collection time point

b. Actual collection times should be documented in the eCRF.

c. Standard triplicate (within 2 min) 12-lead ECG will be obtained after the subject has been rested in semi-recumbent position for at least 5 min at the indicated times. ECGs will be also performed during the End of Treatment and Safety Follow-up Visit (30 ± 7 days). Triplicate ECGs will be read locally. The calculated QTcF interval average of the three 12-lead ECGs must be ≤ 450 ms for males and ≤ 470 ms for females for eligibility. Subjects, in which the calculated QTcF interval average increases to > 500 ms or > 60 ms change over baseline during treatment, must interrupt study treatment until further clinical evaluations (See Section 7.4.5).

2 Sponsor, Investigators and Trial Administrative Structure

This clinical trial will be sponsored by EMD Serono Research & Development Institute, Inc., Billerica, MA, USA.

The Sponsor's legal representative in the EU is Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany.

The Part 1 of the trial will be conducted at approximately 5 sites in USA. The Part 2 of the trial will be conducted at approximately 7 sites in USA.

The Coordinating Investigator PPD), represents all Investigators for decisions and discussions regarding this trial, consistent with the International Council for Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are in Appendix V.

A safety monitoring committee (SMC) will monitor the overall safety of the subjects in this trial (Section 7.4).

Cumulative safety data are reviewed after each cohort during the dose escalation parts (Part 1 and Part 2A) of this trial. The SMC consists of core (voting) members from the Sponsor (Global Drug Safety Product Leader [Chair], Medical Responsible, Clinical Pharmacologist and Biostatistician), the Coordinating Investigator, and the Medical Monitor of the contract research organization (CRO). Ad-hoc members may be invited as needed. During the dose escalation part of the trial, the SMC will evaluate the safety (including dose limiting toxicities [DLTs]), as well as pharmacokinetic (PK), CCI data, if available. Upon review of available data, the SMC will decide on dose escalation, de-escalation, cohort expansion on the same dose level, maximum tolerated dose (MTD), or suspension of enrollment per consensus. The SMC has the final decision whether an Adverse Event (AE) is a DLT or not.

The Sponsor will enlist the support of PPD a CRO, to conduct the clinical part of the trial including trial set-up, coordination, monitoring, medical oversight, data capture, data management, statistical analysis, and clinical trial reporting. The Sponsor will also make use of PPD for sample storage and shipment to specialized bioanalytical laboratories. PK, CCI and CCI assessments will be performed under the responsibility and/or supervision of the Sponsor. The Sponsor will supervise all outsourced activities. Details of structures and associated procedures will be defined in a separate Manual of Operations, which will be prepared under the supervision of the Sponsor.

3 Background Information

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3.2 Background

The discovery of fumagillin with potent anti-angiogenic and anti-proliferative activities promoted the development of MetAP2 antagonists as a novel class of anticancer agents. MetAP2 plays an important role in the development of different types of cancer. MetAP2 inhibition induces cytostasis by cell cycle arrest at the G1 phase selectively in endothelial cells and in a subset of tumor cells. MetAP2 inhibitors block neo-angiogenesis both in vitro and in vivo and show potent antitumor efficacy in a variety of tumor types in murine models.

In clinical trials fumagillin proved unsuitable as an anticancer agent due to its pronounced neurotoxicity. The reversible MetAP2 inhibitor M8891 is not chemically related to fumagillin and has not shown signs of neurotoxicity in toxicology studies. In comparison to irreversible MetAP2 inhibitors it has the promise of an improved safety and tolerability profile, which is the prerequisite for administration over extended periods.

RCC represents a heterogeneous group of cancers that arise from the kidney. The most common histological variant of RCC is clear cell RCC, which comprises about 70% of RCC and has the highest metastatic potential (Moch 2016). The genetic basis of clear cell RCC is via a biallelic inactivation of the VHL tumor suppressor gene (present in 70% of clear cell cancers) located on the short arm of chromosome 3 (3p25.3), which encodes for the degradation of HIFα (Kim 2004).

Medical treatment for mRCC has expanded considerably from a nonspecific immune approach to targeted therapies against VEGFR and mammalian target of rapamycin (mTOR). Today the salvage approach has evolved, to include immune checkpoint blockade (ICB) targeting programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) (Salgia 2019). VEGFR TKIs alone, ICB, or VEGFR TKIs combined with ICB are preferred options for first-line treatment of mRCC. Cabozantinib, nivolumab, and axitinib are preferred subsequent therapy options. Given that cabozantinib appears to be active following earlier ICB and TKI regimens (as monotherapy or as combinations) (Barata 2018; Powles 2018.) and the MoA of MetAP2 inhibition is independent of the ICB MoA, a combination that synergizes with cabozantinib would still be expected to show efficacy.

3.3 Benefit/Risk Assessment

Based on the nonclinical data on M8891 showing evidence of tumor stasis and prolonged survival after single-agent use in xenograft models, and after combination with cabozantinib in RCC patient-derived xenograft models, the conduct of this trial is considered justifiable using the dose(s) and dosage regimen(s) of the investigational drug as specified in this clinical trial protocol. Refer to the M8891 Investigator's Brochure (IB) for further information about the nonclinical program. Based on the clinical data to date from the ongoing single agent study with M8891 (Part 1) and the known safety profile of cabozantinib, the safety measures such as stringent eligibility, routine safety monitoring along with AE reporting for the proposed study are considered adequate.

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

3.3.1 M8891

More detailed information about the anticipated benefits and risks based on nonclinical data of M8891 is presented in Section 3.1 and the M8891 IB.

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CCI [redacted]

Based on the currently available data, M8891 (parent drug) is predicted to exhibit a low drug-drug interaction (DDI) potential as perpetrator of CYP3A4 sensitive substrates at doses at the upper range of the estimated BED (60 mg QD). The DDI potential as victim of strong CYP3A4, 2C19 and 2C9 inhibitors is predicted to be weak, and as victim of a combined CYP3A4, 2C19 and 2C9 inhibitor to be only in the moderate range.

CCI [redacted]

No relevant effects on cardiovascular, respiratory, or central nervous system function are anticipated from the in vitro and in vivo safety pharmacology studies for the expected clinically relevant exposures.

The lymphatic and hematopoietic system including the bone marrow, the spermatogenetic epithelium and epithelia of the gastrointestinal tract were the main toxicity target organs of M8891 in pivotal 4-week oral repeat-dose toxicity studies in rats and dogs with no observed adverse effect levels (NOAELs) of 3 mg/kg/day and 0.75 mg/kg/day, respectively. M8891 was devoid of genotoxic, phototoxic and skin irritating potential.

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Since the start of Part 1, until the 16 Mar 2019 data cut, a total of 17 subjects with various solid tumors have received M8891 in doses ranging from 7 mg to 60 mg with a minimum of 3 subjects per dose level. Preliminary data from this ongoing Part 1 of the study have shown that the oral exposure of M8891 increased reasonably in direct proportion to the dose up to 35 mg QD, whereas at dose of 60 mg QD exposure seems to increase less than in direct proportion to the dose. No safety concerns have been raised (refer to M8891 IB). QT corrected for heart rate according to Fridericia (QTcF) interval prolongation is currently investigated in the ongoing Part 1 of the study using 12-lead triplicate digital ECGs. There is no preclinical or preliminary clinical evidence that M8891 is leading to QTcF interval prolongation.

3.3.2 Cabozantinib

Cabozantinib is indicated for the treatment of patients with mRCC. The recommended dosage of cabozantinib in mRCC is 60 mg once daily without food until the patient no longer experiences clinical benefit or experiences unacceptable toxicity (Cabometyx USPI 2019).

3.3.3 M8891 combined with cabozantinib

Promising signals for the activity of M8891 combined with cabozantinib have been observed in nonclinical studies (Refer to the M8891 IB).

Thromboembolic events have been reported with the use of cabozantinib or MetAP2 inhibitors and specific exclusion criteria have been defined to reduce the risk for this overlapping toxicity. More detailed information about the known and expected benefits and risks and reasonably expected AEs of M8891 and cabozantinib may be found in Sections 3.1 and 6.5.5, the M8891 IB, as well as the cabozantinib US-Prescribing Information (USPI).

Risks for potential DDIs of M8891 with cabozantinib are predicted to be small. This is based on mechanistic static modeling approaches using reported data for cabozantinib, i.e. an observed AUC increase of 38% when combined with the strong CYP3A4 inhibitor ketoconazole and a total fraction metabolized of 0.7 (worst case scenario considering 27.3% renal elimination), respectively (Nguyen 2015; Lacy 2015). Combining with nonclinical DDI and human exposure data of M8891 (Refer to the M8891 IB) a small AUC ratio of only 1.2 (maximal 1.2-fold increase in cabozantinib

exposure) based on time dependent inhibition (TDI) of CYP3A4 by M8891 was estimated. Because labeling information recommends a dose adaption of cabozantinib when used in combination with strong inducers or inhibitors of CYP3A4 only, it is sufficient to monitor cabozantinib exposure when combined with M8891. Based on information reported for cabozantinib, the victim potential of M8891 - when combined with cabozantinib - is considered as very low.

Overall, the available clinical data generated to date indicate a positive benefit risk profile for this new combination and therefore it is considered justifiable to conduct the study, as specified in this protocol.

4 Trial Objectives

4.1 Part 1, M8891 Single Agent, Solid Tumors

In the Part 1 of this study, M8891 will be administered as single agent in subjects with advanced solid tumors.

4.1.1 Primary Objectives

The primary objective is:

- To determine the maximum tolerated dose (MTD) of M8891 as a single agent in subjects with solid tumors.

4.1.2 Secondary Objectives

Secondary objectives are:

- To evaluate the safety profile and tolerability of M8891 as a single agent
- To investigate the PK profile of M8891 as single agent
- To assess the antitumor activity of M8891 as single agent according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- To determine the recommend Phase II dose (RP2D) as single agent.

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4.2 Part 2, M8891 combined with Cabozantinib, mRCC

In Part 2 of this study, M8891 combined with cabozantinib will be administered in subjects with mRCC.

4.2.1 Part 2A, Dose Escalation

Table 6 Part 2A Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)
Primary	
• To determine the recommended dose for expansion (RDE) (MTD, if reached) of M8891 combined with cabozantinib in subjects with mRCC, based on safety, tolerability, and antitumor activity	• Occurrence of DLTs in subjects with mRCC receiving M8891 combined with cabozantinib during the first 22-day treatment cycle (21 days of M8891 combined with cabozantinib, preceded by 1 day of M8891 alone) based on predefined set of AEs. • Occurrence of TEAEs (including TEAEs leading to death or discontinuation of treatment) in subjects with mRCC receiving M8891 combined with cabozantinib. Any AEs that occur or worsen between start of study intervention and 30 days after end of study intervention will be considered TEAEs. • Study clinically relevant abnormal changes in clinical laboratory measures from baseline, vital signs, ECOG performance status, and ECGs from start of study intervention to 30 days after end of study intervention • Objective response according to RECIST v1.1 as assessed by Investigators

Objectives	Endpoints (Outcome Measures)
Secondary	
• To characterize the PK profile of M8891 (single and multiple dose exposure) combined with cabozantinib in subjects with mRCC	• PK parameters of M8891 in terms of C_{max}, t_{max}, AUC_{0-t} on Day 1 Cycle 1, (combined with cabozantinib, single dose) • PK parameters of M8891 in terms of C_{max}, t_{max}, AUC_{0-t} on Day 8 and Day 15 Cycle 1, and Day 1 Cycle 2 (combined with cabozantinib, multiple dose)
• To further assess antitumor activity of M8891 combined with cabozantinib in subjects with mRCC	• DoR according to RECIST v1.1 criteria as assessed by investigators • PFS time according to RECIST v1.1 criteria as assessed by Investigators
CCI [redacted]	

AE: Adverse event; DoR: Duration of response; DLT Dose limiting toxicity; ECG: Electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance Status CCI [redacted]; mRCC: Metastatic renal cell carcinoma; MTD: Maximum tolerated dose; PFS: Progression-free survival; PK: Pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; RDE: Recommended dose for expansion; TEAE-Treatment emergent adverse event; CCI [redacted] CCI [redacted].

4.2.2 Part 2B, Expansion Cohort

Table 7 Part 2B Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)
Primary	
• To determine recommended Phase II dose (RP2D) of M8891 combined with cabozantinib in subjects with mRCC based on antitumor activity and safety	• Occurrence of study serious AEs including deaths from first dose of study intervention to 30 days after end of study intervention • Study clinically relevant abnormal changes in clinical laboratory measures from baseline, vital signs, ECOG PS, and ECGs from start of study intervention to 30 days after end of study intervention • Occurrence of TEAEs (including deaths) from start of the study intervention to 30 days after end of the study intervention • Objective response, according to RECIST v1.1 as assessed by Investigators
Secondary	
• To assess other measures of antitumor activity of M8891 combined with cabozantinib in subjects with mRCC	• DoR according to RECIST v 1.1 criteria as assessed by Investigators • PFS time according to RECIST 1.1 criteria as assessed by Investigators
• To characterize the PK profile of M8891 (single and multiple dose exposure) in subjects with mRCC	• Plasma concentrations of M8891 on Day 1, Day 8 and Day 15 Cycle 1, (combined with cabozantinib, multiple dose)
CCI [redacted]	

AE: Adverse event; DoR: Duration of response; DLT Dose limiting toxicity; ECG: Electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance Status; CCI ; mRCC: Metastatic renal cell carcinoma; MTD: Maximum tolerated dose; PFS: Progression-free survival; PK: Pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; RP2D: Recommended Phase II dose; TEAE-Treatment emergent adverse event; CCI ; CCI

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a 2-part, Phase I/Ib, first in human, multicenter, open-label trial of M8891 administered daily.

Part 1 is a dose-escalation study designed to explore the safety, tolerability, PK and C CI profiles, and clinical activity of M8891 as a single agent in subjects with advanced solid tumors with no surgical, radiation, or systemic anticancer therapies available.

Part 2 is designed to determine the safety, tolerability, PK and antitumor activity of M8891 combined with cabozantinib in subjects with mRCC. Part 2 will be conducted in subjects with mRCC with clear cell component who have progressed to 1 or more prior therapy (Part 2A) or who have progressed to 1 or 2 lines of prior therapy (Part 2B) (Section 5.3.1.2). Part 2 of the study will be performed with a dose escalation (Part 2A) and a dose expansion (Part 2B) design. Part 2A is aimed at determining the MTD/RDE of M8891 combined with cabozantinib based on safety, tolerability, PK, and initial efficacy data.

The Part 2A of the study allows subject accrual in a staggered manner. Thus, enrollment in Part 2A can occur while Part 1 is still ongoing; however, enrollment will only be at a dose level of M8891 that has already been determined safe in Part 1 of the study.

Following Part 2A, the safety and tolerability of M8891 (at the MTD/RDE defined in Part 2A) combined with cabozantinib will be investigated in an expansion cohort (Part 2B) of approximately 30 evaluable for response subjects with mRCC for assessment of early clinical activity.

In Part 2 (Part 2A and 2B) cabozantinib will be given at the approved 60 mg FBE daily dosage with dosage adjustments to 40 or 20 mg FBE permitted to manage AEs. In Part 2A, 3 prespecified dose levels of M8891 are planned (20 mg, 35 mg and 60 mg), although the SMC may add or skip a dose, as long as it does not exceed the dose level of M8891 that has already been declared to be safe in Part 1 (Section 5.1.3.2.1) .

