Clinical Study Protocol

Clinical Study Protocol Number	MS201408-0005
Title	Phase I, First-in-Human, Open-Label, Multiple-Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M4112 an IDO1/TDO2 Inhibitor as Single Agent CCI CCI CCI in Subjects with Metastatic or Locally Advanced Unresectable Solid Tumors
Phase	I
IND Number	CCI
EudraCT Number	To be determined
Coordinating Investigator	PPD Phone: PPD Fax: PPD Email: PPD
Sponsor	Countries outside US: Merck KGaA Darmstadt, Germany. US and Canada: EMD Serono Research & Development Institute, Inc., Billerica, MA, US. Medical Responsible: PPD Merck KGaA Frankfurter Strasse 250, 64293 Darmstadt, Germany Phone: PPD Mobile: PPD Email: PPD
Sponsor Legal Representative in the European Union	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
Clinical Study Protocol Version	08 September 2017 / Version 2.0
Replaces Version	28 July 2017 / Version 1.0

[redacted]

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List of Abbreviations

7+n×3	After treatment Cycle 7 subjects will be assessed at the start of every third cycle
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
AESI(s)	Adverse event(s) of special interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the drug concentration-time curve
AUC_{0-8}	Area under the drug concentration-time curve from 0 to 8 h postdosing
βHCG	β-human chorionic gonadotropin
BID	Twice daily
BOR	Best overall response
CD	Cluster of differentiation
CI	Confidence interval
C_{max}	Maximum plasma concentration observed postdose
C_{min}	Minimum observed postdose (trough) plasma concentration
CR	Complete response
CRO	Contract Research Organization
CT	Computed tomography
CTCAE 4.03	Common Terminology Criteria for Adverse Events Version 4.03
cQTc	Concentration-QTc
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicities
DOR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form

E_{max}	Maximum effect
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
H1	Histamine H1
HBcAb	Hepatitis B core antibody
HBsAb	Antibody to hepatitis B surface antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCVAb	Hepatitis C virus antibody
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
iAP	Integrated analysis plan
IB	Investigator's Brochure
IC_{50}	Half maximal effective concentration
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDO1	Indoleamine-2,3-dioxygenase 1
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
IMP(s)	Investigational Medicinal Product(s)
INF	Interferon
irAE	Immune-related adverse event
IRB	Institutional Review Board
irPD	Immune-related progressive disease
irPR	Immune-related partial response
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
iv	Intravenous

CCI	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not evaluable
NK	Natural killer
NOAEL	No-observed-adverse-effect-level
NSAID	Nonsteroidal anti-inflammatory drug
OBD	Optimal biological dose
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamics
CCI	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PFS	Progression-free survival
CCI	[redacted]
PK	Pharmacokinetic(s)
PPI	Proton pump inhibitor
PR	Partial response
Q 2 weeks	Once every 2 weeks
Q 4 weeks	Once every 4 weeks
Q 8 weeks	Once every 8 weeks
Q 12 weeks	Once every 12 weeks
QD	Once daily
QTc	Corrected QT interval
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Standard deviation
SMC	Safety Monitoring Committee

T4	Thyroxine
TDO2	Tryptophan-2,3-dioxygenase 2
TEAE	Treatment-emergent adverse event
CCI	[redacted]
[redacted]	[redacted]
TLS	Tumor lysis syndrome
t_{max}	Time to reach maximum concentration
TMTB	Total measured tumor burden
TNF	Tumor necrosis factor
TRAE	Treatment-related adverse event
Tregs	Regulatory T cells
CCI	[redacted]
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

1 Synopsis

Clinical Study Protocol Number	MS201408-0005
Title	Phase I, First-in-Human, Open-Label, Multiple-Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M4112 an IDO1/TDO2 Inhibitor as Single Agent CCI [redacted] CCI [redacted] in Subjects with Metastatic or Locally Advanced Unresectable Solid Tumors
Phase	I
IND Number	CCI [redacted]
FDA covered study	Yes
EudraCT Number	To be determined
Coordinating Investigator	PPD [redacted] Phone: PPD Fax: PPD Email: PPD
Sponsor	Countries outside US: Merck KGaA Darmstadt, Germany. US and Canada: EMD Serono Research & Development Institute, Inc., Billerica, MA, US. Medical Responsible: PPD [redacted] Merck KGaA Frankfurter Strasse 250, 64293 Darmstadt, Germany Phone: PPD Mobile: PPD Email: PPD

Sponsor Legal Representative in the European Union	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
Study centers/countries	Approximately 3 to 5 sites in the US for the dose escalation part (Part I).
Planned study period (first subject in-last subject out)	October 2017 to April 2020
Trial Registry	ClinicalTrials.gov and other applicable registries

Objectives:

Primary Objectives

Part IA (Dose Escalation – M4112 as Single Agent)

- To determine safety and tolerability or, if observed, the maximum tolerated dose (MTD), and to define the recommended Phase II dose (RP2D) of M4112 as single agent in subjects with solid tumors.

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Secondary Objectives

Part IA (Dose Escalation – M4112 as Single Agent)

- To characterize the PK parameters of M4112 as single agent
- To assess QT prolongation potential by central tendency, outlier analysis and the slope of exposure-QTc analysis
- To evaluate preliminary clinical activity parameters using RECIST 1.1.

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Methodology:

This study is a Phase I, open-label study designed to determine the safety, tolerability, PK, PD, and preliminary antitumor activity of M4112 as single agent (Part IA only) CCI [redacted] The target population for Part I (Dose Escalation) comprises of subjects with advanced or metastatic solid malignancies for whom no effective standard therapy exists or has failed or subjects who are intolerant to established therapy known to provide clinical benefit for their condition.

The study for an individual subject will include up to 21 + 7 days screening period, a treatment period consisting of 28-day cycles of M4112 either as single agent CCI [redacted], End of Treatment Visit, and a Safety Follow-up period including a visit at 30 ± 3 days CCI [redacted] after the last M4112 intake CCI [redacted] if applicable. M4112 will be administered orally twice daily (BID; or regimen determined by the Safety Monitoring Committee [SMC]). Subjects who tolerate M4112 without significant clinically relevant toxicities may continue to receive their assigned dose as long as there is no evidence of confirmed disease progression. Subjects who discontinue treatment for any reason will complete the Safety Follow-up Visits.

Screening Period:

Screening will be performed within 21 + 7 days prior to Day 1 of M4112 administration. If, at Screening, the subject meets all the protocol-defined inclusion and none of the exclusion criteria, the subject will be considered as eligible and will be enrolled into the study. Subjects who fail to meet the protocol-specified criteria or who withdraw their consent will be considered screening failures.

Treatment Period:

The treatment period will begin at the first dose of M4112 in Cycle 1 Day 1 and consist of consecutive 28-day cycles of continuous M4112 treatment (BID or other regimen determined by the SMC) either as monotherapy CCI [redacted] Subjects will be instructed to take M4112 at least 1 h prior to a meal and at least 2 h after a meal.

Subjects who tolerate study treatment without clinically relevant toxicities may continue to receive their assigned dose as long as there is no evidence of confirmed disease progression.

Part IA to Part IC: Dose Escalation

A broad dose range in monotherapy will be investigated to determine the safety profile, tolerability, PK, and PD markers and to explore signs of antitumor activity in subjects with advanced solid tumors.

Subjects will receive M4112 at the starting dose of 100 mg BID (100 mg BID which equals to 200 mg total daily dose) at least 1 h prior to a meal and at least 2 h after a meal. Cohorts

will consist of 3 subjects each, if not decided differently by the SMC. The first subject of each dose level will be observed for at least 5 days before the second subject can be treated. Subsequent subjects may receive first dosing at no less than 48 h intervals between subjects for the first 2 cohorts of mono CCI . If the safety profile is acceptable and agreed by the SMC, the 48 h observation after Subject 2 may be removed). The safety and tolerability data and available PK and PD data (as minimum Day 1 and Day 15 PK and PD data from previous cohort and all available PK and PD data from the current cohort) will be reviewed by the SMC at the end of each cohort. In cases where enrollment of 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 Cycle 1. The SMC will be assisted in their dosing and regimen (administration schedule) decisions by PK, PD, and a Bayesian 2-parameter logistic regression model modeling dose-limiting toxicity (DLT) rate with overdose control. The model incorporates nonclinical toxicity data in the prior and DLTs observed until the SMC to provide a recommended dose for the next cohort. During the dose escalation part of the study, the SMC will advise, primarily based on safety (DLTs) and additional data relevant for the treatment, on dose escalation, dose de-escalation, dose level expansion or regimen change, or it may recommend suspension of enrollment, with the final decision being a Sponsor decision. The SMC may also recommend a cohort size different from 3 subjects as the Bayesian design allows dose recommendation based on less or more than 3 subjects.

Prespecified ascending doses of 100, 200, 400, 600, 800, and 900 mg BID (means respectively, 100 mg BID for 200 mg total daily dose, 200 mg BID for 400 mg total daily dose, 400 mg BID for 800 mg total daily dose, 600 mg BID for 1,200 mg total daily dose, 800 mg BID for 1,600 mg total daily dose, 900 mg BID for 1,800 mg total daily dose) as single agent in 28-day cycles are foreseen. Dose escalation decisions will be driven primarily by DLT, safety, and tolerability. CCI

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A BID dosing regimen will be followed, based on PK modelling, to achieve the target C_{min} over the dosing interval at a lower total daily dose and thereby reducing C_{max} and AUC over the day to potentially improve safety and tolerability when compared to once daily (QD) dosing. Based on PK data from subjects, the SMC will evaluate whether this regimen can be sustained or needs to be changed.