Each part of the study will include a Screening period of up to 28 days, a study intervention period consisting of 21-day cycles of M8891 single agent (Part 1) and M8891 combined with cabozantinib (Part 2), an End of Study Intervention visit (within 7 days), and a Safety Follow-up period of 30 (± 7) days. Subjects who discontinue study intervention for any reason will complete the End of Study Intervention and Safety Follow-up visits. In Part 2A, before Cycle 1 of all dose levels, subjects will receive a single dose of M8891 in the morning in fed conditions (Day -1, Cycle 1) and the PK profile of M8891 will be evaluated pre-dose, 1, 2, 3, 4, 6, 8 and 24h (Day 1, Cycle 1) after administration (Section 5.1.3.2.1). Subsequently on Day 1 Cycle 1, subjects will initiate

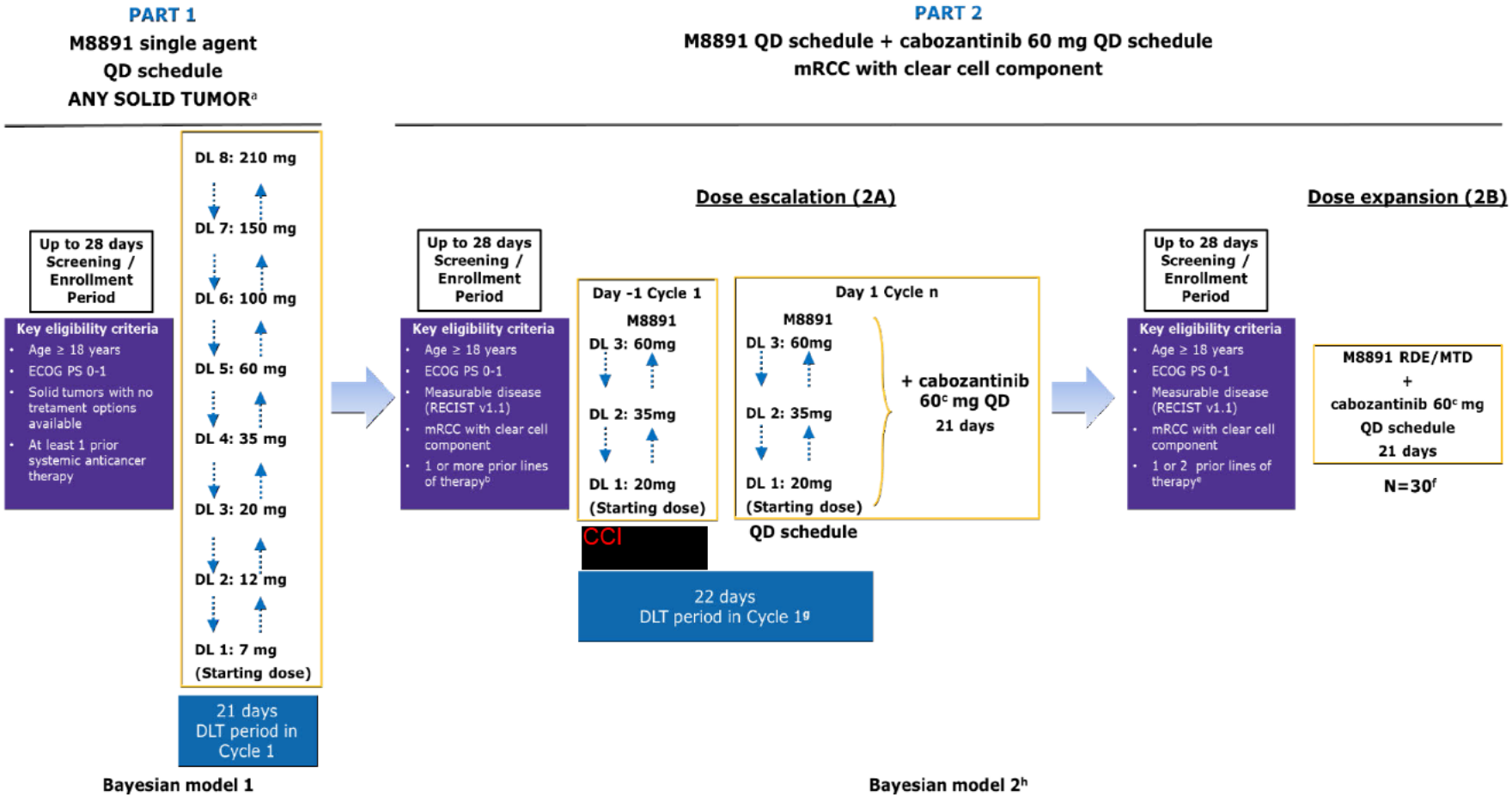
treatment with M8891 combined with cabozantinib QD orally every morning under fasted conditions.

Study duration per subject is approximately 8 months for Part 1, and 12 months for Part 2 including screening, treatment and follow up.

The design of this study is presented in

Figure 1 and a detailed Schedule of Assessments (SoAs) is provided in Table 1, Table 2, Table 3, Table 4, and Table 5.

Figure 1 **Study Design**



AE: Adverse event; DL: Dose level; FBE Free-base equivalent; MTD: Maximum tolerated dose; QD: Once daily; SMC: Safety Monitoring Committee; RP2D: Recommended Phase 2 Dose; mRCC: metastatic renal cell carcinoma; CCI .

a. The MTD of M8891 single agent will be defined, and RP2D of M8891 single agent suggested, by the SMC.
b. Subjects should have progressed to 1 or more previous lines of systemic anticancer therapy, excluding treatment with cabozantinib.
c. Cabozantinib will be given at the approved 60 mg FBE daily dosage with dosage adjustments to 40 mg or 20 mg permitted to manage AEs.

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f. 30 subjects evaluable for response.
g. The DLT assessment period for Part 2A is the Cycle 1 (= 22 days, 21 days of M8891 combined with cabozantinib, preceded by 1 day of M8891 alone) of study treatment. The rest of the Cycles in Part 2A are 21-day cycles of M8891 combined with cabozantinib.
h. See Section 8.5.1 for the Bayesian two-parameter logistic regression model.

5.1.1 Screening Period

Screening will be performed within 28 days prior to first M8891 administration (Part 1 and Part 2). If there are no clinically significant findings based upon the Investigator's assessment, other than underlying tumor disease at Screening and the subject meets all the protocol-defined inclusion and none of the exclusion criteria, the subject will be considered as eligible. For dose-escalation Part 1 and Part 2A, eligible subjects screened for the next cohort will only be treated pending decision by the SMC. Subjects who fail to meet the protocol-specified criteria or who withdraw their consent during the screening period will be considered screening failures.

Subjects in Part 2 who do not meet the laboratory criteria (see Section 5.3.1) or for any reason exceed the screening period time for participation in this study (screen failure) may be rescreened once. Rescreened subjects will be assigned a new subject number.

5.1.2 Doppler Ultrasonography:

Version 2.0, including amendment 1.0, of this protocol excluded subjects with the presence of deep vein thrombosis (DVT) based on screening lower extremity Doppler ultrasonography but not on D-dimer levels. D-dimer has low specificity in the oncology setting (Carrier 2008) and therefore adds little value to the screening. Lower extremity Doppler ultrasonography was performed at screening, the D1, D8, and D15 of Cycle 1, and the D1 of each subsequent cycle (21 days) and withdraw subjects with a positive finding on lower extremity Doppler ultrasonography. Multiple guidelines recommend clinical prediction rules to estimate pretest probability of DVT before ultrasound or other imaging tests ordering. Lower extremity Doppler ultrasonography is the standard imaging test for patients suspected of having lower extremity DVT. A venous ultrasound does not exclude the presence of a pulmonary embolism or portal vein thrombosis, neither predicts their development in the future. After an unlikely clinical pretest probability of DVT based on a clinical decision rule assessment, a venous ultrasound is not appropriate for those individuals (Needleman 2018).

In the current Version 4.0 of this protocol, Part 1 has been revised such that D-dimer will no longer be monitored and the related exclusion criteria altered (See Table 1 and Section 5.3.2). In the remainder of the ongoing Part 1 and in Part 2, of this study, all subjects will have physical examination for the occurrence of venous thromboembolism (VTE), and imaging tests (e.g. lower extremity Doppler ultrasonography, chest computed tomography (CT) angiography, liver ultrasonography, or others) will be performed accordingly. Subjects with thromboembolic events in the last 6 months, requiring therapeutic anticoagulation will be excluded. Low dose aspirin for cardioprotection and low dose LMWH will be permitted (in subjects who are on a stable dose of LMWH for at least 6 months before the first dose of M8891 combined with cabozantinib, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor).

The current clinical trial protocol (Version 4.0) has taken into consideration the updated clinical practice guidelines for VTE risk assessment in cancer patients. The NCCN guidelines describe that cytotoxic chemotherapy regimens, hormone therapy with estrogenic compounds, and

antiangiogenic agents are associated with increased VTE risk. The Khorana Predictive model for chemotherapy-associated VTE is the one recommended (Khorana 2008) for identifying cancer patients receiving chemotherapy who are at high risk for VTE. The risk factors identified by Khorana et al (Khorana 2008), which formed the basis for the risk assessment models, set the stage for prospective, confirmatory randomized clinical trials evaluating the risks and benefits of risk-targeted prophylaxis in ambulatory cancer patients receiving chemotherapy. Doppler ultrasonography is not included in the VTE Clinical Risk. American Society of Clinical Oncology (ASCO) recommends that outpatient candidates for chemotherapy should be scored according to the Khorana model or other validated scores at the time of chemotherapy initiation and periodically thereafter (Lyman 2015). The use of the Khorana Predictive model is a 2A level recommendation (moderate benefit-risk) in the NCCN guidelines. The European Society of Medical Oncology (ESMO) (Mandala 2011), and the National Institute of Health and Care Excellence guidelines (NICE) (Howard 2013) also include the Khorana Score along with other validated scores as an option to guide the decision-making regarding prophylaxis of patients receiving chemotherapy.

5.1.3 Treatment Period:

5.1.3.1 Part 1, M8891 Single Agent, Solid Tumors

The treatment period will begin at the first dose of M8891 in Cycle 1 Day 1 and consist of consecutive 21-day cycles of continuous once daily M8891 monotherapy under fasting conditions.

Subjects will receive M8891 at the pre-specified dose level until disease progression, unacceptable toxicity, withdrawal of consent, or any criterion for withdrawal from the study (Section 5.5.2).

If the subject tumor evaluation indicates that the disease is slowly progressing according to the CT scan as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria (a growth of the target lesions of less than 35% from baseline and no new lesions, or new lesion(s) smaller than 1 cm; bone metastatic lesions or lesions treatable with local radiotherapy would also fall in the same category), but the subject performance status is the same as baseline and there are no safety concerns, i.e. no ongoing symptomatic events Grade 2 or higher in severity, treatment may be continued for another 2 cycles to the next tumor evaluation, upon evaluation by the treating physician and after the continuation of therapy has been discussed with the Sponsor.

CCI [redacted]

In principle, dose escalation of M8891 will proceed according to the decision of the SMC to the MTD, or the SMC may decide ceasing further dose escalation following review of safety, tolerability, PK and CC[redacted] results.

The selection of the recommended dose for the expansion cohort of M8891 is based on the following criteria derived from the PK/C[redacted] model:

CCI [redacted]

The MS100015-0019 trial employs a Bayesian two-parameter logistic regression model with overdose control to assist the SMC with dose selection (Babb 1998; Neuenschwander 2008). The model incorporates nonclinical toxicity and observed DLT information from all previously completed dose escalation cohorts to provide a dose recommendation for the next dose cohort. The SMC will decide on the next dose level based on the Bayesian model, safety, PK analyses CCI [redacted] Dose escalation will start at 7 mg administered once daily.

A preselected set of doses (8 projected escalation steps with doses of 7, 12, 20, 35, 60, 100, 150 and 210 mg QD) are considered by the model, although doses may be skipped and/or others that are not part of the pre-specified set may be chosen as well. Sequential cohorts of 3 subjects at the same dose level will be used.

At each dose level, and following initiation of dosing, the first subject in each cohort will be observed for DLTs for at least 7 days before commencing dosing of 2 subsequent subjects. The SMC may choose to reduce or extend 7-day intra-patient observation interval up to ± 7 days based upon safety observations. The DLT assessment period is Cycle 1 (= 21 days). Subjects who missed more than 4 cumulative days of treatment in the first cycle for any reason other than a DLT will not be considered in the Bayesian model. An SMC meeting with selection of dose for next cohort will also be held if only data from 2 subjects of a 3 subject cohort are available (e.g. if a subject missed more than 4 cumulative days of treatment in the first cycle for any reason other than a DLT). Subject replacement will be considered based on reason for withdrawal and safety evaluation of cumulative data i.e. current and previous cohort data if applicable.

5.1.3.2 Part 2, M8891 combined with Cabozantinib, mRCC

5.1.3.2.1 Part 2A, Dose Escalation

In Part 2A, before Cycle 1 Day 1 of all dose levels, subjects will receive a single dose of M8891 in the morning in fed conditions (Day -1, Cycle 1) and the PK profile of M8891 will be evaluated. Subsequently on Day 1 Cycle 1, subjects will initiate treatment with M8891 combined with cabozantinib QD orally every morning under fasted conditions. Following Cycle 1, all other cycles will start with Day 1 and will include only the 21 days of M8891 combined with cabozantinib.

Subjects will accrue in cohorts of 3 subjects for evaluation of M8891 combined with cabozantinib 60 mg QD (with dosage adjustments to 40 or 20 mg FBE permitted to manage AEs as described in Section 6.5.5). Both drugs will be taken in the morning in fasted conditions. A Bayesian 2-parameter logistic regression model with overdose control will be used to assist the SMC with dose selection for the next cohort and to determine the MTD/RDE of M8891 combined with cabozantinib 60 mg QD for Part 2B.

Three pre-specified dose levels of M8891 are planned (20 mg, 35 mg and 60 mg) combined with 60 mg of cabozantinib. Dose levels may be added or skipped for others that are not part of the pre-specified set but they will never exceed the dose level of M8891 that has already been declared to be safe in Part 1. The dose levels have been chosen based on preliminary data from the ongoing Part 1 of the study. At the time of Amendment 2, M8891 single agent was being investigated at 60 mg QD in subjects with solid tumors. PK[CCI] studies have shown that the 20, 35 and 60 mg QD regimens reached pre-selected exposure (≥ 1500 ng/mL) at steady state while [CCI] [redacted]. Three and 5 Grade ≥ 3 TEAEs have been seen at 20 and 35 mg QD regimen, respectively. One DLT (Grade 4 thrombocytopenia) has been observed in the ongoing 60 mg QD cohort (Refer to the M8891 IB).

Dose escalation of the combination will proceed until the RDE of M8891 is reached in combination with a fixed dose of cabozantinib or dose escalation ends due to occurrence of an MTD, or the SMC decides ending dose escalation following review of safety, tolerability, and PK results, whatever occurs first. The maximum dose of M8891 combined with cabozantinib will not exceed the MTD of M8891 in monotherapy determined in Part 1 of the study.

Subjects will receive M8891 at the assigned dose level and cabozantinib at 60 mg QD until disease progression, unacceptable toxicity, withdrawal of consent, or any criterion for withdrawal from the study (Section 5.5). Unacceptable toxicity in Part 2A is defined as AEs that meet the DLT criteria (Section 5.1.3.3) regardless of when they occur during treatment. An SMC meeting will be held after every cohort to evaluate the safety and tolerability of the combination and to decide on the dose of M8891 for the next cohort.

During Part 2A the selection of the dose will only influence the dose of M8891. Cabozantinib will be given at the approved dose of 60 mg QD. Subjects who develop a DLT during the DLT period, will discontinue treatment with M8891 and will be withdrawn from the study. It will at the Investigator's discretion to continue treatment with cabozantinib or not. The SMC will meet after the completion of each cohort, evaluate the safety of M8891 (combined with cabozantinib), and decide on the recommended dose of M8891. During the treatment phase of the study, guidance for M8891 dose reduction for safety and tolerability is provided in Section 5.1.3.5. Reduction of cabozantinib dose in accordance with the USPI (Refer also to Section 5.1.3.5) will be at the Investigator's discretion based on clinical judgement for safety and tolerability.

At each dose level, the first subject will be observed for DLTs for at least 48 h before commencing dosing of 2 subsequent subjects. The DLT assessment period for Part 2A is the first Cycle (= 22 days, 21 days of M8891 combined with cabozantinib, preceded by 1 day of M8891 alone) of study treatment. Subjects who do not receive at least 80% of the planned cumulative dose of both treatments in Cycle 1 for any reason other than a DLT will not be considered in the DLT evaluation per Bayesian model. Subjects will be replaced to reach a minimum of 2 evaluable subjects per cohort.

In cases where enrollment of the last subject in a dosing cohort is delayed, the SMC may decide (based on available data) upon enrollment and dose for the next dosing cohort before all subjects in a cohort have completed the DLT period. For this subject, the SMC will consider all available data (and any subsequent emerging data) at a subsequent meeting. An ad-hoc meeting will be convened if this subject experiences a DLT.

CCI

[redacted]

5.1.3.2.2 Part 2B, Expansion Cohort

In Part 2B, subjects will receive M8891 at the dose level defined in the Part 2A and cabozantinib at 60 mg QD in 21-day-cycles until disease progression, unacceptable toxicity, withdrawal of consent, or any criterion for withdrawal from the study (see Section 5.5). Both drugs will be taken in the morning under fasted conditions.

In Part 2B, the SMC will continue to monitor the safety, cumulative and unacceptable toxicity of M8891 combined with cabozantinib and may decide by consensus on continuation on the same dose, change in dose (not higher than MTD in Part 2A), or stop of expansion cohort. Unacceptable toxicity in Part 2B is defined as an AE that meet the DLT criteria (as defined in Section 5.1.3.3) regardless of when they occur while on treatment. Once an MTD or RDE of M8891 combined with cabozantinib has been defined in Part 2A (Section 5.1.3.2.1), enrollment into part 2B may proceed. If less than 6 subjects have been treated at the MTD / RDE selected in Part 2A, there will be an SMC meeting after the first 3 subjects have been treated in Part 2B at the MTD / RDE once these subjects have finished their DLT period or have dropped out, in order to additionally evaluate safety and tolerability at this dose. Enrollment will be suspended for this SMC. The SMC will also meet to evaluate the safety and tolerability of the combination therapy after 10 and 20 subjects have finished their DLT period or dropped out for cumulative and unacceptable toxicity. Enrollment will continue during preparation of these SMCs.

The SMC decisions in the expansion cohort will also be supported by a 2-parameter Bayesian logistic regression model. For details on the model, see Section 8.5.

Dose management of cabozantinib in Part 2B will be at the Investigator's discretion based on clinical judgement. The Investigator must refer to study protocol or M8891 dose modification and to USPI for cabozantinib (see also Section 5.1.3.5).

5.1.3.3 Dose-Limiting Toxicities

DLTs will be used to determine dose escalation and de-escalation as well as determination of MTD. A DLT is any Grade ≥ 3 non-hematologic AE or any Grade ≥ 4 hematologic AE according to the National Cancer Institute – Common Terminology Criteria for AEs (NCI-CTCAE) version 4.03, occurring during the DLT observation period (Cycle 1) that is judged not to be related to the underlying disease or any previous or concomitant medication. DLTs, along with other safety information (including AEs assessed as not related to the underlying disease or other concomitant medications), will also be used to determine RP2D for M8891 as single agent (Part 1) and the RDE/MTD for M8891 combined with 60 mg of cabozantinib QD (Part 2A).

- DLTs are defined as any of the following pre-defined set of AEs observed in the first treatment cycle for Part 1 (21 days) and Part 2A (22 days; 21 days of M8891 combined with cabozantinib, preceded by 1 day of M8891 single agent) based on predefined set of AEs and judged to be M8891 (or M8891 combined with cabozantinib) related or clinically relevant, (excluding events to be related to underlying disease, medical history or concomitant medications/ procedures in the opinion of the SMC).
- Any death not clearly due to the underlying disease or extraneous causes
- A treatment-emergent AE (TEAE) attributable to study drug that in the opinion of the SMC is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk
- Evidence of treatment related hepatocellular injury, e.g. alanine aminotransferase or aspartate aminotransferase (ALT/AST) > 3 × upper limit of normal (ULN) with elevation of serum total bilirubin to > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) or other apparent clinical causality, including liver metastasis
- Any Grade 4 liver enzyme elevation that is possibly drug related should be considered a DLT. In case of Grade 3 or 4 values, the subject must be monitored until recovery to ≤ Grade 2
- Grade 4 neutropenia lasting >5 days or Grade ≥ 3 neutropenia with fever (temperature of > 38.3°C)
- Grade 4 thrombocytopenia lasting > 5 days or Grade ≥3 thrombocytopenia with clinically significant bleeding
- Any treatment interruption > 7 days or > 30% of total dose in Cycle 1 due to AEs not related to the underlying disease or concomitant medication
- Any Grade ≥3 non-hematologic toxicity **excluding:**
  - Grade 3 nausea or vomiting that lasts < 48 hours, and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention
  - Grade 3 fatigue ≤ 3 days

- Grade 3 hypertension in the absence of maximal medical therapy
- Grade 3 rash ≤ 3 days
- Grade 3 electrolyte abnormality that lasts < 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention
- Grade ≥ 3 single lab value increase without clinical correlate.

In addition, any TEAE that impairs daily function or considered clinically significant abnormality involving a study subject receiving M8891 (monotherapy or combined with cabozantinib) occurring any time during the study, may be assessed as a DLT.

Subjects screened and eligible for the subsequent cohort will be treated with M8891 (or M8891 combined with cabozantinib) only after a formal SMC decision to proceed to the next dose level has been documented.

5.1.3.4 Maximum Tolerated Dose / Recommended Phase II dose (MTD /RP2D)

In Part 1, the MTD for M8891 as single agent will be investigated and the RP2D for M8891 as single agent will be decided by the SMC. At least 6 subjects need to have been treated at the MTD / RP2D. This might necessitate enrolling additional subjects to fulfill this criterion. In Part 2, the MTD/ RDE and the RP2D for M8891 combined with cabozantinib will be defined. The target toxicity level of the Bayesian 2-parameter model is 30%. The-dose-toxicity model will be used to assist the SMC in selecting the MTD by showing the estimated DLT rate per dose and associated variability of the estimates. In Part 2A, at least 3 subjects need to have been treated at the MTD / RDE. If MTD cannot be determined, the SMC may decide to end dose escalation based on safety, PK and/or [redacted] data (Part 1) or based on safety and/or PK data (Part 2A), and recommended dose for expansion (RDE) will be determined. Once the MTD/RDE of M8891 combined with cabozantinib (see Section 5.1.3.2.1) for a cohort has been identified in Part 2A, enrollment into Part 2B, dose expansion may proceed (Figure 1).

5.1.3.5 Dose Modification

5.1.3.5.1 M8891

In Cycle 1 dose escalation Part 1 and Part 2A, dose modification is not allowed. After completion of the DLT period in subsequent cycles of Part 1 and Part 2A and in all cycles of Part 2B, if Grade ≥ 3 non-hematological AEs (for exceptions see 5.1.3.3 Section) or Grade ≥ 4 hematological AEs occur but they recover to Grade 1 in ≤ 14 days of treatment interruption, and in the absence of disease progression, the subject may continue treatment at a lower dose i.e., 1 level below the current dose or a dose defined by the SMC. If indicated, a further dose und reduction is possible.

In Part 1, if a subject does not tolerate the lower dose, the subject will be withdrawn from the trial, In Part 2A, if a subject does not tolerate the dose of 20 mg M8891, the subject will be withdrawn from the trial (see Section 5.5). AEs assessed by the Investigator to be exclusively related to the

subject's underlying disease or medical condition/concomitant treatment are not applicable to the guidelines for dose modification.

The following dose modification guideline in Cycle 2 and subsequent cycles is recommended (Table 8).

Table 8 Recommendation to the Investigator for M8891 Dose Adjustment Based on Non-hematological Adverse Events

CTCAE v. 4.03 Grade	Guideline for Management	Dose Adjustment
1	No intervention	None
2	Treatment as appropriate according to PI's judgment	Dose reduction can be considered after discussion with the medical monitor or SMC decision.
≥ 3	Treatment as appropriate according to PI's judgment	Treatment held until Grade 1 after ≤14 days, then the subject may continue treatment at a lower dose i.e., 1 level below the current dose or defined by SMC.

PI: Principal Investigator.

Guidelines for the management of specific AEs are provided in Section 6.5.5.

In the case of M8891 dose modifications, the SMC might modify the SoA based on emergent data (e.g. PK sampling, if the dose must be adjusted).

5.1.3.5.2 Cabozantinib

The approved dosage of cabozantinib in mRCC is 60 mg once daily without food until the subject no longer experiences clinical benefit or experiences unacceptable toxicity. In Part 2A, cabozantinib will be used at the approved 60 mg free-base equivalent (FBE) daily dosage. After completion of the DLT period in Part 2A and in all cycles of Part 2B, the dose of cabozantinib can be adjusted to 40 mg and then 20 mg to manage AEs (Section 6.5.5). Subjects unable to tolerate a daily dose of 20 mg should discontinue study treatment.

The following should be taken into consideration in decisions regarding cabozantinib dose modifications (reductions or interruption):

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity (Table 9 and Table 10). Should this be ineffective, dose reductions or interruptions should be considered to prevent worsening of toxicity.
- The assigned dose for cabozantinib is 60 mg QD. Two dose reduction levels of cabozantinib are permitted (Table 9) if appropriate.
- Dose modification criteria for cabozantinib are shown in Table 10**.** Dose reductions and/or interruptions should be implemented for unacceptable toxicity. Doses may be modified at any time while on study.

- Dose modifications or interruptions may also occur in the setting of lower grade toxicity than defined in Table 10, if the Investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.
- Interruption of cabozantinib treatment for AEs may occur at any time (except from Cycle 1 in Part 2A) per Investigator discretion. If treatment is interrupted due to AEs for more than 6 weeks, cabozantinib should be discontinued.
- Dose interruptions for reason(s) other than AEs (e.g. surgical procedures) can be longer than 6 weeks but require Sponsor approval. The acceptable length of interruption will depend on agreement between Investigator and the Sponsor.

Table 9 Dose Reductions of Cabozantinib

Assigned dose	First Dose Level Reduction	Second Dose Level Reduction
60 mg cabozantinib oral QD	40 mg cabozantinib oral QD	20 mg cabozantinib oral QD

QD: Once daily.
Cabozantinib should be discontinued if a QD dose of 20-mg cabozantinib (minimum dose) is not tolerated.

Table 10 Dose Modifications of Cabozantinib for Treatment Related AEs

CTCAE v. 4.03 Grade	Recommended Guidelines for Management[a]
1	Add supportive care as indicated. Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable.
2, tolerable and are easily managed)	Continue cabozantinib treatment at the current dose level with supportive care.
2, intolerable and cannot be adequately managed	At the discretion of the Investigator, cabozantinib should be dose reduced or interrupted[b].
3 (except clinically non-relevant laboratory abnormalities)	Cabozantib should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care[b].
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have cabozantinib interrupted immediately. Discontinue cabozantinib unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the Investigator and agreed by the Sponsor • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care

AE: Adverse event.
[a] Study treatment dose adjustment is only needed if the toxicity was deemed related to cabozantinib treatment or had an unclear relationship to cabozantinib treatment.
[b] It is recommended that dose holds be as brief as possible.

Guidelines for the management of specific AEs are provided in Section 6.5.5.

5.1.3.5.3 Cabozantinib or M8891 Dose Reinstitution

If the subject recovers from his/ her toxicities to CTCAE version 4.03 Grade ≤ 1 or to the baseline value (or lower) and the toxicity was unrelated to study treatment, then study treatment may be restarted with no change in dose.

If the subject recovers from his or her toxicities to Grade ≤ 1 or to the baseline value (or lower) within 2 weeks and the AE was deemed possibly related to study treatment, then study treatment may be restarted at a reduced dose (see Section 5.1.3.5).

In case of dose reduction, re-escalation of cabozantinib or M8891 to the previous dose is not allowed.

5.1.4 Follow-up

For Part 1, all subjects will complete an End of Treatment (EOT) Visit 30 (± 3) days after the last dose of study drug. For Part 2, all subjects will complete an EOT visit within 7 days after the last dose of study drug. For both Part 1 and Part 2, subjects with serious AEs (SAEs) ongoing at EOT Visit must be followed during the safety follow-up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up".

Subjects who tolerate M8891 (or M8891 combined with cabozantinib) without significant clinically relevant toxicities may continue to receive trial treatment, at the Investigator's discretion or after consultation with the Sponsor's physician, as long as there is no evidence of disease progression.

5.2 Discussion of Trial Design

This is a 2-part, Phase I/Ib, first in human, multicenter, open-label trial of M8891 single agent in solid tumors and M8891 combined with cabozantinib in mRCC, administered daily.

5.2.1 Dose Selection

5.2.1.1 Part 1, M8891 Single Agent, Solid Tumors

ICH guideline S9 has been considered as the reference guideline for the determination of the first-in-human starting dose, i.e., a dose that is expected to have pharmacologic effects and reasonably safe to use.

Based on the toxicity profile of M8891 administered to rats and dogs in the 2 pivotal 4-week repeat-dose oral toxicity studies, defining NOAELs of 3 mg/kg in rats and 0.75 mg/kg in dogs, the dog was identified to be the most sensitive species (Table 11). The NOAEL of 0.75 mg/kg dose in dogs also corresponded to the highest non-severely toxic dose (HNSTD). According to ICH guideline S9, when the non-rodent is the most appropriate species, 1/6 of the HNSTD is considered an appropriate starting dose. Hence, the proposed first-in-human starting dose for Part 1 of the

study was calculated to be 7.5 mg (rounded to 7 mg)/subject/day. In the first cohorts of subjects with late stage advanced malignancies, this dose will be given as a once daily oral administration.

Table 11 First in Human Starting Dose Calculated from Results of 4-week Repeat-Dose Toxicity Studies in Rats and Dogs

Species	Treatment regimen	NOAEL (mg/kg/day)	Safety factor	Starting dose based on NOAEL (mg per subject)[a]
Rat	Daily, oral	3	1/10	18
Dog	Daily, oral	0.75[b]	1/6	7.5

NOAEL: No observed adverse effect level.

[a] Based on the assumption of 60 kg patient.

[b] Corresponds to the highest non-severely toxic dose.

This dose is at the lower end of the predicted BED (20 mg QD /subject) and is therefore considered to be pharmacologically active as well as being safe.

A Bayesian two-parameter logistic regression model with overdose control will be used to assist the SMC with dose selection. The model incorporates nonclinical toxicity and observed DLT information from all previously completed dose escalation cohorts to provide a recommended dose for the next cohort. A preselected set of doses are considered by the model, although doses that are not part of the pre-specified set may be chosen as well. Overdose control will be implemented, thus only doses with an estimated probability of less than 25% that the true DLT rate is more than 33% will be recommended by the model. The decision on the next dose is made by the SMC.

5.2.1.2 Part 2, M8891 combined with Cabozantinib, mRCC

5.2.1.2.1 Part 2A, Dose Escalation

In Part 2A, M8891 will be combined with cabozantinib for subjects with mRCC who have progressed to 1 or more previous lines of therapy for metastatic disease. The starting dose of M8891 will be 20 mg QD (See Section 5.1.3.2.1). Three pre-specified dose levels of M8891 are planned (20 mg, 35 mg and 60 mg) although the SMC may add or skip a dose, as long as it does not exceed the dose level of M8891 that has already been declared to be safe in Part 1 (See Section 5.1.3.2.1).

Similar to Part 1, a Bayesian two-parameter logistic regression model with overdose control will be used to assist the SMC with dose selection for the next cohort and to determine the MTD/RDE of M8891 combined with cabozantinib 60 mg QD for Part 2B. For the implemented overdose control, overdose is defined as a DLT rate of > 33%. For each dose level the risk of overdose will be calculated, and only dose levels for which this risk is lower than 25% will be recommended by the model. The decision on the next dose is made by the SMC.