In principle, dose escalation of single agent M4112 (Part IA) will proceed according to the recommendation of the SMC to at least the upper end of the above given dose range, unless the MTD has been reached or there is excess of PK nonlinearity, or the SMC recommends to end dose escalation following review of safety, tolerability, PK and PD results. Depending on the observed toxicity profile and available PK and PD, a dose regimen different to or dose(s) higher/lower than the prespecified doses may be tested.

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The starting dose of M4112 CCI will be dependent on the observed safety, tolerability, and PK/PD profile during dose escalation in the single agent cohort (Part IA) and will lag at least 1 dose level behind the last completed safe dose level of M4112 as single agent, which was confirmed as safe by the SMC. CCI

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DLT Definition

DLTs will be used to determine dose escalation, dose de-escalation, and the MTD (if reached), using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE 4.03). DLTs are defined in the clinical study protocol.

All subjects treated in dose escalation cohorts who miss > 5 planned total daily doses of M4112 CCI in the first cycle (first 28 days) of the dose escalation part for other than safety reasons are not eligible for DLT assessment, will not be considered in the Bayesian model and will not formally be replaced. If no evaluable subject from a cohort is left, the SMC will still convene to decide upon the continuation of the study and the number of subjects for the next cohort.

Subjects with nausea and vomiting will maintain normal schedule without re-dosing.

The MTD is defined by the SMC. An MTD is suggested from the Bayesian logistic regression model with target toxicity of 30%.

Subjects who tolerate M4112 CCI without significant clinically relevant toxicities will continue to receive their assigned dose until discontinuation criteria are met, withdrawal of consent or the study ends, whatever occurs first.

Follow-up Period:

The Safety Follow-up Visit is scheduled 30 ± 3 days and 90 ± 6 days (for Part IB and Part IC; as a phone call) after the last dose of M4112, CCI CCI until resolution of AEs to Grade 1, before start of any new anticancer therapy, whatever comes first.

Subjects who discontinue treatment must be followed on study until resolution of toxicity or until confirmed disease progression.

Planned number of subjects:

Part I (A to C; Dose Escalation): Monotherapy escalation A: Approximately 24 subjects, CCI .

Primary endpoints:

Part IA (Dose Escalation – M4112 as Single Agent)

- Occurrence of DLTs in subjects receiving M4112 as single agent during the first 4 weeks (Day 1 to Day 28 of Cycle 1) of treatment
- Occurrence of treatment-emergent adverse events (TEAEs) and TRAEs according to NCI-CTCAE 4.03 (including deaths) in subjects receiving M4112 as single agent from start of treatment up to the last Safety Follow-up Visit
- Treatment-emergent changes from baseline in clinical laboratory measures, vital signs, Eastern Cooperative Oncology Group Performance Status (ECOG PS), and physical examination findings in subjects receiving M4112 as single agent up to the last Safety Follow-up Visit.

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Secondary endpoints:

Part IA (Dose Escalation – M4112 as Single Agent)

- Plasma PK parameters for M4112: AUC_{0-8}, C_{max}, t_{max}, $AUC_{0-8/dose}$, $C_{max/dose}$, (Days 1 and 15), $R_{acc(AUC0-8)}$ and $R_{acc(Cmax)}$ (Day 15), C_{min}, and $C_{min/dose}$ (Days 8 and 15 of Cycle 1 and Day 1 of Cycle 2)
- Slope of concentration-QTc (cQTc) regression based on time-matched electrocardiogram (ECG) readings (3 or more replicates) and PK samples during Cycle 1 at Day 1 and Day 15, central tendency and outlier analyses for absolute QTcF, and delta QTc
- BOR, DOR, DCR, time to tumor response, and PFS using RECIST 1.1, up to confirmed tumor progression.

[redacted]

CCI [redacted]

Concentration-QTc and safety ECG:

Time-matched ECG readings (3 or more replicates) will be collected at -45, -30, and -15 min predose and at 0.5, 1, 2, 3, 4, 6, and 8 h postdose, just prior to PK sample collections during Cycle 1 at Day 1 and Day 15 during Part IA (M4112 monotherapy).

Safety ECG: Time-matched triplicate digital ECG will be collected (upload for central read) at Day 1 and Day 15 (time points) predose, and 2, 3, 4, and 8h postdose, just prior PK collections in Part IB and IC.

Pharmacokinetics:

- Pharmacokinetic parameters for M4112 will be based on plasma concentrations collected predose and at 0.5, 1, 2, 3, 4, 6 and 8 h postdosing on Days 1 and 15 of Cycle 1. Predose concentrations on Day 8, Cycle 1 and predose and 2 h postdose on Day 1, Cycle 2 will be assessed.
- CCI [redacted]

[redacted]

Efficacy assessments:

In addition to a baseline assessment prior to start of treatment, during treatment, computed tomography (CT) scans will be done for tumor assessments within 7 days prior to Day 1 of Cycles 3, 5, and 7 and thereafter every 3 cycles until progressive disease. These assessment can also be done by magnetic resonance imaging (MRI; if MRI is used, CT of chest is mandatory), using the same method at all subsequent assessment time points. Follow-up assessments will be performed at time points indicated in the Schedule of Assessments.

The clinical endpoints to be assessed for efficacy evaluation include time to tumor response, objective response, BOR, DCR, DOR, and progression-free survival per Investigator according to RECIST 1.1.

Safety assessments:

The safety profile of M4112 will be assessed through the recording, reporting and analysis of baseline medical conditions, adverse events (AEs), adverse events of special interest (AESIs), DLTs in Cycle 1 and any treatment-emergent immune-related AE observed in subsequent cycle (Cycle 2) that in the opinion of the SMC needs to be taken into account for safety and proposal of dose escalation, physical examination findings including vital signs, laboratory tests (chemistry, hematology, and coagulation), ECOG PS, and a 12-lead ECG in triplicate from the date of signature of first informed consent until the either until the 30 ± 3 days Safety Follow-up Visit, or until the 90 ± 6 days Safety Follow-up Visit (Part IB and Part IC only; as a phone call), or before the start of any anticancer therapy, whatever comes first.

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[redacted]

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Diagnosis and key inclusion and exclusion criteria:

Key inclusion criteria for Part IA, CCI

Male or female subjects ≥ 18 years of age with histologically or cytologically proven advanced or metastatic solid malignancies for whom no effective standard therapy exists or has failed or subjects who are intolerant to established therapy known to provide clinical benefit for their condition (dose escalation cohorts; Part I) An ECOG PS of 0 to 1 at Screening and adequate hematological, renal and hepatic function as defined by protocol specified criteria.

Key exclusion criteria for Part IA, CCI

Intolerance to immune checkpoint inhibitor therapy as defined by the occurrence of an adverse drug reaction requiring drug discontinuation (dose escalation cohorts), concurrent anticancer treatment or immunosuppressive agents.

Prior organ transplantation including allogeneic stem cell transplantation, brain metastases (except those meeting certain protocol specified criteria which are acceptable), significant acute or chronic infections, a history of cardiovascular/cerebrovascular disease or current significant cardiac conduction abnormalities and hypokalemia as specified in the protocol.

Warfarin or other Vitamin K antagonists treatment, strong inhibitors or inducers of cytochrome P450 (CYP)3A4, and drugs with a narrow therapeutic index, which are predominantly metabolized by CYP3A4 and drugs known to have a high risk to prolong QTc as per label.

Pregnancy or lactation.

Severe hypersensitivity reactions to monoclonal antibodies, known hypersensitivity to the IMPs or to one or more of the excipients of M4112, CCI, autoimmune diseases (inflammatory bowel diseases, interstitial lung disease, or pulmonary fibrosis), and live vaccines within 28 days prior to study entry.

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

Part I (A CCI **):**

M4112: Subjects will be administered an oral dose of M4112 BID (or a regimen determined by the SMC) at least 1 h prior to a meal and at least 2 h after a meal in 28-day cycles. CCI CCI .

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CCI [redacted]

CCI [redacted]

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

Planned study and treatment duration per subject:

The study for an individual subject will include up to 21 + 7 days screening period, a treatment period consisting of 28-day cycles of M4112 either as single agentCCI [redacted] End of Treatment Visit, and a Safety Follow-up period including a visit at 30 ± 3 days and a visit at 90 ± 6 days (Part IB and Part IC only; as a phone call) after the last M4112 intakeCCI [redacted] Subjects who tolerate M4112 without significant clinically relevant toxicities may continue to receive their assigned dose as long as there is no evidence of confirmed disease progression.

Statistical methods:

Analyses will be prepared by cohort and dose level. There is no formal significance level for this study and all analyses are considered descriptive. Dose escalation will be aided by a Bayesian 2-parameter logistic regression model. The SMCs dedicated to dose escalation decisions will receive results of a Bayesian 2-parameter logistic model with overdose control updated with the observed DLT data. Recommendation will be based on a loss function.