In Part 2A, cabozantinib will be used at the approved 60 mg FBE daily dosage with dosage adjustments to 40 or 20 mg permitted to manage AEs (Section 5.1.3.5). The cabozantinib tablet formulation (Cabometyx™) is approved in USA and in the European Union (EU) at a 60 mg FBE daily dosage for the treatment of patients with advanced RCC. While simulations showed that the

20, 40, and 60 mg cabozantinib starting dosages were all predicted to reduce tumor growth, the 60 mg dose resulted in the greatest reduction in tumor growth, best objective response rate (ORR), and lowest rate of disease progression. In the review of the New Drug Application for cabozantinib for the treatment of patients with RCC, FDA addressed the issue regarding the appropriateness of dose selection given the high percentage of dose reductions in the METEOR study (A Study of Cabozantinib vs Everolimus in Subjects with Metastatic Renal Cell Carcinoma). Based on their review, FDA concluded that: (1) most adverse reactions were successfully managed with dose interruptions and supportive measures; (2) Exposure-Response modeling indicated that lower starting doses could possibly compromise activity of the drug with decreased response rates; and (3) the dose selection of 60 mg daily was adequate based on Exposure-Response analyses and a safety profile that is acceptable for the patient population (Lacy 2018).

5.2.1.2.2 Part 2B, Dose Expansion

Following Part 2A, the safety and tolerability of M8891 combined with cabozantinib will be investigated in an expansion cohort of 30 evaluable for response subjects with mRCC, for assessment of early clinical activity with an interim analysis after 15 subjects. The dose of M8891 in Part 2B will be determined by Part 2A and cabozantinib will be given at 60 mg QD (See Section 5.1.3.2.1).

5.2.2 Endpoint Selection

5.2.2.1 Part 1, M8891 Single Agent, Solid Tumors

The study endpoints are standard Phase I endpoints, namely to define the safety and PK of the drug in humans, and activity in terms of tumor growth control (using RECIST v1.1 guidelines) for solid tumors in subjects with advanced disease with no other therapeutic options, and toxicity.

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5.2.2.2 Part 2, M8891 Combined with Cabozantinib, mRCC

The study endpoints are standard Phase Ib endpoints, namely to define that the combination of M8891 and cabozantinib is safe and tolerable in subjects with mRCC who have progressed to one or more previous lines of therapies (See Section 5.1). The efficacy of the combination therapy will be determined by the ORR with response including complete and partial response rate/proportion as assessed by RECIST v1.1 criteria.

5.2.3 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

5.3.1.1 Part 1, M8891 Single Agent, Solid Tumors

Subjects are eligible to be included in the study only if all the following criteria apply:

1. Subjects must be refractory to or intolerant of existing cancer therapy(ies) known to provide clinical benefit.

2. Histologically confirmed advanced solid tumors with no clear curative treatment options available after at least 1 prior systemic anticancer therapy

3. Male and female subjects age 18 years and older who are able and willing to give written informed consent

4. A male subject must agree to use and to have their female partners to use a highly effective contraception (i.e., methods with a failure rate of less than 1% per year) as detailed in Appendix I of this protocol before first dose of study treatment (as appropriate), during the treatment period and for at least 92 days (3 months) after the last dose of study treatment and refrain from donating sperm during this period.

5. A female subject is eligible to participate if she is not pregnant (see Appendix I), not breastfeeding, and at least one of the following conditions applies:

   a. Not a woman of childbearing potential (WOCBP) as defined in Appendix I

   OR

   b. A WOCBP who agrees to use a highly effective contraception (i.e., methods with a failure rate of less than 1% per year) as detailed in in Appendix I of this protocol before start of first dose of study treatment (as appropriate), during the treatment period and for at least 92 days (3 months) after the last dose of study treatment.

6. Tumor accessible for biopsies and agreement to conduct pre-dose and post-dose fresh tumor biopsies. Archival tumor tissue is not mandatory for the inclusion in the study but is strongly recommended.

5.3.1.2 Part 2, M8891 combined with Cabozantinib, mRCC

Subjects are eligible to be included in the Part 2 of the study only if all the following criteria apply:

1. Male and female subjects age 18 years and older who are able and willing to give written informed consent before the performance of any study-specific procedures.

2. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1 at Screening.

3. Histologic or cytologic evidence/proven of mRCC with clear cell component.

4. Previous treatments:

    a. **Part 2A**: Subjects should have progressed to 1 or more previous lines of systemic anticancer therapy, excluding treatment with cabozantinib.

    b. **Part 2B**: Subjects should have progressed to 1 or 2 previous lines of systemic anticancer therapy, excluding treatment with cabozantinib. Subjects should have failed to only 1 previous TKI for metastatic disease. Adjuvant therapy with sunitinib will be considered as 1 line of therapy for metastatic disease in the case that disease progression occurs during or within 3 months of the completion of the treatment.

5. At least 1 lesion that is measurable using RECIST v1.1.

6. Ability to swallow capsules and tablets.

7. Recovery from any acute toxicities from the previous therapy to Grade 1.

8. Predicted life expectancy of > 3 months (according to the opinion of the Investigator).

9. Adequate organ function (i.e. liver, kidney, bone marrow), as evidenced by multiple laboratory value results within specific parameters. Specifically:

    - Hemoglobin ≥ 9.0 g/dL (no transfusion in the past 2 weeks before first dose); neutrophil count > 1.5 x 10^9/L; platelets > 100 x 10^9/L (no transfusion in the past 2 weeks before first dose).

    - Glomerular filtration rate ≥30 mL/min (according to the Cockcroft-Gault formula)

    - Total bilirubin ≤1.5 x ULN, AST/ALT ≤ 2.5 x ULN. For documented Gilbert's syndrome a total bilirubin < 3 x ULN is accepted.

10. Patients with central nervous system (CNS) metastases must have received surgical and/or radiation treatment and be neurologically stable no evidence of CNS disease progression as determined by CT or MRI within 21 days prior to the first dose of study drug.

11. Subjects on bisphosphonates may continue receiving bisphosphonates therapy during study treatment.

12. A male subject must agree to use and to have their female partners use a highly effective contraception (i.e., methods with a failure rate of less than 1% per year) as detailed in Appendix I of this protocol before first dose of study treatment (as appropriate), during the treatment

period and for at least 92 days (3 months) after the last dose of study treatment and refrain from donating sperm during this period.

13. A female subject is eligible to participate if she is not pregnant (see Appendix I), not breastfeeding, and at least one of the following conditions applies:

    a. Not a woman of childbearing potential (WOCBP) as defined in Appendix I

    OR

    b. A WOCBP:

    - who agrees to use a highly effective contraception (i.e., methods with a failure rate of less than 1% per year) as detailed in in Appendix I of this protocol before start of first dose of study treatment (as appropriate), during the treatment period and for at least 92 days (3 months) after the last dose of study treatment.

    - Who has a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test on Day 1 before dosing, as required by local regulations, within 24 hours before the first dose of study intervention.

5.3.2 Exclusion Criteria

5.3.2.1 Part 1, M8891 Single Agent, Solid Tumors

For Part 1, subjects are excluded from the study if any of the following criteria apply:

1. Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥2

2. Bone marrow impairment as evidenced by hemoglobin < 9.0 g/dL, neutrophil count < 1.5 x 10^9/L, platelets < 100 x 10^9/L. Transfusion is not allowed within 3 weeks before first dose

3. Renal impairment as evidenced by calculated creatinine clearance < 60 mL/min (according to the Cockcroft-Gault formula)

4. Liver function abnormality as defined by total bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN, for subjects with liver involvement AST/ALT > 5 x ULN

5. Extensive prior radiotherapy to more than 30% of bone marrow reserves, or prior bone marrow/stem cell transplantation within 5 years of study start

6. Clinically significant cardiac conduction abnormalities, including QTcF interval prolongation of > 480 ms and/or pacemaker or impaired cardiovascular function such as New York Heart Association classification score > 2

7. Thromboembolic events requiring therapeutic anticoagulation. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (i.e., warfarin, direct thrombin

and Factor Xa inhibitors) or platelet inhibitors (i.e., clopidogrel) started within the last 6 months of screening.

Note: Low dose aspirin for cardio-protection and low dose LMWH are permitted (in subjects who are on a stable dose of LMWH for at least 6 weeks before the first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor).

8. Pregnant or nursing female subject

9. Any other severe clinical condition that in the opinion of the treating physician may compromise the trial participation

10. Subjects used any investigational agents 14-28 days or 5-half-lives (whichever is shorter) of the initiating study treatment

11. History of difficulty swallowing, malabsorption, or other chronic gastrointestinal disease or conditions that may hamper compliance and/or absorption of the investigational drugs

12. Life expectancy < 3 months

13. Known hypersensitivity to the trial treatment or to one or more of the excipients used

14. Legal incapacity or limited legal capacity.

5.3.2.2 Part 2, M8891 combined with Cabozantinib, mRCC

For both Part 2A and Part 2B, subjects are excluded from the study if any of the following criteria apply:

1. Previous use of cabozantinib or a MetAP2 inhibitor.

2. Receipt of other anticancer therapy within 2-4 weeks (wash-out period of 5 half-lives) or radiotherapy within 1 week prior to first dose of study treatment or patients who have not recovered from the side effects of such therapy to Baseline or Grade 1 (except for alopecia or potentially neuropathy).

3. Subjects used any investigational agents 14-28 days or 5-half-lives (whichever is shorter) of the initiating study treatment.

4. Tumor in contact with, invading or encasing major blood vessels or radiographic evidence of significant cavitary pulmonary lesions.

5. Pathologic evidence of tumor invading the gastrointestinal tract, or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of study treatment.

6. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding (e.g. pulmonary hemorrhage) within 3 months before the first dose of study treatment.

7. Major surgery within 12 weeks before the first dose of study treatment. Complete wound healing from major surgery must have occurred 1 month before the first dose of study treatment. Minor surgery within 28 days before the first dose of study treatment. Complete wound healing from minor surgery must have occurred at least 10 days before the first dose of study treatment.

8. Active symptomatic fungal, bacterial (requiring IV antibiotics) and/or viral infection. Individuals with known or seropositive testing for human immunodeficiency virus (HIV) or actively infected viral hepatitis (B or C) are excluded. However, individual with Hepatitis C treated with curative therapy are not considered actively infected.

9. Uncontrolled hypertension defined as sustained Blood Pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment.

10. Current significant cardiac conduction abnormalities, including QTcF interval prolongation of > 450 ms for males and > 470 ms for females or cardiovascular disorders, including symptomatic congestive heart failure, unstable angina pectoris, and serious cardiac arrhythmias.

11. The subject is pregnant or breastfeeding.

12. Cerebrovascular accident/stroke (< 6 months prior enrollment) or neurologic instability per clinical evaluation due to tumor involvement of the CNS.

13. Thromboembolic events requiring therapeutic anticoagulation. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (i.e., warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (i.e., clopidogrel) started within the last 6 months of screening.

    Note: Low dose aspirin for cardio-protection and low dose LMWH are permitted (in subjects who are on a stable dose of LMWH for at least 6 weeks before the first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor).

14. Presence of clinically significant cardiac, respiratory, or other medical or psychiatric condition that might interfere with participation in the trial or interfere with the interpretation of trial results.

15. History of allergic reactions attributed to compounds of similar chemical or biologic composition to cabozantinib or M8891.

16. An active second malignancy or evidence of disease of cancer (other than RCC) before the date of enrollment (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the Investigator, with

concurrence with the Sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years).

5.4 Criteria for Initiation of Trial Treatment

Not applicable.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Trial Therapy

A subject must be withdrawn from M8891 if any of the following occur:

- Subject withdrew consent
- Subject lost to follow up
- Participation in another clinical trial
- Any events that unacceptably endanger the safety of the subject
- Discontinuation is considered necessary by the Investigator and/or Sponsor due to occurrence of an exclusion criterion or AE which is clinically relevant and affects the subject's safety
- Discontinuation of M8891 (or M8891 combined with cabozantinib) is desired or considered necessary by the Investigator and/or the subject (if applicable) due to occurrence of > Grade 2 AEs for more than 6 days
- If at any time on study the average QTcF interval from the 3 ECGs is > 500 ms and
    - Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation or
    - Recurrence of QTcF interval prolongation after reinitiation of study treatment at a reduced dose (see Section 6.5.5 for cabozantinib)
- Any DLTs as described in Section 5.1.
- Stroke (including transient ischemic attack, TIA), myocardial infarction, or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism)
- Occurrence of pregnancy
- Noncompliance that is deemed by the Investigator or the Sponsor to compromise the subject's safety or trial integrity.

5.5.2 Withdrawal from the Trial

A subject may withdraw from the study at any time, at his/her own request without giving a reason or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

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

- Subject withdrew consent
- Documented disease progression (see Section 5.3.1.1 for exception)
- Lost to follow-up
- Noncompliance that is deemed by the Investigator or the Sponsor to compromise the subject's safety or trial integrity
- Occurrence of AEs for which discontinuation is desired or considered necessary by the Investigator and/or the subject
- Participation in any other interventional trial during the duration of treatment in this trial.

At the time of discontinuing from the study, an EOT visit will be conducted, as listed in the SoAs. The SoAs specifies the data to collect at EOT and follow-up, and any additional evaluations that need to be completed.

If the subject withdraws consent for future involvement in the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected after consent withdrawal will be destroyed.

A subject has the right at any time to request destruction of any biological samples taken. The Investigator must document this in the site study records.

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

During dose escalation (Part 1 and Part 2A), subjects who prematurely discontinue treatment during Cycle 1 for any other than DLT reason, will be replaced to reach a minimum of 2 evaluable subjects in each cohort. Subjects discontinuing due to DLT in Cycle 1 are not replaced.

5.6 Premature Termination of the Trial

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

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of M8891 (or M8891 combined with cabozantinib), e.g., due to:
  - Evidence of inefficacy of M8891 (or M8891 combined with cabozantinib)
  - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions
  - Other unfavorable safety findings.

(Note: evidence of inefficacy may arise from this trial or from other trials; unfavorable safety findings may arise from examinations within clinical or nonclinical studies, e.g., toxicology.)

- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely
- Discontinuation of development of M8891.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

5.7 Definition of End of Trial

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

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

If the trial is not prematurely discontinued for a reason given in Section 5.6, the end of the trial is defined as the last subject enrolled in the trial having treatment up to 2 years or either stopped M8891 (or M8891 combined with cabozantinib), i.e., having withdrawn because of disease progression, death, unacceptable toxicity, or Investigator/subject decision, or having completed the EOT visit and Safety Follow-up visit if applicable. Subjects who are on ongoing treatment at this time may be offered continued treatment outside of the study under observation of local regulations.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" (IMP) refers to an active substance or a placebo being tested or used as a reference therapy in a clinical trial, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form. The IMP for this study is M8891.

6.1 Description of the Investigational Medicinal Product

6.1.1 M8891

The chemical name of M8891 drug substance is (S)-3-Hydroxy-1-(1H-indol-5-yl)-2-oxo-pyrrolidine-3-carboxylic acid 3,5-difluoro-benzylamide.

M8891 is formulated as 1 mg (size "3", color white), 5 mg (size "3", color white) and 30 mg (size 0, color Swedish orange) hard gelatin capsules for oral administration. No other excipients are used.

6.1.2 Cabozantinib (Cabometyx)

Cabozantinib is indicated for the treatment of patients with mRCC, metastatic medullary thyroid cancer and hepatocellular carcinoma. The approved dosage of cabozantinib in mRCC is 60 mg once daily without food until the patient no longer experiences clinical benefit or experiences unacceptable toxicity. Cabozantinib malate is the (S)-malate salt of cabozantinib, a kinase inhibitor. Cabozantinib (S)-malate is described chemically as N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide,(2S)-hydroxybutanedioate.
The commercial cabozantinib drug product tablet formulation (Cabometyx; Exelixis, Inc.) is marketed in three strengths (20, 40, and 60 mg). Complete information for cabozantinib may be found in the USPI (Cabometyx USPI 2019).

6.2 Dosage and Administration

6.2.1 Part 1, M8891 Single Agent, Solid Tumors

M8891 will be administered orally as single agent continuously in 21-day cycles at the starting dose of 7 mg QD. In subsequent cohorts subjects will take the total assigned dose of M8891 once daily in the morning with a full glass of water (approximately 240 mL/8 fluid ounces). The subjects should be instructed to swallow the capsules whole and not to bite into the capsules, break or open them, or attempt to dissolve the contents in water prior to taking their assigned dose.