Table 1 Schedule of Assessments – Part IA (Dose Escalation – M4112 as Single Agent)

Duration (Days)		28				28		28		28		28		28		28	nx28		
Assessment	Screening[b]	Treatment Period																End of Treatment	Safety Follow-up
Treatment Cycle (28-day cycles)		1 (DLT observation period)				2		3		4		5		6		7	7+n×3 Until Progression	Within 7 Days of Decision to Discontinue[c,d]	30 ± 3 Days
Visit Day[a]	21 + 7	1	8	15	22	1	15	1	15	1	15	1	15	1	15	1	1		
Written informed consent	X																		
Review of inclusion/exclusion criteria	X	X[e]																	
Demographic data	X																		
Medical history including malignant disease and malignant disease drug therapy or radiotherapy or surgery	X																		
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q 4 weeks	X	X
Physical examination[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q 4 weeks	X	X
Height/weight/vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q 4 weeks	X	X
ECOG PS	X	X		X		X		X		X		X		X		X	Q 4 weeks	X	X
Chest X-ray	X																		
Triplicate digital 12-lead electrocardiogram[h]	X	X	X	X		X				X				X			Q 8 weeks	X	X
Hematology[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q 4 weeks	X	X
Coagulation[j]	X	X		X		X				X				X		X	Q 8 weeks	X	X
Serum chemistry[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q 4 weeks	X	X
Troponin–T[k]		X		X		X	X	X	X										
CCI [redacted]		[redacted]																	

Duration (Days)		28				28		28		28		28		28		28	nx28		
Assessment	Screening[b]	Treatment Period																End of Treatment	Safety Follow-up
Treatment Cycle (28-day cycles)		1 (DLT observation period)				2		3		4		5		6		7	7+n×3 Until Progression	Within 7 Days of Decision to Discontinue[c,d]	30 ± 3 Days
Visit Day[a]	21 + 7	1	8	15	22	1	15	1	15	1	15	1	15	1	15	1	1		
Free T4, TSH	X			X				X				X				X	Q 8 weeks	X	
Hepatitis B and C[m]	X																		
Serum, urine pregnancy test (if applicable)[n]	X	X				X		X		X		X		X		X	Q 4 weeks		X
Urinalysis[o]	X	X						X				X				X	Q 8 weeks	X	X
M4112 dispensation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q 4 weeks		
M4112 administration		Continuous administration[p]																	
M4112 compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q 4 weeks	X	
Adverse events assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Q 4 weeks	X	X
CCI																			
PK blood sample for M4112 as single agent[r]		X	X	X		X													
CCI																			
CCI																			
CCI																			
4β-hydroxycholesterol and cholesterol[t]		X		X					X										
CT (chest, abdomen, pelvis) or MRI[u]	X							X				X				X	Q 12 weeks		
Tumor evaluation, staging[u,v]	X							X				X				X	Q 12 weeks		

Treatment cycles: 28 days; after treatment Cycle 7 (on Day 1 only) subjects will be assessed at the start of every third cycle (7+n×3).

aPTT = activated partial thromboplastin time; CD = cluster of differentiation; CT = computed tomography; ECG = electrocardiogram; DLT = dose-limiting toxicities; ECOG PS = Eastern Cooperative Oncology Group Performance Status; βHCG = β-human chorionic gonadotropin; HBcAb = hepatitis B core antibody; HBsAb = antibody to hepatitis B surface antigen; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; CCI ; Ig = immunoglobulin; IL = interleukin; INF = interferon; CCI ; MRI = magnetic resonance imaging; NK = natural killer; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; CCI PK = pharmacokinetic; TNF = tumor necrosis factor; CCI ; TSH = thyroid-stimulating hormone; QTc = corrected QT interval.

a Time window of assessment visits: Cycle 1 and 2: ± 1 day; every cycle thereafter: ± 3 days.

b Screening tests must be performed within 21 + 7 days before the first administration of M4112, unless indicated otherwise.

c All subjects should undergo an End of Treatment Visit after M4112 is discontinued for any reason. This visit should be performed within 7 days after the decision to discontinue study treatment but before any new antineoplastic therapy is started (if possible), whichever occurs earlier.

d All subjects who discontinue M4112 treatment must undergo the End of Treatment Visit (within 7 days) and Safety Follow-up Visit (within 30 ± 3 days) for full safety evaluation.

e Inclusion/exclusion criteria should be reviewed before Cycle 1 Day 1 before the subject's enrollment, which needs to be confirmed by the Sponsor (see Section 5.3).

f The physical examination at Screening will including, general appearance, skin, pulmonary, cardiovascular, gastrointestinal, external genitourinary only as medically relevant, lymphatic, neurologic and musculoskeletal systems, head/neck, extremities, eyes, ears, nose, throat, and cognitive status.

g On Day 1 and Day 15 of every cycle, vital signs (blood pressure, pulse, respiratory rate, temperature) will be assessed predose (within 15 min of oral dosing after the subject has rested in the semi-recumbent position for 3 to 5 min), and then every 15 min from dosing of M4112 for an additional 2 h. Observation can be extended per investigator's discretion. Height and weight at Screening only.

h For ECG time points of safety monitoring: 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 at Screening, predose and 2, 3, 4 and 8 h postdose on Days 1 and 15 of Cycle 1, predose on Day 8 of Cycle 1, and on Day 1 Cycle 2 (and + 2 h postdose), Day 1 Cycle 4, Day 1 Cycle 6 and then every second cycle thereafter at predose and at least 60 min postdose on these visits. ECGs will be also performed during the End of Treatment and Safety Follow-up Visit (30 ± 3 days). Triplicate ECGs will be read locally. The calculated QTc average of the three 12-lead ECGs must be ≤ 450 ms for continued eligibility. Subjects, in which the calculated QTc average increases to > 500 ms or > 60 ms change over baseline during treatment with M4112, have to interrupt study treatment until further clinical evaluation of QT prolongation.

During single agent dose escalation (Part IA), replicate digital 12-lead ECGs within 2 min after a minimum of 5 min rest in semi-recumbent position will also be collected on Days 1 and 15 of Cycle 1 for concentration-QTc analysis, for time points, see Table 4.

For Part 1A only, replicate ECGs (Holter) will also be collected on Days 1 and 15 of Cycle 1 for exposure-QTc analysis.

i Hematology includes complete blood count with differential and platelet counts. Blood samples for hematology will be obtained prior to administration of study drug (see Table 10).

j Coagulation with aPTT and prothrombin time. Blood samples will be collected prior to administration of study drug (see Table 10).

k Blood samples for serum chemistry profile will be obtained prior to the administration of the study drug (see Table 10). Full serum chemistry will be performed at Screening and in Cycle 1 on Day 1 and Day 15; core chemistry in Cycle 1 on Day 8 and Day 22. In Cycle 2 to 6 thereafter, full chemistry will be performed on Day 1 and core chemistry on Day 15. From Cycle 7 onwards, full chemistry will be performed on Day 1 of every cycle and at the End of Treatment and Safety Follow-up Visits. **Troponin-T will be measured at Day 1 and 15, predose every 2 weeks for the first 3 cycles.**

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m Hepatitis B screening: HBsAg, HBsAb, HBcAb IgG and IgM; hepatitis C screening: HCVAb with reflex to HCV RNA.

n βHCG must be determined from serum at Screening and from serum or urine thereafter in women of childbearing potential. Appropriate menopausal status of women can be confirmed by testing for increased FSH levels at Screening. A negative pregnancy test must be available on Day 1 of each cycle, prior to M4112 administration. Results of the most recent pregnancy test (within last 28 days) must be available prior to next administration of the study drug. Women who have undergone hysterectomy or bilateral oophorectomy and postmenopausal women are exempt from pregnancy testing.

o A full urinalysis is required at Screening, the End of Treatment Visit and at Safety-follow-up Visit and includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose and a basic urinalysis (protein content only) on Day 1 of Cycles 1, 3, 5, 7 and every second cycle thereafter prior to administration of M4112. If urinalysis (full or basic) is positive for protein, sediment will be evaluated.

p **On study site visit days, the morning dose of M4112 will be administered at the study site.** M4112 will be administered at least 1 h prior to a meal and at least 2 h after a meal. Meal times should be collected on the appropriate eCRF.

CCI [redacted]

t Used as endogenous metabolite and substrate to assess metabolism by cytochrome P450 3A4.

u During treatment, CT or MRI scans will be done for tumor assessments within 7 days prior to Day 1 of Cycles 3, 5 and 7 and thereafter every 3 cycles until progressive disease or use of an alternative anticancer therapy. Of note: The method used for baseline assessment must be used for all subsequent assessments. A CT or MRI scan is mandatory to confirm a complete response, partial response and progressive disease at least 4 weeks later.

v Pretreatment tumor assessment should be performed within 21 + 7 days before the first dose of M4112. A chest X-ray should be performed before a CT or MRI scan to exclude prohibitive entry criteria. CT scans (with contrast media, unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (eg, neck) should be performed. Alternatively, tumor assessment at Screening can be done by MRI, using the same method at all subsequent assessment time points. Tumor assessment should be continued until confirmed disease progression or stop of study.

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t Post corresponds to end of infusion.