M8891 will be taken under fasted conditions in the morning before breakfast (i.e. at least 2 hours fasted) and subjects will be instructed to continue to fast for 1 hour post-dosing.

Except for water consumed with M8891 administration, water will be withheld for 1 hour before and 1 hour after dose administration.

Dose escalation is described in Section 5.1.3.1

6.2.2 Part 2, M8891 with Cabozantinib, mRCC

In Part 2A M8891 will be administered orally at a starting dose of 20 mg QD combined with cabozantinib continuously in 21-day cycles.

Dose escalation is described in Section 5.1.3.2.1.

CCI [redacted]

Cabozantinib will be used at the approved 60 mg FBE daily dosage with dosage adjustments to 40 or 20 mg permitted to manage AEs (Section 5.1.3.5).

When the MTD/RDE has been defined in Part 2A (Section 5.1.3.4), the Part 2B expansion cohort with M8891 combined with cabozantinib will be initiated.

In Part 2 CCI [redacted], M8891 combined with cabozantinib will be taken under fasted conditions in the morning before breakfast (i.e. at least 2 hours fasted) and subjects will be instructed to continue to fast for 1 hour post-dosing. Except for water consumed with M8891 and cabozantinib administration, water will be withheld for 1 hour before and 1 hour after dose administration.

6.3 Assignment to Treatment Groups

Not applicable. This is a single-arm open-label study.

6.4 Non-investigational Medicinal Products to be Used

Not applicable.

6.5 Concomitant Medications and Therapies

All concomitant medications taken by the subject during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the electronic case report form (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 trial medication may be given at the Investigator's discretion, e.g. hormone therapy is allowed for subjects with prostate cancer.

Rescue medications may be administered to address ineffective treatment, anticipated adverse reactions or anticipated emergency situations.

6.5.2 Prohibited Medicines

6.5.2.1 Part 1, M8891 Single Agent, Solid Tumors

Not applicable for Part 1.

6.5.2.2 Part 2, M8891 with Cabozantinib, mRCC

For cabozantinib the investigators should refer to Section 7 of the cabozantinib USPI (Cabometyx USPI 2019).

6.5.3 Other Interventions

Not applicable.

6.5.4 Special Precautions

Subjects will be instructed to avoid or to replace medications that are potent combined inhibitors of CYP3A4, CYP2C9 and CYP2C19 (i.e. fluconazole and voriconazole) during treatment of M8891. (See Appendix II for details).

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

Based on nonclinical data, the main anticipated toxicity for M8891 may include anemia, neutropenia, leukopenia, thrombocytopenia, opportunistic infections, nausea, diarrhea, gastrointestinal (GI) hemorrhage and osteoporosis (see Section 3.3.1). Cabozantinib safety profile has been established (Cabometyx USPI 2019).

Potential occurring AEs that study subjects are likely to encounter during the study period and guidance on the management is presented in the Table 12.

Table 12 Management of Specific AEs with M8891 Combined with Cabozantinib

Adverse Event	Management Recommendation[a]
Diarrhea	• Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. • Administration of antidiarrheal/ antimotility agents is recommended at the first sign of diarrhea as initial management. • Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study treatment should be temporarily interrupted, or dose reduced (Section 5.1.3.5). • When the diarrhea is controlled, retreatment with study treatment may be acceptable per Investigator decision. • In addition, general supportive measures should be implemented including continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals, and alcohol.
Nausea and Vomiting	• Antiemetic agents are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care according to clinical practice guidelines. • In the case of cabozantinib, the 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure (see Section 7 in cabozantinib USPI (Cabometyx USPI 2019). • For cabozantinib, caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4.
Stomatitis and Mucositis	• Preventive measures may include a comprehensive dental examination to identify any potential complications before study treatment is initiated. Removal of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis (dental examination/procedures before study initiation will be recommended but not covered by the study). • During treatment good oral hygiene and standard local treatments such as nontraumatic cleansing and oral rinses (e.g., with a weak solution of salt and baking soda) should be

Adverse Event	Management Recommendation[a]
	maintained. The oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque. • Local treatment should be instituted at the earliest onset of symptoms. • Obtain bacterial/viral culture if oral infection is suspected and treat infection as indicated by local guidelines. • When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of study treatment should be considered.
Hepatobiliary Disorders	• It is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. • If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin. • Dose reductions of study treatment should be considered in any subject who develops drug-related Grade 2 elevated ALT, AST, or bilirubin lasting longer than 1 week. • A subject who develops Grade ≥ 3 elevated ALT, AST, or bilirubin should have study treatment held and restarted at a reduced dose (Section 5.1.3.5) after ALT, AST, and bilirubin levels resolve to at least Grade ≤ 1 or baseline. • In subjects with recurrence of drug-related Grade ≥ 3 elevated ALT, AST, or bilirubin at the lowest dose level, study treatment should be discontinued. • In subjects who develop ALT/AST elevations > 3 × ULN in combination with a bilirubin elevation > 2 × ULN without reasonable other explanation, drug-induced liver injury should be suspected and study treatment should be interrupted. • Reinstitution of study treatment after recovery of ALT, AST, and bilirubin to Grade 1 or baseline level must be discussed and approved with the Sponsor.
Hematological Disorders	• Hematological toxicities (i.e., neutropenia and thrombocytopenia) and associated complications may be managed with dose interruptions and/or dose reductions. Use of granulocyte colony-stimulating factor support for neutrophil recovery is allowed per Investigator discretion and in accordance with accepted guidelines after the first incidence of clinically relevant cytopenia. • Complete blood counts with differentials and platelets should be performed regularly. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines. • Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines. • Dose reductions or dose interruptions for anemia are not mandated but can be applied as clinically indicated. Supportive care such as red blood cell transfusions may be managed according to institutional guidelines.
Fatigue, Anorexia, and Weight Loss	• Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or these causes treated according to standard of care. Individual non-pharmacological and/or pharmacologic interventions directed to the contributing and treatable factors should be given. • Pharmacological management with psychostimulants such as methylphenidate should be considered after disease specific morbidities have been excluded. Note: Chronic use of modafinil should be avoided because of its potential to reduce cabozantinib exposure (see Section 7 in cabozantinib USPI (Cabometyx USPI 2019). • Dose reduction of study treatment should be considered when general or pharmacological measures have not been successful in reducing symptoms. • Dose interruption may be considered for Grade ≥ 3 fatigue despite optimal management, at the Investigator's discretion. • Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy such as megestrol acetate should be considered for appetite enhancement. Should these interventions prove ineffective, dose hold and reductions may be considered for Grade ≥ 3 anorexia or weight loss.
Skin Disorders	• All subjects on study should be advised on prophylactic skin care. This includes the use of hypoallergenic moisturizing creams, ointment for dry skin, and sunscreen with sun protection factor ≥ 30, avoidance of exposure of hands and feet to hot water, protection of

<table>
<tr><th>Adverse Event</th><th>Management Recommendation[a]</th></tr>
<tr><td></td><td>pressure sensitive areas of hands and feet, and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry.
• Subjects with skin disorders should be carefully monitored for signs of infection (e.g., abscess, cellulitis, or impetigo).
• Early signs of hand-foot syndrome could be tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or peri-ungual zones may also be affected.
• Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Aggressive management of symptoms is recommended, including early dermatology referral.
• In the case of study treatment-related skin changes (e.g., rash, hand-foot syndrome), the Investigator may request that additional assessments be conducted with the subject's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve
• VEGF inhibitors can cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed prior to starting study treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with M8891 with cabozantinib.</td></tr>
<tr><td>Hypertension</td><td>• Hypertension is a common class effect of drugs that inhibit VEGF pathways
• Blood pressure should be monitored in a constant position at each visit (either sitting or supine).
• In general, subjects with known hypertension should be optimally managed prior to study entry.
• Decisions to decrease or hold the dose of study treatment must be based on blood pressure readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement.
• Other than for hypertension requiring immediate therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking therapeutic action. It is recommended that this second visit occurs within 1 week.
• In the case of hypertensive crisis or hypertensive encephalopathy, study treatment should be discontinued.</td></tr>
<tr><td>Thromboembolic Events</td><td>• Study treatment should be discontinued in subjects who develop PE or DVT, an acute myocardial infarction or any other clinically relevant arterial thromboembolic complication (Section 5.5).</td></tr>
<tr><td>Proteinuria</td><td>• During each safety assessment visit, proteinuria will be quantified by measuring the urine protein-to-creatinine (UPCR) ratio. In addition, urine dipstick analysis will be performed (see Table 2 and Table 3).

Severity of Proteinuria (UPCR) — Action To Be Taken
1 mg/mg (≤ 113.1 mg/mmol) — • No change in study treatment or monitoring
> 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol) — • No change in study treatment required
• Consider confirming with a 24-hour protein assessment within 7 days
• Repeat UPCR within 7 days and once per week. If UPCR < 1 on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.)
≥ 3.5 mg/mg (≥ 395.9 mg/mmol) — • Hold study treatment pending repeat UPCR within 7 days and/or 24-hour urine protein.
• If ≥ 3.5 on repeat UPCR, continue to hold study treatment and check UPCR every 7 days. If UPCR decreases to < 2,</td></tr>
</table>

Adverse Event	Management Recommendation[a]
	Nephrotic syndrome: restart study treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1. • Discontinue study treatment
Corrected QTcF interval Prolongation	If at any time on study the average QTcF interval from the 3 ECGs is > 500 ms, the following actions should be taken: • Withhold study treatment • Immediately notify the Sponsor • Hospitalize symptomatic subjects (e.g., with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management • Consider cardiology consultation for asymptomatic subjects for evaluation and management • Check electrolytes, especially magnesium, calcium, and potassium; correct abnormalities as clinically indicated • Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (refer to http://www.qtdrugs.org) • Repeat ECG triplicates hourly until the average QTcF interval is ≤ 500 ms • Subjects with QTcF interval prolongation and symptoms must be monitored closely until the QTcF interval prolongation and symptoms have resolved. Study treatment may be restarted at a reduced dose level if **ALL** the following conditions are met: • Symptoms are determined to be unrelated to the QT interval prolongation • The QTcF interval value returns to ≤ 500 ms • Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF interval to ≤ 500 ms • QT prolongation can be unequivocally associated with an event other than study treatment administration and is treatable/has been resolved • Sponsor has reviewed all available information and has agreed to the continuation of study treatment Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points. Study treatment must be permanently discontinued if either of the following applies: • Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation • Recurrence of QTcF interval prolongation after reinitiation of study treatment at a reduced dose
Hypophosphatemia	• Serum phosphorus should be monitored frequently while receiving study treatment. • Mild hypophosphatemia is usually asymptomatic or symptoms can be non-specific such as weakness, bone pain, rhabdomyolysis, or altered mental status. • Other causes of hypophosphatemia such as poor nutrition, chronic alcoholism, malabsorption, excessive antacid use, glucocorticoids use, kidney dysfunction, respiratory alkalosis, vitamin D deficiency should be ruled out and/or these causes treated according to standard of care. • Mild to moderate hypophosphatemia should be managed by oral replacement including food that are high in phosphate (diary items, meats, beans) and/or oral phosphate supplements according to standard clinical practice guidelines • Clinically relevant hypophosphatemia should be managed according to the dose modification guidelines as outlined in Section 5.1.3.5 or as clinically indicated
Thyroid Function Disorders	Management of thyr.oid dysfunction (e.g., symptomatic hypothyroidism) should follow accepted clinical practice guidelines and dose modification guidelines as outlined in Table 10.

[a] Subjects with pre-existing conditions who are at greater risk of experiencing serious toxicities should be monitored carefully throughout the study. For cabozantinib, Investigators are encouraged to refer to local product label; dose modification of any study treatment should always be considered in consultation with the Sponsor's Medical Responsible.

6.6 Packaging and Labeling of the Investigational Medicinal Product

M8891 will be packed in wallets containing 3 blisters with 6 capsules each for the dose strengths 1 mg (only for Part 1, M8891 single agent) and 5 mg and with 5 capsules each blister for the 30 mg dose strength.

M8891 will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

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

M8891 must be stored at the recommended temperature CCI until use and must not be frozen. Any deviations from the recommended storage conditions should be immediately reported and the trial drug should not be used until authorization has been received from the Sponsor.

The Investigator or a trained designee will dispense M8891 to subjects according to their dose level.

At the end of the trial drug will not be returned to depot for destruction and will be destroyed on site by either site followed process or designated study drug destruction process.

6.8 Investigational Medicinal Product Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate document and returning it to the location specified. A copy will be archived for the Investigator Site File.
- Only subjects enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:

- Confirmation of receipt, in good condition and in the defined temperature range.
- The inventory provided for the clinical study and prepared at the site.
- The dose(s) each subject used during the study.
- The disposition (including return, if applicable) of any unused study intervention(s).
- Dates, quantities, batch numbers, kit numbers, expiry dates, and the subject numbers.

- The Investigator site will maintain records, which adequately documents that subjects were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a subject may be re-dispensed to a different subject.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Operations Manual.

6.9 Assessment of Investigational Medicinal Product Compliance

The information of each IMP administration including the date, time, and dose of IMP will be recorded on the eCRF. The Investigator will make sure that the information entered into the eCRF regarding IMP administration is accurate for each subject. Any reason for noncompliance should be documented.

6.10 Blinding

This is a single-arm study, blinding procedures are not applicable.

6.11 Emergency Unblinding

Not applicable. This is an open-label trial without randomization.

6.12 Treatment of Overdose

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

6.13 Medical Care of Subjects after End of Trial

After a subject has completed the trial or has withdrawn early, usual treatment on Investigator's choice will be administered, if required, in accordance with the trial site's generally accepted

medical practice and depending on the subject's individual medical needs. The Sponsor will not provide any additional care to subjects after they leave the trial because such care should not differ from what is normally expected for the patients.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

Prior to performing any trial assessments that are not part of routine medical care for the subject, the Investigator will obtain written informed consent as described in Section 9.2.

Complete SoAs for Part 1, Part 2A, and Part 2B of the trial is provided in Table 1 (Part 1), Table 2 (Part 2A) and Table 3 (Part 2B). Sample collection for PK, and ECG safety evaluations are provided in Table 4 and Table 5.

7.2 Demographic and Other Baseline Characteristics

At screening, demographic and other baseline characteristic data will be collected, e.g., age, sex (gender), race, ECOG PS, and complete medical history should be undertaken.

7.3 Efficacy Assessments

No more than 28 days before the first dose of study medication, CT scan or magnetic resonance imaging (MRI) in regions where disease is located, and metastases may be expected (based on the tumor type) will be performed to document the baseline status using the most appropriate criteria for the malignancy type. The target and non-target lesions will be selected based on the initial scan and all subsequent scans should use the same methodology.

Clinical efficacy will be assessed by the Investigators according to RECIST v1.1 at the time points defined in the SoAs in Table 1 (Part 1), Table 2 (Part 2A) and Table 3 (Part 2B). Specifically, in Part 1 tumor response will be assessed on Day 1 of Cycles 3, 5 and 7, and every 18 weeks (6 Cycles) thereafter. In Part 2 tumor response will be assessed on Day 1 of Cycles, 3, 5, 7 and every third cycle thereafter. PFS, defined as time from first dose to objective disease progression or death, whichever occurs first, by Investigator will also be considered.

7.4 Assessment of Safety

The safety profile of M8891 single agent and M8891 combined with cabozantinib will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs and laboratory tests at specified times during the study.

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

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

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

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

The Investigator is required to grade the severity or toxicity of each AE. Investigators will reference the NCI-CTCAE, version 4.03, a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If 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 IMP/study treatment (including any other non-IMPs, radiation therapy, etc.) using the following definitions. Decisive

factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP, known side effects of study treatment, medical history, concomitant medication, course of the underlying disease, trial procedures.

Unrelated: Not reasonably related to the IMP/study treatment. AE could not medically (pharmacologically/clinically) be attributed to the IMP/study treatment under study in this clinical trial protocol. Only events clearly not related (disease progression, environmental, unrelated trauma, etc.) should be categorized as unrelated to the study treatment.