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Table 4 Schedule of Assessments – Pharmacokinetic, Pharmacodynamic, and Electrocardiogram Schedule – Part IA (Dose Escalation – M4112 as Single Agent) – Cycle 1 and Day 1 of Cycle 2

Cycle/Day	Time points (h postdose) of M4112	PK sampling (blood)[a,b]	Triplicate digital ECG[c]	CCICCI	PK volume for M4112[a] (mL)	CCICCI	Time window (± min[b])
Cycle 1 Day:							
1	Predose	X	X[e] (within 45 min)		4		- 45
1	0.5	X	X[c]		4		± 5
1	1	X	X[c]		4		± 5
1	2	X	X[c,f]		4		± 10
1	3	X	X[c,f]		4		± 10
1	4	X	X[c,f]		4		± 10
1	6	X	X[c]		4		± 10
1	8	X	X[c,f]		4		± 10
8	Predose[d]	X	X[f] (within 30 min)		4		- 30
15	Predose[d]	X	X[e] (within 45 min)		4		- 45
15	0.5	X	X[c]		4		± 5
15	1	X	X[c]		4		± 5
15	2	X	X[c,f]		4		± 10
15	3	X	X[c,f]		4		± 10
15	4	X	X[c,f]		4		± 10
15	6	X	X[c]		4		± 10
15	8	X	X[c,f]		4		± 10
Cycle 2 Day:							
1	Predose[d]	X	X[f] (within 30 min)		4		- 30
1	2	X	X[f]		4		± 10
Total					76		

ECG = Electrocardiogram; eCRF = electronic case report form; CCI ; CCI ; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamics; PK = pharmacokinetics; QTc = corrected QT interval; CCI .

a Including optional metabolite analysis from samples. For all study medication administration, a physician must be present at the site or immediately available to respond to emergencies during all administrations. Critical care and resuscitation facilities should be available immediately.

b Actual collection times should be collected in the eCRF along with the times of the last dose administration.

c For subjects in single M4112 dose escalation:

QTc monitoring: In addition to the ECGs collected for safety monitoring, subjects will undergo replicate (at least 3) digital 12-lead ECGs after a minimum of 5 min rest in the semi-recumbent position on Cycle 1 at Day 1 and Day 15 at -45, -30 and -15 min predose and at 0.5, 1, 2, 3, 4, 6 and 8 postdose. ECG recordings must be performed before PK sampling time points. Time points may change if C_{max} is not as predicted.

d Predose = approximately 12 (± 4) h post the last evening dose.

e Predose replicate readings will be collected -45, -30 and -15 min predose; a triplicate digital 12-lead ECG will also be collected predose (within 30 min) for local reading.

f In addition, standard digital triplicate (within 2 min) 12-lead safety ECGs are to be collected predose and at 2, 3, 4 and 8 h postdose on Days 1 and 15 and predose on Day 8 during Cycle 1, and predose and + 2 h postdose on Day 1 Cycle 2. Safety ECGs will be read locally and **all ECGs should be assessed on the day of collection to determined continued eligibility**. The calculated QTc average of the triplicate 12-lead ECGs must be ≤ 450 ms for eligibility. Subjects, in which the calculated QTc average increases to > 500 ms or > 60 ms change over baseline during treatment with M4112, have to interrupt study treatment until further clinical evaluation**.**

ECGs should be repeated if QTc is outside the range until resolution. To assess the safety and tolerability of the IMP, an ECG can be repeated at the Investigator's discretion at unscheduled visits. Start of resting time, ECG time, and PK sampling time will be recorded in the eCRF. Day 1 and Day 15 triplicate digital ECGs will be also be uploaded for summary statistics, outlier and exposure-QTc analyses.

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2 Sponsor, Investigators and Study Administrative Structure

The Sponsor of this clinical study is EMD Serono Research & Development Institute, Inc., Billerica, MA, in the US and Canada and Merck KGaA, Darmstadt, Germany, in the rest of the world.

The study will be conducted at approximately 3 to 5 sites in the US for the dose escalation part (Part 1).

A contract research organization (CRO), PPD will undertake the operational aspects of this study. Details of such structures and associated procedures will be defined in a separate Integrated Project Management Plan maintained by PPD. The Integrated Project Management Plan will be prepared by the PPD Clinical Project Manager in cooperation with other PPD operational team leads.

The Sponsor will coordinate the study and will utilize the support of the CRO for the management of most activities of the study. Sponsor will perform oversight of the activities performed by the CRO.

The study will appear in the following clinical study registry: ClinicalTrials.gov and other applicable registries.

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

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

The Clinical Study Supplies department of the Sponsor will supply the study medication of CCI M4112, and CCI to the sites.

Safety laboratory assessments will be performed locally. Results from these local laboratories will be recorded according to the electronic case report form (eCRF) completion guidelines.

Pharmacokinetic (PK), CCI (central laboratory), and CCI assessments will be performed under the responsibility and/or supervision of the Sponsor.

The Drug Safety department, Merck KGaA, Darmstadt, Germany, or their designated representatives will supervise drug safety and the timely reporting of adverse events (AEs) and serious adverse events (SAEs).

Monitoring and data management will be performed by PPD, and the Sponsor will be responsible for regulatory submission.

Quality assurance of the study conduct will be performed by the Development Quality Assurance Department, Merck KGaA, Darmstadt, Germany.

PPD will write the study statistical analysis plan, perform the statistical analyses, and will provide the outputs from the statistical analyses. The Sponsor's department of Global Biostatistics will supervise the statistical analyses.

2.1 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will review the safety data on a regular basis. The SMC consists of members of the Sponsor (Drug Safety Product Leader, Medical Responsible, Clinical Pharmacologist and Biostatistician), the CRO (Medical Responsible) and the Coordinating Investigator. Ad hoc members may be invited as needed. During the dose-escalation part of the study, the SMC will evaluate the safety, tolerability, pharmacokinetics (PK) and available CCI [redacted] Based primarily on dose-limiting toxicities (DLTs), the SMC will advise on dose escalation, dose de-escalation, dose expansion, change in administration schedule/regimen (change for example from twice daily [BID] to once daily [QD]), or recommend suspension of enrollment, with the final adjudication being a Sponsor decision. The SMC will recommend the starting dose for M4112 CCI [redacted] based on the observed safety, tolerability, available PK and PD markers of M4112 as single agent CCI [redacted] The SMC will decide, by consensus, on continuation of the study, or recommend modification or suspension of the study, with the final adjudication being a Sponsor decision. During the course of the study, the SMC may modify the frequency of its meetings as deemed appropriate. In cases where enrollment of the last subject in a dosing cohort was 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 Cycle 1. Subjects will be assigned sequentially to cohorts of either M4112 as a single agent, CCI [redacted] The specific working procedures will be described in an SMC charter, which will be established prior to the start of recruitment.

3 Background Information

Immunotherapy has shown encouraging response rates in different solid tumors, however, the majority of subjects will not receive significant benefit from these agents, suggesting the existence of additional immunoregulatory pathways.

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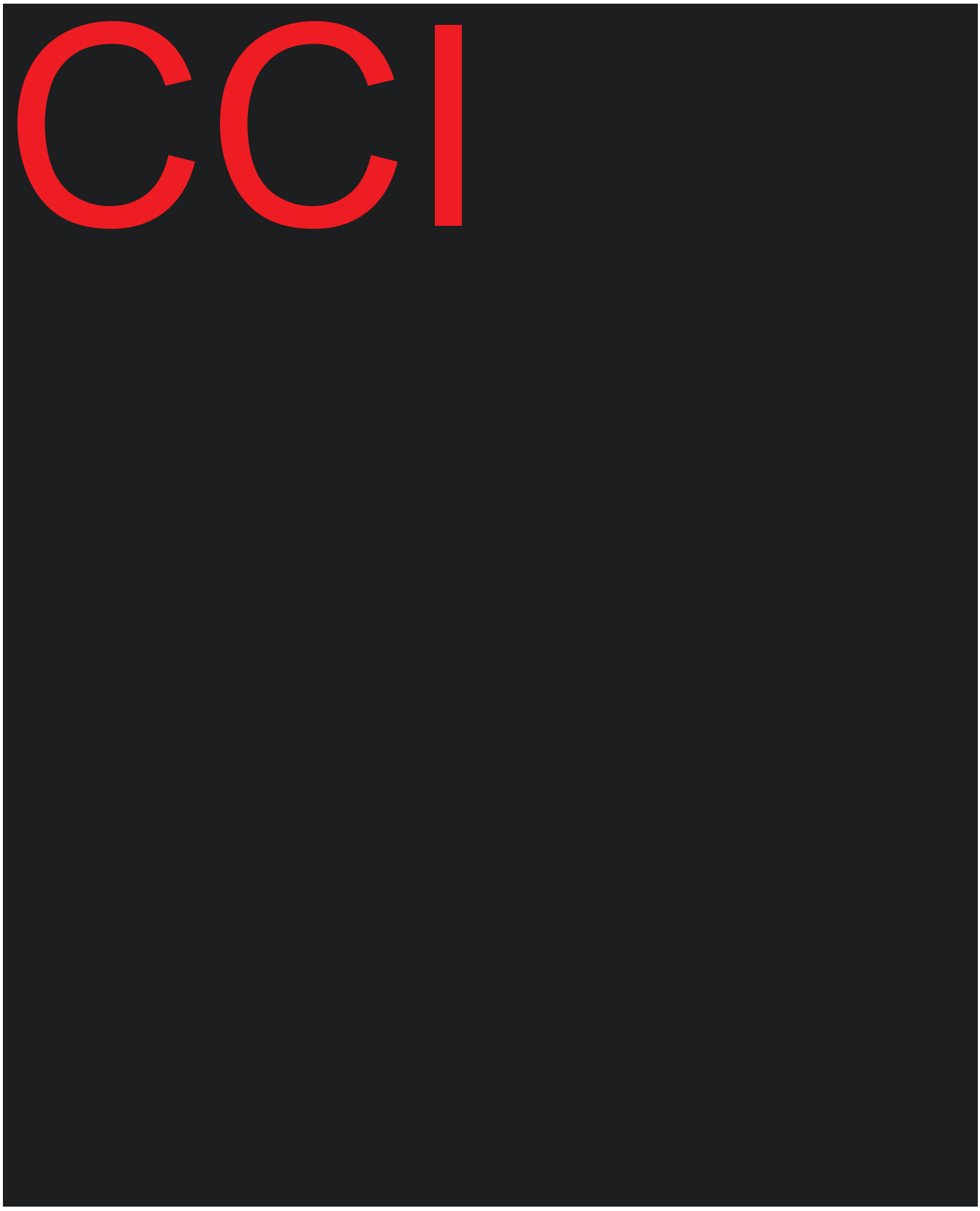
3.1 M4112

M4112 Pharmacology in Animal Models

M4112 (also known as MSC2579448) is an orally available small molecule inhibitor of the immunoregulatory metabolic enzymes indoleamine 2,3-dioxygenase 1 (IDO1) and tryptophan 2,3-dioxygenase (TDO2) (41). CCI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3.4 Rationale for the Current Clinical Study and Overall Benefit and Risk Considerations

Refer to the IB for further information about the nonclinical and clinical programs and guidance for the Investigator.

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

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

3.4.1 Rationale for the Current Clinical Study

The purpose of this study is to evaluate the safety, tolerability, PK, PD, and preliminary efficacy of M4112 as single agent, CCI [redacted] 2 immune checkpoint inhibitors with distinct modes of action, in subjects with proven advanced or metastatic solid malignancies for whom no effective standard therapy exists or has failed or subjects who are intolerant to established therapy known to provide clinical benefit for their condition. The dose escalation part of the study will establish the RP2D of M4112 as single agent CCI [redacted].

The administration of M4112 to subjects with advanced solid tumors for whom no approved/established effective treatment option exists is justified by the following:

- M4112 is a dual IDO1/TDO2 inhibitor able to inhibit immune suppression in vitro when administered as a monotherapy and with enhanced efficacy CCI [redacted] with immune check point inhibitors in animal models

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CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Together, these findings suggest that M4112, CCI [redacted], may have the potential to be an effective anticancer therapy and thus support its clinical development.

3.4.2 Overall Risk-Benefit Assessment

The administration of M4112 to subjects with advanced solid tumors for whom no approved/established effective treatment option exists is justified by the following:

- M4112 is a dual IDO1/TDO2 inhibitor able to inhibit immune suppression in vitro when administered as a monotherapy and with enhanced efficacy in preclinical models [redacted]
- Clinical experience with IDO1 inhibitor agents described in the literature demonstrate an acceptable safety profile as single agent [redacted] and encouraging clinical antitumor activity in solid tumors in Phase I studies.
  - [redacted]

IDO1/TDO2 are key regulators of adaptive and innate immunity. [redacted]

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

The safety monitoring and reporting as well as risk management and mitigation measures inherent to early phase clinical studies in oncology patients are considered adequate for this study.

3.4.2.1 Risk-Benefit Ratio of M4112

The **risk-benefit ratio of M4112** has been determined based on the following:

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The following potential risks of M4112 are

1. Gastrointestinal intolerance including ulceration, bleeding with anemia and inflammation of gastric mucosa.
2. Liver toxicity either due to liver hypertrophy or direct liver lesions.
3. QT/QTc prolongation.
4. Inhibition/autoinduction of CYP3A4.
5. irAEs/autoimmune disorders.

Gastro-intolerance including ulceration and inflammation of gastric mucosa is a potential risk for M4112. The symptoms of gastrointestinal intolerance (nausea, vomiting, and diarrhea etc.) will be closely monitored, reported, and investigated. Discontinuation/interruption of treatment will be recommended for higher grade (Grade ≥ 3) events.

Liver toxicity is the clinically significant potential risk and relates to findings in animal toxicity studies. Subjects must be screened for potential impaired liver function or liver disease prior to treatment with a detailed medical history and clinical examination. All subjects enrolled in the clinical study should be counseled for early recognition and reporting of drug-related liver disease, and should be closely monitored in case of increased liver function tests and bilirubin (see Section 6.2.3).

QT/QTc prolongation is another important potential risk for M4112. A detailed medical history and medical examination to rule out a pre-existing heart disease and history of QT/QTc prolongation must be conducted (see Section 5.3.2). Subject inclusion and exclusion criteria and withdrawal criteria will exclude subjects deemed to be at risk for increase of QT. Time-matched triplicate digital ECG will be collected at Screening and at multiple time points (predose and postdose [C_{max}]) in Cycle 1 and subsequent follow-up ECGs through all cycles. In M4112 monotherapy cohorts only (Part IA only), replicate ECGs (Holter) will also be collected on Days 1 and 15 of Cycle 1 for exposure-QTc analysis. Treatment modification guidance is described in Section 6.2.3.

M4112 is a sensitive substrate to CYP3A4 and it cannot be excluded that it inhibits or induces CYP3A4 to a clinically relevant extent. Strong inhibitors or inducers of CYP3A4 and drugs with a narrow therapeutic index, which are predominantly metabolized by CYP3A4, should be discontinued 7 days prior to treatment and avoided during treatment.

Subjects treated with M4112 should also be monitored for potential irAEs, which may first manifest after weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy or uveitis and other inflammatory eye conditions. Risk management guidance is provided in Section 6.5.5.3.

No embryo-fetal toxicity study have been performed to date, therefore effects on pregnancy cannot be excluded, pregnancy and lactation are excluded from the study. Highly effective contraception must be used for men and women of childbearing potential (Section 5.3.1 and Section 5.3.2).

Liver toxicity and irAEs will be considered AESIs for M4112 requiring expedited reporting from the Investigator to the Sponsor within 24 h of learning of its occurrence.

CCI [redacted]

[redacted]

CCI [redacted]

Instructions for treatment interruption/discontinuation or modification of infusion-related reactions/hypersensitivity will be provided to investigators as well as guidance for medical management (Table 8).

CCI [redacted]. Inclusion criteria for the study will require adequate entry hemoglobin value. Respective hematological parameters will be monitored every week during the 1st cycle of dose escalation phase. Treatment modification, interruption, and discontinuation rules, depending on severity, will be provided. CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

4 Study Objectives

4.1 Primary Objectives

Part IA (Dose Escalation – M4112 as Single Agent)

- To determine safety and tolerability or, if observed, the MTD, and to define the RP2D of M4112 as single agent in subjects with solid tumors.

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4.2 Secondary Objectives

Part IA (Dose Escalation – M4112 as Single Agent)

- To characterize the PK parameters of M4112 as single agent
- To assess QT prolongation potential by central tendency, outlier analysis and the slope of exposure-QTc analysis to evaluate preliminary clinical activity parameters using RECIST 1.1.
- To evaluate preliminary clinical activity parameters using RECIST 1.1.

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4.3 Exploratory Objectives

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5 Investigational Plan

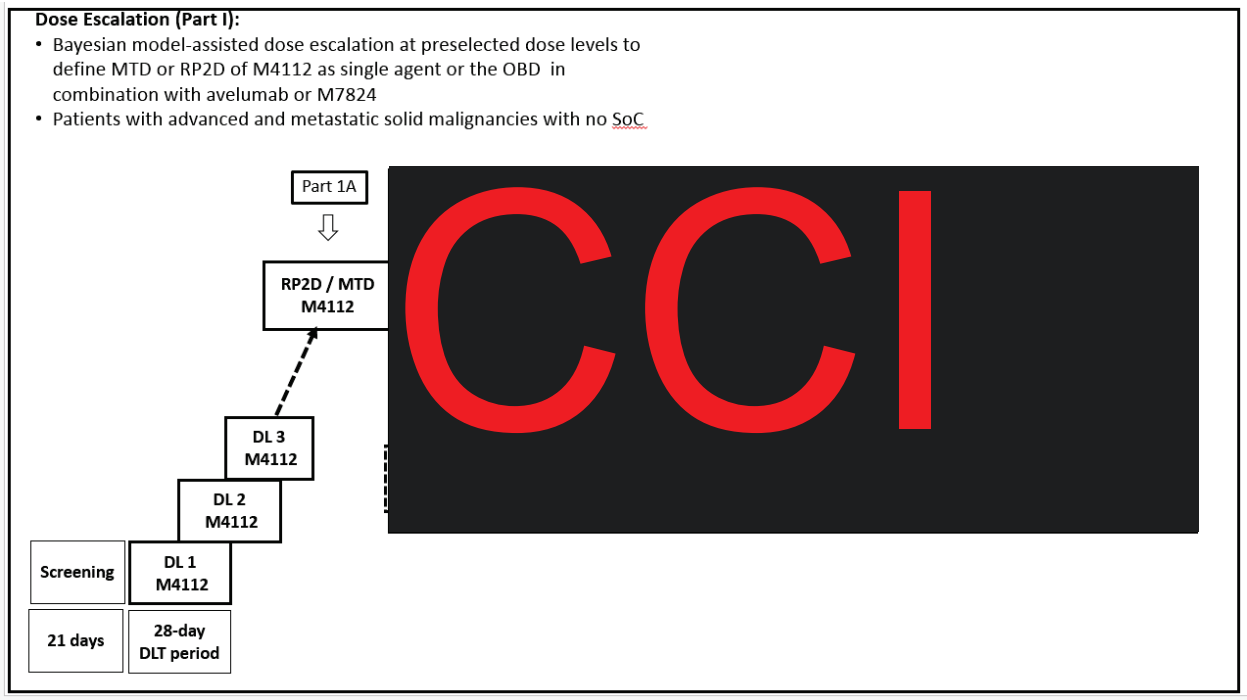
5.1 Overall Study Design and Plan

This study is a Phase I, open-label study designed to determine the safety, tolerability, PK, PD, and preliminary antitumor activity of M4112 as single agent (Part IA only) CCI [redacted] (see Figure 1). The target population for Part I (Dose Escalation) comprises of subjects with advanced or metastatic solid malignancies for whom no effective standard therapy exists or has failed or subjects who are intolerant to established therapy known to provide clinical benefit for their condition.