Related: Reasonably related (ie, any toxicities considered related, probably related, or possibly related) to the IMP/study treatment. AE could medically (pharmacologically/clinically) be attributed to the IMP/study treatment under study in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

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

Serious Adverse Events

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

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

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

Events that Do Not Meet the Definition of an SAE

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

Events Not to Be Considered as AEs/SAEs

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

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an AE/SAE, unless the subject's general condition is more severe than expected for the subject's condition and/or unless the outcome is fatal within the AE reporting period (as defined in Section 7.4.1.3).

7.4.1.2 Methods of Recording and Assessing Adverse Events

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

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

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

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

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of first informed consent) and continues until the EOT visit and through the safety follow-up period for SAEs. Subjects with SAEs ongoing at EOT Visit must be followed during the safety follow-up.

Any SAE assessed as related to M8891 must be reported whenever it occurs, irrespective of the time elapsed since the last administration of M8891.

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

Serious Adverse Events

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

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

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, 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.

Dose Limiting Toxicities

Each event meeting the criteria of a DLT (see Section 5.1.3.3) must be recorded in the eCRF within 24 HOURS after becoming aware of the event. Serious DLTs must be reported in an expedited manner as SAEs as outlined above.

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

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

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

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

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

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

7.4.1.6 Monitoring of Subjects with Adverse Events

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

7.4.2 Pregnancy and In Utero Drug Exposure

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

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

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

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

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

7.4.3 Clinical Laboratory Assessments

Blood and urine samples will be collected for the following clinical laboratory tests, following the timing noted in the SoAs (Table 1 for Part 1 and Table 2 and Table 3 for Part 2)**.** For maximal blood volumes refer to the Laboratory Manual.

All samples should be clearly identified.

The Sponsor should receive a list of laboratory normal ranges before shipment of trial drug. Any change in laboratory normal ranges during the trial should be forwarded to the CRO.

For Part 1 of the study, clinical laboratory assessments include hemoglobin, WBC count, differential, platelet count, PT, aPTT, creatinine, creatinine clearance, AST, ALT, GGT, AP, lipase, amylase, BUN, total bilirubin, total protein, albumin, uric acid, sodium, chloride, bicarbonate, potassium, calcium, phosphorus, magnesium and glucose.

For Part 2 of the study, clinical laboratory assessments include hematology, serum chemistry, coagulation, urine chemistry, serology and thyroid function tests (See Appendix III Laboratory Tests (Only for Part 2 of the study).

Additional details regarding laboratory assessments (e.g., sampling methods, processing, and storage) will be included in the Laboratory Manual.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

Vital sign, physical exam, and other assessments include: heart rate, diastolic blood pressure systolic blood pressure, weight, temperature, and additional assessments as included in Table 1, Table 2, and Table 3.

For timings of assessments, see the SoAs (Table 1, Table 2, and Table 3). For detailed procedures refer to the Manual of Operations.

7.4.5 Electrocardiograms

ECG will be performed throughout the study at specified time points (during Part 1 and Part 2) as indicated in the SoAs (Table 1 for Part 1, and Table 4 and Table 5 for Part 2).

The Fridericia formula is depicted below for calculation of the corrected QT (QTcF) interval.

QTcF interval = $QT/RR^{1/3}$, where QT = measured QT interval in milliseconds; RR = measured R to R interval (which can be derived from the heart rate as 60/heart rate).

7.4.5.1 Part 1 M8891 Single Agent, Solid Tumors

ECGs for QT/QTc Evaluation

At screening, standard triplicate (within 2 min) digital 12-lead ECG will be obtained after the subject has been rested in semi-recumbent position for at least 5 min using standard 12-lead equipment to determine the QTcF interval. If the average of these three consecutive results for QTcF interval is > 480 ms the subject does not meet eligibility in this regard.

12-lead triplicate digital ECG will be performed within 2-minutes after at least 10 minutes rest in supine position, on Cycle 1 Day 1 and Day 15 at pre-dose and 1, 2, 4, 5, 6, 8, 12 hours and 24 hours post-dose (± 15 minutes) and on pre-dose on Day 8. The SMC may decide that the Day 15/Day 16 assessment can be waived in case no relevant drug accumulation is being observed. ECG assessments at subsequent cycles will be performed pre-dose at time points as indicated in Table 1. ECGs should be performed directly before PK sampling time-points on days where both assessments are performed.

Digital ECGs will be stored for a later independent analysis: ECG extractions will be made by the central ECG laboratory and over-read of interval measurements will be provided by experienced, qualified, and certified cardiac safety specialists. The readers will be blinded to subject details, treatment, visit day, and time points of the ECG recording, and a single reader will read all ECGs of a given subject. Time-matched, replicate ECGs and PK samples collected will be used to analyze for QTcF interval responses using slope analysis of exposure/response. This analysis may be reported separately.

7.4.5.2 Part 2 M8891 with cabozantinib, mRCC

Safety ECGs

Safety ECGs are standard triplicate 12-lead ECGs obtained for safety monitoring according to the SoAs (Table 4 for Part 2A and Table 5 for Part 2B). Subjects will rest in semi-recumbent position for at least 5 minutes. Safety ECGs will be read locally, and all ECGs should be assessed on the day of collection to determine continued eligibility. The calculated QTcF interval average of 3 12-lead ECGs must be ≤ 450 ms for males and ≤ 470 ms for female participants' eligibility. To confirm suitability for treatment after screening, ECGs must be repeated on Day -1, Cycle 1, prior to administering the first dose of study treatment unless the screening tests were performed within 14 days prior to first dose.

During the scheduled safety visits, subjects, in whom the calculated QTcF interval average increases to > 500 ms or > 60 ms change over baseline during treatment with M8891 combined with cabozantinib, must interrupt study treatment until further clinical evaluation. ECGs should be repeated if QTcF interval is outside the range until resolution (Table 12, Section 6.5.5). To assess the safety and tolerability of the study intervention, an ECG can be repeated at the Investigator's discretion at unscheduled visits. Start and end of resting time and ECG time will be recorded in the eCRF.

Abnormalities in the ECG that lead to a change in subject management (e.g., dose reduced or withheld, treatment discontinued, requirement for additional medication or monitoring as described in Table 12, Section 6.5.5) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be deemed adverse events. If values meet criteria defining them as serious, they must be reported as SAEs.

7.5 Pharmacokinetics

7.5.1 Part 1, M8891 Single Agent, Solid Tumors

For the PK analysis, the plasma level of M8891 will be analyzed by the analytical laboratory selected under responsibility of the Sponsor, using an appropriate validated bioanalytical method. Urine level of M8891 will be analyzed using an appropriate qualified method.

Full details of the bioanalytical method used will be described in a separate bioanalytical report. Plasma concentrations of M8891 and its metabolites will be analyzed as indicated in Table 1.

At each time point, 3 mL (2 aliquots of 1.5 mL) blood will be collected. The exact blood volume will be indicated in the Laboratory Manual. For all clinical and research studies, the total blood volume (mL) drawn in a 30-day period will never exceed the 280 mL.

Actual date and time of M8891 administration and PK actual sampling date and time will be recorded in the eCRF.

The PK sampling (and corresponding CCI sampling) schedule may be modified based upon emerging PK information collected during the study with the provision that the overall amount of blood to be collected for PK sampling is not increased.

List of PK parameters:

- C_{max}: Observed maximum plasma concentration
- t_{max}: Time to reach maximum observed plasma concentration
- $AUC_{0-\infty}$: Area under the concentration-time curve from time zero extrapolated to infinity, based on the predicted value for the concentration at t_{last}
- AUC_{0-t}: Area under the concentration-time curve from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification (LLOQ)
- $AUC_{0-\tau}$: Area under the plasma concentration versus time curve within one dosing interval
- $t_{1/2}$: Apparent terminal half-life
- λ_z: Apparent terminal rate constant
- CL/F: Apparent body clearance of drug following extravascular administration
- CLss/F: Apparent body clearance of drug following extravascular administration at steady state
- V_z/F: Apparent volume of distribution during the terminal phase following extravascular administration
- Racc(AUC_τ): Accumulation ratio for AUC_τ
- Racc(C_{max}): Accumulation ratio for C_{max}.

In dose level 4 and dose level 5, urine samples for exploratory determination of M8891 and its metabolites will be taken from the total pooled urine sample provided during the 12-hour collection period on Day 1 and Day 15. The start and stop date/time of each pooled urine collection should be recorded in the eCRF. The volume of each urine collection will also be recorded.

Additional analyses may be conducted on the plasma and/or urine samples to further investigate the presence and/or identity of drug metabolites. Any results from such analyses on plasma and/or urine may be reported separately from the clinical trial report.

Details on sample shipment and handling will be provided in the Laboratory Manual.

7.5.2 Part 2, M8891 with Cabozantinib, mRCC

Sampling time schedules for determination of M8891 and cabozantinib can be found in the SoAs (Table 4 for Part 2A and Table 5 for Part 2B).

For the PK analysis, the plasma level of M8891 and cabozantinib will be analyzed by the analytical laboratory selected under responsibility of the Sponsor, using an appropriate validated bioanalytical method. Full details of the bioanalytical method used will be described in the Laboratory Manual.

At each time point, 3 mL (2 aliquots of 1.5 mL) blood will be collected. The exact blood volume will be indicated in the Laboratory Manual.

Actual date and time of M8891 and cabozantinib administration and PK actual sampling date and time need be recorded in the eCRF.

The following M8891 and cabozantinib PK parameters in Part 2A, if applicable:

- C_{max}: Observed maximum plasma concentration
- t_{max}: Time to reach maximum observed plasma concentration
- AUC_{0-t}: Area under the concentration-time curve from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification (LLOQ)
- AUC_{0-t}/Dose: Dose normalized AUC_{0-t} (Part 2A, M8891 only)
- C_{max}/Dose: Dose-normalized C_{max} (Part 2A, M8891 only)

For Part 2B the plasma concentration time profile of M8891 and cabozantinib will be described via modeling and simulation. Full details of the relevant population PK modeling work (including objectives, relevant endpoints, methodology, software etc.) will be defined in a separate pharmacology analysis plan or the study Integrated Analysis Plan. The actual elapsed time from dose will be used in the final PK modeling and parameter calculations. The results of these analyses will be described in a separate report from the CSR.

CCI [redacted] Integrated analyses across studies, such as the population PK and population PK analyses will be presented separately from the main clinical study report.

The PK concentration will be summarized by descriptive statistics per time point.

Additional analyses may be conducted on the plasma samples to further investigate the presence and/or identity of drug metabolites. Any results from such analyses may be reported separately from the clinical trial report.

At each time point, 3 mL (2 aliquots of 1.5 mL) blood will be collected. The exact blood volume will be indicated in the Laboratory Manual. For all clinical and research studies, the total blood volume (mL) drawn in a 30-day period will never exceed the 280 mL.

Details on sample shipment and handling will be provided in the Laboratory Manual.

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

7.7 Other Assessments

Not applicable.

8 Statistics

Statistical methodology is generally described within this Section 8. Additional details will be provided in an Integrated Analysis Plan.

8.1 Sample Size

8.1.1 Part 1, M8891 Single Agent, Solid Tumors

A Bayesian model is applied to assist the SMC in dosing decisions. For details on the model see Section 8.5.3.1

As this is the dose escalation part of the trial, with M8891 single agent, sample size cannot be exactly prespecified, but depends among other things on the number of DLTs seen.

The sample size for Part 1 dose escalation (QD) is capped at a maximum of 42 subjects.

At least 6 subjects need to have been treated at the suggested MTD or RP2D. That might necessitate the enrollment of additional subjects after dose escalation was stopped. For this sample size assessment, it is assumed that it is not necessary to enroll additional subjects to fulfill this criterion.

It is anticipated that 36 evaluable subjects (8 dose levels with 3 to 12 subjects, e.g. assuming a scenario with 5 dose levels with 3 subjects, 2 dose levels with 6 subjects (2 cohorts) and one dose level with 9 subjects (3 cohorts) may be needed in order to determine the MTD of QD dosing of M8891.

The anticipated total number of evaluable subjects is approximately 36 (42 if the maximal sample size stopping criterion is reached).

8.1.2 Part 2, M8891 with Cabozantinib, mRCC

8.1.2.1 Part 2A, Dose Escalation

In Part 2A, a Bayesian model is applied to assist the SMC in dosing decisions. For details on the model see Section 8.5.3. Like Part 1, the sample size for the dose escalation in Part 2A cannot be exactly prespecified but depends among other things on the number of DLTs seen. The planned cohort size is 3 subjects. The SMC may decide to change the planned cohort size. The total sample size will depend on the number of cohorts to be evaluated. It is anticipated that 6 to 15 subjects maximum will be needed. The following scenario is possible: 2 dose levels with 3 subjects each and 1 dose level with 6 subjects, resulting in 12 subjects.

8.1.2.2 Part 2B, Expansion Cohort

In the Part 2B expansion cohort, a 2-stage design with a total of 30 subjects evaluable for response will be applied. If 11/30 responses are seen at the final analysis, the posterior probability that the ORR $\geq$ 30% is 81%.

An interim analysis for futility will occur after enrollment of 15 subjects treated at the same dose who are evaluable for response. The cut-off for the interim analysis for futility was chosen to balance sufficient information for decision with the potential of sparing subjects an additional treatment from the standard of care cabozantinib. The boundary and operational characteristics are described in Section 8.5.2

In case the SMC decides to decrease the M8891 dose during the expansion phase, then only subjects treated at the same dose will be considered in the 2-stage design. Therefore, the number of subjects in the expansion cohort might increase to reach the required number of 30 subjects treated on the same dose who are evaluable for response. The increase in sample size is limited to maximally 40 subjects in Part 2B.

8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Part 1, M8891 Single Agent, Solid Tumors

8.3.1.1 Primary Endpoints

The primary endpoint of the Part 1 of this trial is DLTs during the first 21-day treatment cycle, based on a predefined set of AEs, to determine the MTD.

8.3.1.2 Secondary Endpoints

Secondary endpoints include:

- Occurrence and severity of TEAEs, and deaths, including cause of death, from screening up to the End of Treatment Visit
- Changes in clinical laboratory measures, ECG measures, vital signs, ECOG PS
- PK parameters of M8891 after QD dosing:
  - C_{max}, t_{max}
  - $AUC_{0\text{-}t}$,
  - $AUC_{0\text{-}\infty}$,
  - $AUC_{0\text{-}\tau}$,
  - $t_{1/2}$,
  - λ_z,
  - CL/F,
  - CL_{ss}/F,
  - V_z/F,
  - Racc(AUC_τ)
  - Racc(C_{max})

  Time points for PK assessments for QD dosing: Cycle 1 Day 1: 0 hour (pre-dose within 60 minutes prior to each treatment administration) and 1 (± 10 minutes), 2 (± 10 minutes), 3 (± 10 minutes), 4 (± 20 minutes), 5 (± 20 minutes), 6 (± 30 minutes), 8 (± 30 minutes), 12 hours post-dose (± 60 minutes), on Day 2 at 24 hours post-dose (before next drug administration) (± 60 minutes). Cycle 1 Day 8: 0 hour (pre-dose within 60 minutes prior to treatment administration), Cycle 1 Day 15: 0 hour (pre-dose within 60 minutes prior to each treatment administration) and 1 (± 10 minutes), 2 (± 10 minutes), 3 (± 10 minutes), 4 (± 20 minutes), 5 (± 20 minutes), 6 (± 30 minutes), 8 (± 30 minutes), 12 hours post-dose (± 120 minutes), on Day 16 at 24 hours post-dose (before next drug administration) (± 60 minutes), 63 mL blood in Cycle 1. Cycle ≥2 Day 1: 0 hour (pre-dose within 60 minutes prior to each treatment administration).

- Best overall response (BOR: CR, PR, SD, or PD) according to RECIST v 1.1. criteria as assessed by Investigators
- Clinical benefit defined as CR, PR, or SD for ≥ 12 weeks
- PFS is defined as the time from first study drug administration to either first observation of PD (as assessed by RECIST v 1.1) or occurrence of death due to any cause, whichever occurs first.