The study for an individual subject will include up to 21 + 7 days screening period, a treatment period consisting of 28-day cycles of M4112 either as single agent CCI [redacted] End of Treatment Visit (within 7 days), and a Safety Follow-up period including a visit at 30 ± 3 days and a visit at 90 ± 6 days (as a phone call) after the last M4112 intake CCI [redacted] M4112 will be administered orally daily BID (or regimen determined by SMC) (see Section 6.2). Subjects who tolerate M4112 without significant clinically relevant toxicities may continue to receive their assigned dose as long as there is no evidence of confirmed disease progression (see Section 5.5.1). Subjects who discontinue treatment for any reason will complete the End of Treatment and Safety Follow-up Visits.

The study design schematic is presented in Figure 1.

Figure 1 First-in-Human Study Design for Single Agent CCICCI Dose Escalation of M4112



DL = Dose level; DLT = dose-limiting toxicity; OBD = optimal biological dose; MTD = maximum tolerated dose; RP2D= recommended Phase II dose; SMC = Safety Monitoring Committee; SoC = standard of care.

In addition, any treatment-emergent immune related adverse event observed in subsequent cycle (Cycle 2) that in the opinion of the SMC needs to be taken into account for the overall evaluation of the safety and proposal of dose escalation will be considered.

Screening Period:

Screening will be performed within 21 + 7 days prior to Day 1 of M4112 administration. If, at Screening, the subject meets all the protocol-defined inclusion and none of the exclusion criteria, the subject will be considered as eligible and will be enrolled into the study. Subjects who fail to meet the protocol-specified criteria or who withdraw their consent will be considered screening failures.

Treatment Period:

The treatment period will begin at the first dose of M4112 in Cycle 1 Day 1 and consist of consecutive 28-day cycles of continuous M4112 (BID or other regimen determined by the SMC), either as monotherapy CCI Subjects will be instructed to take M4112 at least 1 h prior to a meal and at least 2 h after a meal. Meal times should be collected on the appropriate eCRF.

Eligible subjects will initiate therapy at the dose level appropriate at the time of enrollment. The Sponsor's Medical Responsible, or designee, must confirm enrollment and dose level (during dose escalation only) after receipt of the appropriate information relating to study entry.

Subjects who tolerate study treatment without significant clinically relevant toxicities may continue to receive their assigned dose as long as there is no evidence of confirmed disease progression.

Part IA to Part IC: Dose Escalation

A broad dose range in monotherapy is planned to be investigated to determine the safety profile, tolerability, PK, and PD markers and to explore signs of antitumor activity in subjects with advanced solid tumors.

Subjects will receive M4112 at the starting dose of 100 mg BID (100 mg BID which equals to 200 mg total daily dose) at least 1 h prior to a meal and at least 2 h after a meal. Cohorts will consist of 3 subjects each, if not decided differently by the SMC. Cohorts will consist of 3 subjects each, if not decided differently by the SMC. The first subject of each dose level will be observed for at least 5 days before the second subject can be treated. Subsequent subjects may receive first dosing at no less than 48 h intervals between subjects for the first 2 cohorts of mono CCI If the safety profile is acceptable and agreed by the SMC, the 48 h observation after Subject 2 may be removed. The safety and tolerability data and available PK and PD data (as minimum Day 1 and Day 15 PK and PD data from previous cohort and all available PK and PD data from the current cohort) will be reviewed by the SMC at the end of each cohort. In cases where enrollment of last subject in a dosing cohort was 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 Cycle 1. The SMC will be assisted in their dosing and regimen (administration schedule) decisions by PK, PD, and a Bayesian 2-parameter logistic regression model modeling DLT rate with overdose control. The model incorporates nonclinical toxicity data in the prior and DLTs observed until the SMC meeting to provide a recommended dose for the next cohort. The SMC can choose a dose different from the one recommended by the model. During the dose escalation part of the study, the SMC will advise, primarily based on safety (DLTs) during the first cycle, and any TEAE observed in subsequent cycle that in the opinion of the SMC needs to be taken into account (additional DLT criteria, see Section 6.2.4), for the overall evaluation of the safety and proposal of dose escalation dose, dose de-escalation, dose level expansion or regimen change, or it may recommend suspension of enrollment, with the final adjudication being a Sponsor decision. A Bayesian 2-parameter logistic regression model will incorporate observed DLTs from all previously completed cohorts to provide a recommended dose for the next cohort. The SMC may also recommend a cohort size different from 3 subjects as the Bayesian design allows dose recommendation based on less or more than 3 subjects.

Based on the absence of clinical signs or other adverse findings, the 30 mg/kg/day in the dog was considered the NOAEL in this study. The subsequent dose, 100 mg/kg/day, was considered not tolerated due to the adverse findings in an early sacrificed (Day 15) male dog administered 100 mg/kg/day. No HNSTD was defined in dogs in the 4-week toxicity study. The dose of 30 mg/kg/day was defined as the NOAEL and the starting dose in Phase I takes into consideration the HNSTD according to the guideline ICH S9 as well as margins relative to the NOAEL in the dog the most sensitive animal species (described further in Section 5.2.3) and translates to a human equivalent dose (HED) of approximately 16.7 mg/kg/day; the starting dose

is approximately 1/6 of the HED at 2.8 mg/kg/day or approximately 100 mg for a 70 kg human administered BID.

Prespecified ascending doses of 100, 200, 400, 600, 800, and 900 mg BID (means respectively, 100 mg BID for 200 mg total daily dose, 200 BID for 400 mg total daily dose, 400 mg BID for 800 mg total daily dose, 600 mg BID for 1,200 mg total daily dose, 800 BID for 1,600 mg total daily dose, 900 mg BID for 1,800 mg total daily dose) as single agent in 28-day cycles are foreseen. Dose escalation decisions will be driven primarily by DLT, safety, and tolerability. The MTD may not be reached in the anticipated PD active dose range of M4112, therefore, the assessment of PD effects may be used to explore the optimal biological dose (OBD) and to inform on the RP2D.

A BID dosing regimen will be followed based on PK modelling to achieve the target C_{min} over the dosing interval at a lower total daily dose and thereby reducing C_{max} and AUC over the day to potentially improve safety and tolerability when compared to QD dosing. Based on PK data from subjects, the SMC will evaluate whether this regimen should be continued or a different regimen explored.

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In principle, dose escalation of single agent M4112 will proceed according to the recommendation of the SMC to the upper end of the above given dose range, unless the MTD has been reached or there is excess of PK nonlinearity, or the SMC recommends to end dose escalation following review of safety, tolerability, PK and PD results. Depending on the observed toxicity profile and available measured PK and PD, or dose regimen different or higher than the prespecified doses may be tested.

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This dose level will then be studied in ≤ 6 evaluable subjects to establish safety, tolerability, PK and PD and will be defined as RP2D of M4112 as single agent.

Consecutively, the following groups of dose escalations CCI CCI are foreseen, starting while monotherapy dose escalation is still ongoing:

- M4112 administered orally BID CCI in subjects with advanced and metastatic solid tumors
- M4112 administered orally BID CCI in subjects with advanced and metastatic solid tumors.

The starting dose of M4112 CCI will be dependent on the observed safety, tolerability, and PK/PD profile during dose escalation in the single agent cohort (Part IA) and will lag at least 1 dose level behind the last completed safe dose level of M4112 as single agent, which was confirmed as safe by the SMC. For selection of the starting dose, predictions based on an updated PK/PD, CCI

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Dose escalation will proceed until the OBD of M4112 CCI dose escalation ends due to occurrence of DLTs establishing an MTD, or the SMC recommends to end dose escalation following review of safety, tolerability, PK and PD results, whatever occurs first. The maximum dose of M4112 CCI in monotherapy determined in Part I of the study.

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DLT Definition

DLTs will be used to determine dose escalation, dose de-escalation, and the MTD (if reached), using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE 4.03). DLTs are defined in Section 6.2.4.

All subjects treated in dose escalation cohorts who miss > 5 planned total daily doses of M4112 CCI in the first cycle (first 28 days) of the dose escalation part for other than safety reasons are not eligible for DLT assessment, will not be considered in the Bayesian model and will not formally be replaced. If no evaluable subject from a cohort is left, the SMC will still convene to decide upon the continuation of the study and the number of subjects for the next cohort.

Subjects with nausea and vomiting will maintain normal schedule without re-dosing.

The MTD is defined by the SMC. An MTD is suggested from the Bayesian logistic regression model with DLT target rate of 30%.

Subjects who tolerate M4112 CCI without significant clinically relevant toxicities will continue to receive their assigned dose until discontinuation criteria are met, withdrawal of consent or the study ends, whatever occurs first (see Section 5.5.1 for exceptions).

Follow-up Period

The Safety Follow-up Visit is scheduled 30 ± 3 days and 90 ± 6 days (as a phone call) after the last dose of M4112, CCI or until resolution to Grade 1, before start of any new anticancer therapy, whatever comes first (see Section 5.5.1).

Subjects who discontinue treatment must be followed on study until resolution of toxicity or until confirmed disease progression.

5.2 Discussion of Study Design

5.2.1 Inclusion of Special Populations

Not applicable

5.2.2 Scientific Rationale for Study Design

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5.2.3 Justification for Dose

5.2.3.1 Single Agent M4112 (Part IA)

The starting dose for the First-in-Human study of M4112 was determined based on the ICH Guideline S9 "Nonclinical Evaluation for Anticancer Pharmaceuticals" (2009):

- Considering the severely toxic dose and HNSTD according to guideline ICH S9
- Considering PK/PD modeling of the predicted pharmacological active dose range in humans.

Two pivotal 4-week toxicity studies in rats and dogs have adequately defined the safety and risk profile of M4112 to support multiple dosing in humans. CCI

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5.2.4 Rationale for Endpoints

The study objectives and endpoints are standard Phase I objectives and endpoints, namely to define the safety, tolerability, PK, and PD of M4112 as single agent CCI [redacted] in humans, and to explore its preliminary antitumor activity in subjects with advanced disease.

The subject population and the key endpoints are well selected to address the primary objectives and key secondary objectives of this study.

5.3 Selection of Study Population

Only individuals who fulfill all inclusion criteria without matching any exclusion criteria may be enrolled into the study as subjects. Prior to performing any study assessments not part of the subject's routine medical care, the investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled:

1. Signed written informed consent form (ICF) before any study-related procedure is undertaken that is not part of the standard subject management.

2. Male or female subjects ≥ 18 years of age.

3. Subject population

   In the dose escalation cohorts (Part IA CCI [redacted]): Histologically or cytologically proven advanced or metastatic solid malignancies for whom no effective standard therapy exists or has failed or subjects who are intolerant to established therapy known to provide clinical benefit for their condition

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

5. Subjects who have been treated previously with a checkpoint inhibitor may enroll.

6. Adequate hematological function as defined below:
   a. Absolute neutrophil count ≥ 1,500/mm^3 or ≥ 1.5 × 10^9/L
   b. Platelet count ≥ 100,000/mm^3 or ≥ 100 × 10^9/L
   c. Hemoglobin ≥ 9 g/dL.

7. Adequate hepatic function defined: by a total bilirubin level ≤ 1.5 × upper limit of normal (ULN), an AST level ≤ 2.5 × ULN, and an ALT level ≤ 2.5 × ULN

a. Subjects with documented Gilbert disease are allowed if total bilirubin > 1.5 × ULN but < 3 × ULN

b. Subjects with tumor involvement in their liver: AST < 3.0 × ULN, ALT < 3.0 × ULN, with normal bilirubin ≤ 1.5 × ULN and INR < 1.5.

8. Adequate renal function defined by an estimated glomerular filtration rate > 50 mL/min according to the Cockcroft-Gault formula or normal creatinine laboratory values

   (Glomerular filtration rate [mL/min/1.73 m^2] = 175 × serum creatinine $(S_{cr})^{-1.154}$ × age -0.203 × 1.212 [if African American] × 0.742 [if female])

9. Male participants 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 30 days before first dose of study treatment (as appropriate), during the treatment period and for at least 60 days after the last dose of study treatment of M4112 as single agent CCI [redacted] d must refrain from donating sperm during this period.

10. Female participants:

    A female participant 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 Appendix I of this protocol 30 days before start of first dose of study treatment (as appropriate), during the treatment period and for at least 60 days after the last dose of study treatment of M4112 as single agent CCI [redacted]

    Since the effect of potential of M4112 to induce/inhibit CYP3A4 is unknown at this time, WOCBP that are currently using hormonal contraception that is a substrate for CYP3A4 should also use double barrier contraception.

11. Women of childbearing potential must have a negative plasma pregnancy test at the Screening Visit and a negative urine pregnancy test on Day 1 before enrollment and dosing.

5.3.2 Exclusion Criteria

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

1. Prior therapy with:

   CCI [redacted] Intolerance to immune checkpoint inhibitor therapy as defined by the occurrence of an adverse drug reaction (ADR) requiring drug discontinuation.

2. Persisting toxicity related to prior therapy Grade > 1 NCI-CTCAE 4.03, however sensory neuropathy Grade ≤ 2 is acceptable and alopecia is acceptable.

3. Prior organ transplantation including allogeneic stem cell transplantation.

4. All subjects with known brain metastases, except those meeting the following criteria:
   a. Brain metastases that have been treated locally and are clinically stable for at least 4 weeks prior to the start of treatment.
   b. No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable).
   c. Subjects must be either off steroids or on a stable or decreasing dose of < 10 mg daily prednisone (or equivalent).

5. Concurrent treatment with a nonpermitted drug/intervention:
   a. Strong inhibitors or inducers of CYP3A4, and drugs with a narrow therapeutic index, which are predominantly metabolized by CYP3A4 should be discontinued 7 days prior to treatment and avoided during treatment (see Appendix II for a list. The link to the website to be consulted, in case of doubt, is provided in Section 6.5).
   b. Drugs known to have a high risk of prolonging QTc as per label (see Appendix II for a list and Section 6.5.1 for exceptions to nonpermitted drugs).
   c. Drugs that are known to increase gastric pH should be stopped at least 1 week before the start of study treatment
   d. Anticancer treatment (eg, cytoreductive therapy, radiotherapy, immune therapy, cytokine therapy, monoclonal antibody, targeted small molecule therapy) or any investigational drug within 4 weeks prior to start of study treatment, or not recovered from AE related to such therapies, with the following exceptions:
      i. Palliative bone-directed radiotherapy is permitted (concurrently or within pretreatment period).
      ii. Hormonal therapies acting on the hypothalamic-pituitary-gonadal axis are permitted (ie, luteinizing hormone-releasing hormone agonist/antagonists). No other hormonal anticancer therapy is permitted.

e. Major surgery (as deemed by the Investigator) for any reason, except diagnostic biopsy, within 4 weeks of the study treatment and/or if the subject has not fully recovered from the surgery within 4 weeks of the study treatment.

f. Subjects receiving immunosuppressive agents (such as steroids), for any reason, should be tapered off these drugs before start of study treatment, with the following exceptions:

   i. Subjects with adrenal insufficiency, may continue corticosteroids at physiologic replacement dose, equivalent to $\leq$ 10 mg prednisone daily.

   ii. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation).

   iii. Previous or ongoing administration of systemic steroids for the management of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the dose after 14 days will be equivalent to $\leq$ 10 mg prednisone daily.

g. Warfarin or other Vitamin K antagonists.

6. Current significant cardiac conduction abnormalities, including corrected QT interval (QTc) prolongation of > 450 ms or impaired cardiovascular function, ventricular tachycardia, hypokalemia or a history of paroxysmal atrial fibrillation, serious cardiac arrhythmia and family history of sudden death or long QT syndrome.

7. A history of cardiovascular/cerebrovascular disease as follows: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina or congestive heart failure (New York Heart Association Classification Class $\geq$ II).

8. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:

   a. Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

   b. Autoimmune diseases: eg, inflammatory bowel diseases, interstitial lung disease or pulmonary fibrosis

9. Pneumonitis and history of pneumonitis.

10. A history of difficulty of swallowing, gastric or small bowel surgery with history of malabsorption or other chronic gastro-intestinal disease or conditions that may hamper compliance and/or absorption of the M4112.

11. Any psychiatric condition that would prohibit the understanding or rendering of Informed Consent, or interfere with compliance to study requirements and procedures in the opinion of Investigator and/or Sponsor.

12. Known current alcohol and drug abuse as determined by the Investigator.

13. Hepatocellular carcinoma

14. Legal incapacity or limited legal capacity if no consent by legal representative.

15. Significant acute or chronic infections requiring systemic therapy including, among others:
    a. History of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.
    b. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (defined as, HBV surface antigen positive and HBV core antibody positive with reflex to positive HBV DNA or HBV core antibody positive alone with reflex to positive HBV DNA or positive HCV antibody with reflex to positive HCV RNA). Subjects with a history of infection must have polymerase chain reaction documentation that infection has cleared.
    c. Active tuberculosis (history of exposure or history of positive TB test with presence of clinical symptoms, physical, or radiographic findings).

16. Known hypersensitivity to the IMPs or to one or more of the excipients of M4112, CCI CCI

17. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE 4.03), or uncontrolled asthma (ie, 3 or more features of partially controlled asthma).

18. Pregnancy or lactation.

19. Administration of a live vaccine within 28 days prior to study entry.

5.4 Criteria for Initiation of Study Treatment

The inclusion and exclusion criteria will be checked at the Screening Visit. This is an open-label study without randomization. Eligible subjects who have provided written informed consent will be enrolled after verification of fulfilling all inclusion criteria without matching any exclusion criteria.

The Sponsor's Medical Responsible, or designee, must confirm enrollment and dose level during dose escalation after receipt of the appropriate information relating to entry.

Individuals who do not meet the criteria for initiating treatment (screen failure) may be rescreened once.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Study Treatment

A subject must be withdrawn from study treatment if any of the following occurs:

- Subject withdrew consent
- Subject lost to follow-up
- Participation in another clinical study
- Any events that unacceptably endanger the safety of the subject
- Occurrence of an exclusion criterion which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor
- Occurrence of AEs, for which discontinuation is desired or considered necessary by the Investigator and/or the subject (if applicable)
- Any DLT during the DLT observation period (applicable for Part I): Subjects experiencing DLTs as described in Section 6.2.4 will not receive further protocol therapy. Subjects who discontinue treatment must be followed on study until resolution of toxicity or until disease progression
- Disease progression: In case of disease progression per RECIST 1.1 (Appendix III), the subject should be withdrawn from study treatment. However, treatment may continue past the initial determination of disease progression per RECIST 1.1 (Appendix III) as long as the following criteria are met:
    - No new symptoms or worsening of previous symptoms (including laboratory values) indicating disease progression
    - Tolerance of treatment either as single agent CCI [redacted]
    - Stable ECOG PS
    - Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).
- The decision to continue treatment should be discussed with the Medical Monitor and documented in the study records.
- Subjects should be discontinued from treatment if there is further evidence of progressive disease (further progression is defined as an additional 10% increase in tumor burden volume from time of initial progressive disease) at the control ≥ 4 weeks and < 6 weeks from the initial scan documenting disease progression; however, continued treatment is possible in consultation with the Medical Monitor. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment. If the Investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the

study and continue to be monitored according to the Schedule of Assessments (Table 1, Table 2, and Table 3).