8.3.1.3 Other Endpoints

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[redacted]

8.3.2 Part 2, M8891 with Cabozantinib, mRCC

Endpoints for Part 2A are provided in Table 6 and endpoints for Part 2B are provided in Table 7.

8.4 Analysis Sets

For purposes of analysis, the following populations are defined in Table 13.

Table 13 Analysis Sets

Population	Description
Screening	All subjects who sign informed consent
Dose Escalation	All subjects treated in dose escalation cohorts who either Part 1: • did not miss > 4 cumulative days of planned doses of M8891 in the first cycle of the dose escalation part or • who experienced a DLT Part 2A and 2B: • Received at least 80% of the planned cumulative dose of each treatment in the first cycle of the dose escalation part or • who experienced a DLT
Safety	The Safety Analysis Set will include all subjects who receive at least one dose of trial treatment.
Pharmacokinetic	All subjects from the safety analysis set without major protocol deviations/violations or events that would affect PK. Subjects in the PK analysis set must have received at least 1 dose of M8891, and M8891 combined with cabozantinib and have sufficient M8891/cabozantinib plasma concentration data to enable the calculation of at least one PK parameter. Sufficient concentration data is defined as at least 3 valid, post-dose concentration points in the PK profile to obtain any PK parameter.
Pharmacodynamics in WBCs	All subjects who received at least one dose of M8891 and provide the pre-dose and at least one post-dose WBC assessment. (Only for Part 1 of the study.)
CCI [redacted]	

PK: Pharmacokinetic; WBC: White blood cell.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

The following summary statistics will be used to summarize the trial data per Part and dose level unless otherwise specified:

- Continuous variables: number of not missing observations, mean, standard deviation, median, minimum, and maximum
- Categorical variables: frequencies and percentages.

All summary statistics will be described in detail in the respective Integrated Analysis Plan. There is no formal significance level for this trial and all analyses are considered descriptive.

The cutoff for the analysis will be as follows:

For the analysis after the end of Part 1, the cutoff will be Last Subject Last Visit (LSLV), or 4 months after the last subject enrolled into the monotherapy dose escalation cohort has finished their DLT period, whichever comes first.

For both dose escalation parts, the analysis will focus on the number of subjects experiencing a DLT. The SMC will receive results of a Bayesian two-parameter logistic model with overdose control updated with the observed DLT data for SMCs dedicated to dose escalation decisions (Babb 1998; Neuenschwander 2008). Recommendation is based on a loss function (probabilities of being in one of the four toxicity probability intervals will be multiplied with a loss term as follows:

0 * P(target dosing (0.17-0.33]) + 1 * P(for over (0.33-0.67] or under dosing [0-0.17]) + 2 * P(excessive dosing (0.67-1]).

Glossary:
(x.xx-y.yy] = lower limit excluded, upper limit included in the penalties
[x.xx-y.yy] = lower limit included, upper limit included in the penalties

In addition, only doses that have a corresponding probability of less than 25% that the true DLT rate is more than 33% (overdose control) are recommended by the model. The recommended dose level from the Bayesian model for the next cohort is the dose with the lowest loss function from all doses fulfilling the overdose control rule.

- MTD definition

The target DLT rate for the MTD definition is 30%. The MTD suggested by the model (if reached) will be defined as follows:

Highest tested dose with estimated DLT rate ≤ 30%. Additionally, the following needs to be fulfilled:

- The upper bound of the 95% credible interval of a potential MTD is not more than 40%

and

- The estimated DLT probability for the suggested MTD is above or equal to 17%.

The SMC will be notified of a potential MTD if a tested dose fulfills the above last 2 criteria. The SMC defines the MTD and can deviate from the suggestion of the model.

8.5.2 Efficacy Analysis

Summary statistics as described in Section 8.5.1 will be used for the summary of efficacy endpoints by dose level.

The 95% exact Clopper Pearson confidence intervals and, additionally for Part 2 posterior probabilities (2.5%, 25%, 50%, 75%, and 97.5% quantiles), for clinical benefit will be estimated.

Kaplan-Meier estimates (product-limit estimates) will be presented for the analysis of PFS together with a summary of associated statistics (median survival time, 6-, 12-, 18-, 24-month survival rate estimates and estimates for every 6 months thereafter if applicable) including the corresponding two-sided 95% confidence intervals. The confidence intervals for the median will be calculated according to Brookmeyer and Crowley (1982) and confidence intervals for the survival function

estimates at above defined time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (1980). The estimate of the standard error will be computed using Greenwood's formula.

The Safety Analysis Set will be used for the efficacy analyses.

Additionally, in Part 2B, a 2-stage design is planned with an interim analysis for futility after 15 subjects treated on the same dose who are evaluable for response are included in the study. If less than 4 responses are seen out of 15 subjects evaluable for response, the expansion cohort is stopped for futility. CCI [redacted] Else the study continues, until 30 subjects are evaluable for response.

8.5.3 Safety Analysis

All AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using CTCAE (version 4.03) toxicity grades.

For all study parts, AEs will be summarized according to MedDRA System Organ Classes (SOCs) and Preferred Terms. The incidence of the following TEAEs and SAEs will be analyzed:

- TEAEs and SAEs
- TEAEs and SAEs related to trial treatment
- TEAEs with CTCAE Grade ≥ 3
- TEAEs with CTCAE Grade ≥ 3 related to trial treatment
- TEAEs leading to withdrawal, dose modifications, temporary and permanent interruptions of trial drug, and death.

Of note, missing classifications concerning relationships with trial treatment will be considered related to the trial treatment.

Subjects who terminated treatment will be summarized by primary withdrawal reason by dose level.

All deaths after first dose of trial treatment as well as reasons for death will be tabulated.

Safety analyses will be performed on the safety population. The safety endpoints will be tabulated by dose-level, using descriptive statistics. Further details will be provided in the Integrated Analysis Plan based on current safety experience applying the latest MedDRA version.

8.5.3.1 Part 1 M8891 Single Agent, Solid tumors

The number and proportion of subjects experiencing DLTs will be reported by dose level, based on observations during the first treatment cycle.

Posterior probabilities (2.5%, 25%, 50%, 75%, and 97.5% quantiles) for DLT probabilities at selected doses will be estimated from the Bayesian logistic regression model. The Dose Escalation Analysis Set will be used for this analysis.

The Bayesian escalation approach will be used to assist the SMC to select the next dose from a predicted set of acceptable doses (e.g. 7, 12, 20, 35, 60, 100, 150, and 210 mg QD). The SMC may choose a different dose than suggested by the Bayesian escalation approach.

Subjects who miss > 4 cumulative days of planned doses of M8891 in the first cycle of the dose escalation part for other reasons than a DLT are not eligible for DLT assessment and will not be considered in the Bayesian model. Subject replacement will be considered based on reason for withdrawal and safety evaluation of cumulative data i.e. current and previous cohort data if applicable. If a subject out of a cohort of 3 is not eligible for the Bayesian model, the Bayesian model will be updated with the data from the evaluable subjects only and the SMC can decide upon next dose level.

The target probability for the MTD will be 30%.

The two-parameter logistic regression model will be set up as follows:

The relationship between dose and toxicity rate is defined by

$$P\left(DLT\middle|d_j,\alpha,\beta\right)=\frac{\exp\left(\alpha+\exp(\beta)*\log\left(\frac{d_j}{d_{ref}}\right)\right)}{1+\exp\left(\alpha+\exp(\beta)*\log\left(\frac{d_j}{d_{ref}}\right)\right)}$$

Where $d_j \in$(7 mg, 12 mg, 20 mg, 35 mg, 60 mg, 100 mg, 150 mg, 210 mg) (QD dosing) and (α,β) are bivariate normally distributed and the reference dose (d_{ref}) is 340 mg.

CCI [redacted] the following could be derived:

E(α)=log(0.8/0.2)=1.386

E(β)=log((log(0.33/0.67)-log(0.8/0.2))/log(210/340))=1.469

Variances are chosen as follows: Var(α)=2², Var(β)=2², Cov(α, β)=0.2

Posterior distribution and the recommended next dose level will be calculated using R version 3.1.2 or higher with library packages bcrm (Sweeting 2013) or crmPack (Bove 2019), or SAS Software version 9.3 or higher, or EAST version 6.4 or higher.

In Part 1, dose escalation will stop as soon as one of the following rules applies:

- A maximum number of 42 subjects are evaluable in dosing escalation (i.e. ≤4 missed planned doses in Cycle 1 except subject was qualified to have had a DLT)

- More than 4 cohorts are assigned to the same dose level,
- Or the estimate for DLT probability of the MTD reaches sufficient precision.

At least 6 subjects need to have been treated at the suggested MTD. That might necessitate the enrollment of additional subjects after dose escalation was stopped.

8.5.3.2 Part 2A M8891 with cabozantinib, mRCC

The Bayesian escalation approach will be used to assist the SMC to select the next dose from a predicted set of acceptable doses (e.g. 20, 35, and 60 mg QD) (See Section 5.1.3.2.1). The SMC may add or skip dose levels for others that are not part of the pre-specified set, but they will never exceed the dose level of M8891 that has already been declared to be safe in Part 1

The number and proportion of subjects experiencing DLTs will be reported by dose level, based on observations during the first treatment cycle.

Posterior probabilities (2.5%, 25%, 50%, 75%, and 97.5% quantiles) for DLT probabilities at selected doses will be estimated from the Bayesian logistic regression model. The same type of two-parameter logistic regression model will be used as described in Section 8.5.3.1 for Part 1.

The Dose Escalation Analysis Set will be used for this analysis.

If a subject out of a cohort of 3 is not eligible for the Bayesian model, the Bayesian model will be updated with the data from the evaluable subjects only and the SMC can decide upon next dose level.

The target probability for the MTD will be 30%.

The two-parameter logistic regression model will be set up using data from Part 1 and will be specified in the SMC charter prior to dosing of the first subject.

8.5.3.3 Part 2B M8891 with cabozantinib, mRCC

The SMC will continue to monitor the safety of M8891 combined with cabozantinib and may decide on continuation on the same dose, change in dose (not higher than MTD in Part 2A), modifications of the study protocol, or stop of expansion cohort. The same DLT criteria as for the monotherapy dose escalation will apply. If less than 6 subjects have been treated at the MTD / RDE selected in Part 2A, there will be an SMC meeting after the first 3 subjects have been treated in Part 2B at the MTD / RDE once these subjects have finished their DLT period or have dropped out, in order to additionally evaluate safety and tolerability at this dose. Enrollment will be suspended for this SMC. The SMC will also meet to evaluate the safety and tolerability (cumulative and unacceptable toxicity) of the combination therapy after 10 and 20 subjects have finished their DLT period or dropped out. Enrollment of subjects will not be interrupted between these SMCs.

The SMC decisions in the expansion cohort will also be supported by a two-parameter Bayesian logistic regression model, as described in Section 8.5.3.1 for Part 1. This model will either use the

same prior as Part 2A, or, if the data seen in Part 2A conflict with the prior, a new prior will be set up and will be specified in the SMC charter.

8.5.4 Pharmacokinetics

8.5.4.1 Descriptive Statistics

The PK variables will be analyzed descriptively for each dose level and day, separately. Descriptive statistics for PK concentrations are: number of non-missing observations (N), arithmetic mean (Mean), standard deviation, coefficient of variation (CV%), minimum, median and maximum. Descriptive statistics of PK Parameters should additionally show the geometric mean, the geometric coefficient of variation and the 95% confidence interval for the geometric mean. The drug concentration in plasma at each sampling time will be presented on the original scale for all subjects in the PK analysis set. Values below the LLOQ will be taken as zero for descriptive statistics of concentrations.

Individual plasma concentration-time profiles (linear and semi-logarithmic scale) will be plotted. Mean plasma concentrations per dose level and day will be plotted with standard deviation using scheduled time points. If evidence is given that the weight affects the PK parameters, the analyses will also be performed for weight normalized PK parameters.

All statistical tests will be performed in an exploratory way.

All analyses will be based on the PK data set.

Details of the statistical analyses will be described in the Integrated Analysis Plan.

8.5.4.2 Analysis of dose proportionality

For the assessment of dose proportionality, the PK endpoints, $AUC_{0-\tau}$ (or $AUC_{0-\infty}$ if appropriate), and C_{max} of M8891 will be compared between dose levels for Day 1 and Day 15 separately.

The PK parameters will be dose normalized. The dose normalized parameters and the overall mean will be plotted. Modeling on the log transformed scale will be applied to the dose normalized parameters including dose as covariate. Dose proportionality will also be checked using the power model, if appropriate. The relationship between the PK parameter y and the actual total dose is defined as follows:

$$y = \alpha \, dose^{\beta}$$

On the log transformed scale this becomes a linear relationship to which a linear regression approach can be applied:

$$\log(y) = \log(\alpha) + \beta * \log(dose)$$

The estimate of β and 95% confidence intervals will be computed to quantify dose proportionality. If dose proportionality is given, β in theory is equal to 0 and the estimate of the model should not deviate strongly from 0.

8.5.5 Analysis of Other Endpoints

Laboratory variables

Laboratory results will be classified by Grade according to NCI-CTCAE. The worst on-trial Grades after the first trial treatment will be summarized. Shifts in toxicity grading from first treatment to highest Grade will be displayed. Results for variables that are not part of NCI-CTCAE will be presented as below, within, or above normal limits. Only subjects with post-baseline laboratory values will be included in these analyses.

Physical examination (including vital signs)

Physical examination, vital signs (body temperature, respiratory rate, heart rate, and blood pressure) and ECG recorded at baseline and after drug administration will be presented. For Part 1 of the study, the ECG parameter will be summarized by descriptive statistics per time point, changes from baseline will be calculated. Data will be further analyzed using concentration effect modeling for baseline corrected QTcF interval values.

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8.6 Interim and Additional Planned Analyses

8.6.1 Part 1, M8891 Single Agent, Solid Tumors

The cutoff for dose escalation assessments by the SMC will be triggered by the completion of the DLT period (or drop-out) of the last subject in the respective cohort.

For the analysis after the end of dose escalation for monotherapy, the cutoff will be LSLV, or 4 months after the last subject enrolled into the monotherapy dose escalation cohort has finished their DLT period, whichever comes first.

Additional analyses during the study might be conducted, e.g. for publication purposes.

8.6.2 Part 2, M8891 with Cabozantinib, mRCC

In part 2A, the cutoff for dose escalation assessments by the SMC will be triggered by the completion of the DLT period (or drop-out) of the last subject in the respective cohort.

In Part 2B, there will be an interim analysis for futility after 15 subjects evaluable for response are included, as described in Section 8.5.2.

Additional analyses during the study might be conducted, e.g. for publication and decision-making purposes. Analyses for decision-making purposes will include analyses to assess whether the criterion for the 2-stage design of 11 responses (see Section 8.5.2.) has already been reached at an early read out.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

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

According to United States Code of Federal Regulations Part 54.2 (e), for trials conducted in any country that could result in a product submission to the United States Food and Drug Administration 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 trial and for 12 months following completion of the trial.

9.2 Subject Information and Informed Consent

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

information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

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

If permitted by national regulations, a person other than the Investigator may inform the subject about the trial 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 site and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and Informed Consent Form should be provided to the subject prior to participation.

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

9.3 Subject Identification and Privacy

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

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

The Investigator will complete the subject registration form and fax it to the subject registration center. If the subject meets all inclusion criteria and does not meet any of the exclusion criteria,

the subject registration center will receive confirmation, register the subject and inform the Investigator and the Sponsor of the registration number by fax. If the subject is ineligible for the trial, a subject number will be allocated and documented.

9.4 Emergency Medical Support and Subject Card

Generally, each subject will receive a card that includes certain minimum information pertaining to the trial, their participation, Investigator contact details and the appropriate Call Center Vendor or Phase I Unit for emergency medical support.

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

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, 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 Sponsor provides the appropriate means to contact a Sponsor physician. This includes the provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage will be provided and conditions shall meet good local standards, as applicable.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents to the responsible IEC or 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 IEC or 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 trial, the clinical trial 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 trial protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes (see Section 10.5). Relevant safety information will

be submitted to the IEC or IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

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

10 Trial Management

10.1 Case Report Form Handling

Refer to the Manual of Operations for eCRF completion guidelines.

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

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

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

10.2 Source Data and Subject Files

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

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site

- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

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

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

10.3 Investigator Site File and Archiving

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

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

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

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

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

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/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 site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3.

10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoints and will include data from all trial sites that provided evaluable data. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. 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.

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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 site personnel's: review of subject'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 hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. 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.

• 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 • Intrauterine hormone-releasing system • 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 subject.)
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 subjects 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 92 days (3 months) after the last dose of study treatment.

Appendix II Drugs which are potent combined CYP2C9, CYP2C19 and CYP3A4 inhibitors

Table 14 contains a list of drugs which are combined potent inhibitors of CYP2C9, CYP2C19 and CYP3A4 (moderate and/or potent inhibitors for at least 2 of the CYP enzymes).

Table 14 Combined Potent Inhibitors

	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP2C9	-	amiodarone, felbamate, fluconazole[a], miconazole, piperine	diosmin, disulfiram, fluvastatin, fluvoxamine[b], voriconazole
CYP2C19	Fluconazole[a], fluoxetine[c], fluvoxamine[b], ticlopidine	-	omeprazole, voriconazole
CYP3	boceprevir, cobicistat[d], conivaptan[d], danoprevir, ritonavir[e], elvitegravir, grapefruit juice[f], indinavir, itraconazole[d], ketoconazole, lopinavir, paritaprevir, ombitasvir, dasabuvir[e], posaconazole, saquinavir, telaprevir[d], tipranavir, troleandomycin, voriconazole, clarithromycin[d], diltiazem[d], idelalisib, nefazodone, nelfinavir[d]	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone[d], erythromycin, fluconazole[a], fluvoxamine[a], imatinib, tofisopam, verapamil[d]	chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor[d], lomitapide, ranitidine, ranolazine[d], tacrolimus, ticagrelor[d]

a) Strong inh bitor of CYP2C19 and moderate inhibitor of CYP2C9 and CYP3A.
b) Strong inh bitor of CYP1A2 and CYP2C19, and moderate inhibitor of CYP2D6 and CYP3A. Strong inhibitor of CYP2C8, weak inh bitor of CYP2B6, and inh bitor of OATP1B1.
c) Strong inh bitors of CYP2C19 and CYP2D6.
d) Inhibitor of P-gp (defined as those increasing AUC of digoxin to ≥1.25-fold).
e) Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.
f) The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inh bitor” when another preparation was used (e.g., low dose, single strength).

Note: Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold, ≥2 to < 5-fold, and ≥1.25 to < 2-fold, respectively. This table is prepared to provide examples of clinical inhibitors and is not intended to be an exhaustive list. Data are based on a search of the University of Washington Metabolism and Transport Drug Interaction Database (Hachad 2010). Additional information can be found in the Drug Interaction Flockhart Table. For further details and update refer to the websites: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2; https://drug-interactions.medicine.iu.edu/Main-Table.aspx.

Appendix III Laboratory Tests (Only for Part 2 of the study)

Serum Chemistry	Hematology	Coagulation
Albumin	Absolute lymphocyte count	Activated partial thromboplastin time
Alkaline phosphatase	Absolute neutrophil count	Prothrombin time/International normalized ratio (Quick, INR)
Alanine aminotransferase	Hematocrit	Thyroid function
Amylase	Hemoglobin	TSH
Aspartate aminotransferase	Platelet count	Free T4 (required at screening; after screening only if TSH is outside normal range)
Gamma glutamyltransferase	Red blood cell count	
Blood urea nitrogen/total urea	White blood cell count and differential count	
Calcium	Red blood cell morphology	
Chloride	Reticulocytes	
Creatinine	Mean corpuscular hemoglobin	
C-reactive protein	Mean corpuscular volume	
Glucose	Mean corpuscular hemoglobin concentration	
Lactate dehydrogenase		**Urine Chemistry**
Lipase		Protein (spot urine; fully quantitative)
Phosphorus/phosphates		Creatinine (spot urine; fully quantitative)
Magnesium		UPCR (spot urine)
Potassium		
Sodium	**Serology (at Screening only)**	**Serum and urine pregnancy test**
Total bilirubin/indirect bilirubin	HBsAg, HBcAb	Serum pregnancy test at screening
Total protein	HBV DNA (quantitative PCR)	Urine pregnancy test at Follow-up
Uric acid	HCVAb, HCV RNA (quantitative PCR)	
	HIV test	

HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HBV = Hepatitis B virus; HCV = hepatitis C virus; HCVAb = Hepatitis C virus antibody; HIV = Human immunodeficiency virus.

Full hematology, serum chemistry and coagulation will be performed at Screening, at timepoints indicated on the Schedule of Assessments (Table 1, Table 2, and Table 3) including at the EOT and Safety Follow-up visits.

Appendix IV Protocol Amendment History

The information for the current amendment is on the title page.

Amendment #1, 02 January 2018 (Global, Substantial), Protocol Version 2.0

This amendment was initiated by the Sponsor.

Major Scientific Changes

This amendment:

- Clarifies the procedure related to screening and dosing subjects for a next cohort during dose escalation
- Adds a recommendation for dose modification
- Removes the screening level of D-dimer from Exclusion Criterion #8
- Increases monitoring of lower extremity by Doppler ultrasonography and adds a stopping criterion related to this monitoring
- Removes potential inconsistencies between Section 7.6 and Section 9.3 regarding handling of samples after completion of the study
- Clarification of schedule for ECG.

Administrative and Editorial Changes

The following generally describes administrative and editorial changes included in this amendment:

- Window for PK sampling for Cycle 1 Day 15 increased from 60 min to 120 min.
- Table numbers adjusted.
- Typos on Schedule of Assessment (drug administration) corrected.
- The protocol version number and date were updated.
- Personnel were updated.
- Correction of errant punctuation.
- The Table of Contents was updated

Amendment #2, 27 August 2019 (Global, Substantial), Protocol Version 3.0

This amendment was initiated by the Sponsor.

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purpose of this amendment is to introduce investigation of M8891 combined with cabozantinib in subjects with metastatic renal cell carcinoma (mRCC) with clear cell component. This is referred to as Part 2, and the original investigation (dose escalation of M8891 single agent) is referred to as Part 1. This amendment additionally makes some changes to improve the study design and clarity of Part 1. Important changes from the previous protocol (Version 2.0) are included in the table below. Changes that do not meaningfully affect the design, conduct, or rationale for Part 1 are not included in the table below. Examples of revisions not included are those related to navigating or distinguishing the 2 parts of the study, minor edits to improve clarity, abbreviations, table/figure numbering, and formatting.

Section # and Name	Description of Change	Brief Rationale
Throughout	Added Part 2 for combination with cabozantinib. Part 2A for dose escalation and Part 2B for expansion cohort	Expand study to investigate M8891 combination therapy with cabozantinib.
Title page, Synopsis	Change in Coordinating Investigator Change in Medical Responsible	Administrative change and alignment with the clinical needs of the Part 2 of the study
Synopsis	More detailed specification of Part 1 population	Clarification
Synopsis	Revised Part 1 exclusion criteria related to thrombosis and Doppler ultrasonography	Updated guidelines regarding the mitigation of the risk for a thromboembolic event
Synopsis Section 2 (Sponsor, investigators, and trial administrative structure) Section 3.1 (Study rationale) Section 5.1.3 (Treatment period) Section 6.2.(Dosage and administration) Section 8.1 (Sample size) Section 8.3.1.2 (Secondary endpoints) Section 8.5.1 (General considerations)	Removed the potential for twice daily dosing of M8891 in Part 1	Initial findings from Part 1 have led to a focus on QD dosing only
Synopsis / Schedule of Assessments	Schedule of Assessments for Part 2, including detailed Table 4 and 5 for PK and safety ECGs assessments	Clarity
Schedule of Assessments for Part 1	Revised monitoring related to coagulation and Doppler	Updated guidelines regarding the mitigation of the risk for a thromboembolic event
Schedule of Assessments for Part 1	Footnote on imaging analysis has been updated	Consistency with Schedule of Assessments for Part 2
Schedule of Assessments for Part 1	Footnote on detailed neurological examination has been deleted	No longer considered relevant for the study
Section 3 (Background information)	Reorganized into 3 subsections (study rationale, background, benefit risk) disperse original Part 1 text into these subsections and integrate with Part 2 information.	Clarity
Section 3.3 (Benefit/risk assessment)	Updated information regarding M8891 PK based on preliminary results of Part 1, including new estimated biologically effective dose.	New clinical PK data available.

Section # and Name	Description of Change	Brief Rationale
Section 3.3 (Benefit/risk assessment)	Updated discussion of potential M8891 safety concerns based on preliminary results from Part 1	New clinical safety data available.
Section 5.1	Additional detail on Part 1 population	Clarification
Figure 1	New study design figure incorporation Part 2	Clearly represent Part 1, Part 2A and Part 2B of the study in a schematic.
Section 5.1.2 (Doppler Ultrasonography)	New discussion of monitoring with Doppler ultrasonography in Part 1 and new approach for Part 2	Updated guidelines and information on other MetAP2 inhibitors.
Section 5.1.3.1 (Part 1 M8891 single agent, solid tumors)	Explanation of the criteria for the dose escalation	Clarification
Section 5.1.3.1 (Treatment Period, M8891 single agent, Solid Tumors)	Clarification of actions that may be taken by Safety Monitoring Committee	Clarification
Section 5.1.3.3 (Dose-limiting Toxicities)	Clarification of the roles of dose limiting toxicity data in this study	Clarification
Section 5.1.3.3 (Dose-limiting Toxicities)	Revisions to criteria for some dose limiting toxicities	Clinical judgement for the safety of the subjects
Section 5.1.3.5 (Dose Modification)	Revisions to criteria for M8891 dose modification.	Clarification for dose modification of M8891 as single agent and combined with cabozantinib outside of the DLT period
Section 5.2 (Discussion of Trial Design)	Reduced discussion of general trial design.	Extensive discussion in Section 3 (Study Rationale, Background and Benefit/Risk assessment)
Section 5.3.2 (Exclusion Criteria)	Modified Part 1 exclusion related to participation in another clinical study / other investigational agents	Corrected wording
Section 5.3.2.1 (Exclusion Criteria)	Modified Part 1 exclusion related to deep vein thrombosis / thromboembolic events.	Accuracy on the clinical utility of doppler ultrasonography and safety of the patients
Section 5.3.2.1 (Exclusion Criteria)	Modified Part 1 exclusion related to stroke, heart attack, thrombosis (e.g. deep vein thrombosis and pulmonary embolism) or genetically-determined hypercoagulopathy	Accuracy and clarification. Thromboembolic events are included as exclusion criteria number 7.
Section 5.5.1 (Withdrawal from trial therapy)	Added criteria related to ECG findings and to stroke	Relevant to therapy with cabozantinib
Section 5.5.2 (Withdrawal from the trial)	Additional criteria for withdrawal and clarification of subsequent activities	Administrative
Section 5.5.2 (Withdrawal from the trial)	Explanation of replacement of subjects	Clarification
Section 5.7 (Definition of end of trial)	Clarification of disposition of subjects on ongoing treatment.	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 6.2.1 (Dosage and administration)	Added instruction on withholding water around dosing	Clarification
Section 6.5.5 (Management of specific adverse events…)	List anticipated M8891 toxicities based on nonclinical data.	Clarification
Section 6.8 (IMP Accountability)	Clarification to collection of accountability forms	Clarification
Section 7.3 (Efficacy assessments)	Time points for efficacy assessments have been accurately defined	Clarification
Section 7.4.1.3 (Definition of the Adverse Event Reporting Period)	The window period of the EOT visit and the safety follow-up period has been updated	Clarification
Section 7.4.3 (Clinical laboratory assessments) Section 7.5. (Pharmacokinetics)	Reference to blood volumes in Laboratory Manual	Clarification
Section 7.4.4 (Vital signs, physical examinations, and other assessments); Section 8.5.5 (Analysis of other endpoints)	Physical exam no longer includes a complete neurological exam	Medical evaluation that this is no longer warranted.
Section 7.4.5 (Electrocardiograms)	New Section 7.4.5 that includes an updated explanation of ECG evaluations.	Clarity: Part 1 ECGs for QTcF interval evaluation; Part 2 Safety ECGs
Section 8.4	Revised dose limiting toxicity as included in Dose Escalation analysis set.	Clarification and consistency with the ongoing data analysis
Section 8.5 (Statistics)	Subsections reordered	Improve flow of text.
Section 8.5.1 (General considerations)	Updated to include the new timing for the Part 1 analysis and the definition of MTD	Clarification
Section 8.5.2 (Efficacy analysis)	Added information on confidence intervals for all the study and posterior probabilities for Part 2	Clarification on the statistical analysis plan for efficacy
Section 8.5.3 (Safety analysis)	Safety analysis for Part 1 has been updated to include when subject replacement will be considered	Clarification
Section 8.5.3. (Safety analysis)	Addition of posterior probabilities for DLT analysis in Part 1	Clarification on the statistical analysis plan for safety
Section 8.6 (Interim and additional planned analyses)	Updated to include the new timing for the Part 1 analysis	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 11 (References cited)	References added	To support new text, primarily related to Part 2
Appendix II	Updated to include more details on pan-inhibitors that simultaneously inhibit CYP2C9, 2C19 and 3A4	Clarity and relevant to therapy with cabozantinib
Previous Appendix III (Blood Volumes)	An appendix on blood volumes is no longer included in the protocol	The exact blood volume will be indicated in the Laboratory Manual The limit on total blood volume has been added in the protocol at the respective sections related with blood collection
Previous Appendix V (Protocol Amendments and List of Changes)	Replaced by current Appendix IV (Protocol Amendment History) and this Summary of Changes	Details of changes from Version 1.0 to 2.0 no longer relevant, and only summary now provided. Summary of current changes from Version 2.0 to 3.0 provided in a more succinct and clearer format.
Previous Appendix V table “Comparison with Clinical Trial Protocol Version 1.0, 28 March 2017)”	Deleted	No longer relevant with this amendment from Version 2.0 to 3.0.
Signature pages	Updated for Sponsor’s signatory, Coordinating Investigator, and other Sponsor Responsible Persons	New personnel

Appendix V Signature Pages and Responsible Persons for the Trial

Sponsor Signature Page

Study Title:	An Open-label, Phase I, Dose Escalation Trial of Methionine Aminopeptidase 2 Inhibitor M8891 in Subjects with Advanced Solid Tumors
IND Number:	PPD
Clinical Study Protocol Version:	11 March 2020 / Version 4.0

I approve the design of the clinical study:

PPD

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	Medical Responsible
Institution:	Merck Healthcare KGaA.
Address:	Frankfurter Str. 250, 64293 Darmstadt, Germany
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Signature Page –Coordinating Investigator

Trial Title	An Open-label, Phase I, Dose Escalation Trial of Methionine Aminopeptidase 2 Inhibitor M8891 in Subjects with Advanced Solid Tumors
IND Number	PPD
Clinical Trial Protocol Date / Version	11 March 2020 / Version 4.0

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

PPD PPD

Signature Date of Signature

Name, academic degree: PPD

Function / Title: PPD

Institution: PPD

Address: PPD

Telephone number: PPD

Fax number:

E-mail address: PPD

Signature Page – Principal Investigator

Trial Title	An Open-label, Phase I, Dose Escalation Trial of Methionine Aminopeptidase 2 Inhibitor M8891 in Subjects with Advanced Solid Tumors
IND Number	PPD
Clinical Trial Protocol Date / Version	11 March 2020 / Version 4.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation 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 trials 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.

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Sponsor Responsible Persons Not Named on the Cover Page

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

Sponsor Responsible Persons Not Named on the Cover Page

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	Merck Healthcare KGaA
Address:	Frankfurter Str. 250, Darmstadt, Germany
Telephone number:	PPD
Fax number:	NA
E-mail address:	PPD

Sponsor Responsible Persons not Named on the Cover Page

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