- If the administration of a prohibited concomitant medication (see Section 6.5.2) becomes necessary during the study, the subject will be withdrawn from study treatment (the Sponsor may be contacted to confirm whether study treatment must be discontinued prior to doing so)
- Occurrence of pregnancy
- Noncompliance that is deemed by the Investigator or the Sponsor to compromise subject safety or study integrity (see Section 6.9).
- Occurrence of any Grade ≥ 3 AEs and irAEs as defined in Section 6.2.4 or deemed necessary by Investigator or the Sponsor for subject safety.

All subjects who discontinue M4112 treatment CCI [redacted] should undergo the End of Treatment Visit (within 7 days), Safety Follow-up Visit (within 30 ± 3 days), and a second Safety Follow-up Visit CCI [redacted]) as indicated in the Schedule of Assessments (Table 1, Table 2, and Table 3) for full safety evaluation. Subjects who discontinue treatment must be followed on study until resolution of toxicity or until confirmed disease progression.

5.5.2 Withdrawal from the Study

Subjects may withdraw from the study at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the study. In case of withdrawal, subjects will be asked to continue Safety Follow-up Visits.

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

- Withdrawal of the subject's consent
- Participation in any other interventional study during the treatment duration of this study
- Subject lost to follow-up.

In case of withdrawal from the study, the assessments scheduled for the End of Treatment Visit should be performed (see Section 7.1.3), if possible, with focus on the most relevant assessments. In any case, the appropriate eCRF section must be completed.

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

Subjects who do not complete the DLT period for reasons other than a DLT/AE will not be replaced.

5.6 Premature Termination of the Study

The clinical study may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable benefit-risk assessment for any IMP. The Sponsor may discontinue the study if it becomes unjustifiable for

medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of an IMP or withdrawal of an IMP or comparator from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the study in accordance with applicable regulations. The study may be terminated or suspended upon request of the Health Authorities.

In the situation of a premature termination of the study, subjects on treatment who are having a clinical benefit may continue to receive the IMP based on the Investigator's request and in consultation and agreement with the Sponsor.

5.7 Definition of End of Study

The end of study is defined as the last subject having completed the last Safety Follow-up Visit, and/or stopped due to unacceptable toxicity, disease progression, Investigator/subject decision, withdrawn consent, lost to follow-up or has died, whichever comes first.

6 Investigational Medicinal Product and Other Drugs Used in the Study

The term "Investigational Medicinal Product" refers to an active substance or a placebo being tested or used as a reference therapy in a clinical study, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form. In this study, the IMPs are M4112, CCI [redacted].

6.1 Description of Investigational Medicinal Products

CCI [redacted]

CCI [redacted]

CCI [redacted].

6.2 Dosage and Administration

Subjects will be administered an oral dose of M4112 BID (or a regimen determined by the SMC) at least 1 h prior to a meal and at least 2 h after a meal in 28-day cycles. The SMC may need to make changes on the dosing and regimen (eg, BID to QD) of M4112. Meal times should be collected on the appropriate eCRF.

6.2.1 Dose Escalation Cohort (Part I)

6.2.1.1 Subjects Receiving M4112 as Single Agent

Administration of M4112:

BID continuous administration of M4112 as single agent at doses recommended by the SMC is foreseen. On study site visit days, the morning dose of M4112 will be taken at the study site.

CCI [redacted]

Administration of M4112:

BID continuous administration of M4112 as single agent at doses recommended by the SMC is foreseen. On infusion day visits, **M4112 will be administered after premedication (within 30 min)** CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

CCI

CCI

CCI

CCI

CCI

CCI

- Subjects in Part I of the study who experience a Grade ≥ 3 nonhematological AEs (for exceptions see DLT criteria) or Grade 4 hematological ADR, **after completion** of the DLT assessment period (ie, first 28 days of treatment with M4112), need to interrupt study treatment; however, subjects may continue on study treatment of M4112 at a reduced dose provided the reaction has resolved to baseline value or Grade ≤ 1 within 2 weeks and there is no progressive disease. The dose of M4112 will be reduced to a dose defined by the SMC. If indicated, a further dose reduction is possible.

CCI [redacted]

- At evidence of hepatocellular injury attributable to study drug, such as increase in AST or ALT ≥ 5-fold ULN or ≥ 3 x ULN elevation of ALT or AST and elevation of serum total bilirubin to ≥ 2 x ULN, without initial findings of cholestasis (elevated serum alkaline

phosphatase) or other apparent clinical causality (eg, viral hepatitis A, -B, or -C, alcohol abuse or co-medication (ie, paracetamol [acetaminophen]), subjects should interrupt study treatment and undergo close observation. This should include monitoring for symptoms (clinical signs of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash) and hepatic function (AST, ALT, alkaline phosphatase [ALP]) and fractionated bilirubin) at least every 3 days, until symptoms and/or hepatic function abnormalities resolve, stabilize or return to baseline values. This event should be reported to the Sponsor within 24 h of learning of its occurrence. Re-exposure of the subject to the study drug and possible dose level reduction will be determined by the SMC.

- Once the dose of M4112 has been reduced in an individual subject, it must not be escalated again
- If more than 2 dose reductions of M4112 are indicated, the subject will be permanently discontinued from study treatment
- M4112 must also be permanently discontinued in case study treatment delays exceed 2 weeks, regardless of the reason for delay
- Subjects who experience an increase in QT: Subjects in which the calculated QTc average (using the Fridericia correction calculation) increases to > 500 ms on any triplicate reading or ≥ 60 ms change over baseline during treatment with M4112 have to interrupt study treatment until further clinical evaluation.

6.2.4 Dose Limiting Toxicities

DLTs will be used to determine dose escalation, dose de-escalation, and the MTD (if reached), using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE 4.03).

DLTs are defined as any Grade ≥ 3 AEs and irAEs, during treatment of either M4112 as single agent CCI [redacted] by the Investigator and/or the Sponsor, during Cycle 1 at any dose level:

- Any Grade ≥ 3 nonhematological AE or irAE assessed by the Investigator or Sponsor during the first Cycle (first 28 days) of study treatment **except**:

    a. Diarrhea of ≤ 6 days duration following adequate and optimal therapy that resolves to Grade ≤ 1

    b. Grade 3 skin toxicity that resolves to Grade 1 or less with supportive measures within 7 days

    c. Nausea and vomiting of ≤ 72 h duration with adequate and optimal therapy

    d. Single laboratory values out of the normal range that have no clinical correlate, and resolve to Grade ≤ 2 within 6 days with adequate medical management (except Grade ≥ 3 liver function test increase without any clinical correlate)

e. Grade 3 infusion-related reactions resolving within 6 h from the end of infusion and controlled with medical management

f. Transient (≤ 72 h) Grade 3 fatigue, local reactions, flu-like symptoms, fever, headache that resolves to Grade ≤ 1 with adequate treatment

g. Keratoacanthoma and SCC of the skin. Any suspicious skin lesion that is local and should be resected with negative resection margin

h. Symptomatic thyroid dysfunction which is manageable with adequate treatment and resolves to Grade 2 within 6 days

i. Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor that resolve to Grade 2 within 6 days

j. Asymptomatic Grade ≥ 3 lipase or amylase elevation not associated with clinical manifestations of pancreatitis.

- Any TEAE observed in subsequent cycle that in the opinion of the SMC needs to be taken into account for the overall evaluation of the safety and proposal of dose escalation
- Any Grade 4 neutropenia of > 5 days duration, Grade ≥ 3 febrile neutropenia
- Grade 3 hemoglobin decrease (< 8.0 g/dL) despite blood transfusion or erythroid growth factor
- Grade 4 hemoglobin decrease assessed as related to study drug
- Any Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding
- Any Grade ≥ 3 clinical signs and symptoms related to increased QTc
- Evidence of hepatocellular toxicity attributable to study drug, such as increase in AST or ALT ≥ 5-fold ULN for at least or ≥ 3 x ULN elevation of ALT or AST and elevation of serum total bilirubin to ≥ 2 x ULN, without initial findings of cholestasis (elevated serum ALP) or other apparent clinical causality (eg, viral hepatitis A, B, C, or co-medication).

If the above criteria are met, subjects should undergo close observation, including monitoring for symptoms (clinical signs of hepatitis, hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash) and hepatic function (AST, ALT, ALP and fractionated bilirubin) at least every 3 days, until symptoms and/or hepatic function abnormalities resolve, stabilize or return to baseline values. This event should be reported to the Sponsor within 24 h of learning of its occurrence.

Subjects experiencing DLTs during the DLT observation period (applicable for Part I only) as described in Section 6.2.4 will not receive further protocol therapy. Subjects with nausea and vomiting will maintain normal schedule without re-dosing.

In addition, any immune-related toxicity event observed in the next cycle will be reviewed and taken into account by the SMC for the overall evaluation of the safety and proposal of dose escalation of M4112 CCI .

All subjects treated in dose escalation cohorts who miss > 5 planned total daily doses of M4112 CCI in the first cycle (first 28 days) of the dose escalation part for other than safety reasons are not eligible for DLT assessment, will not be considered in the Bayesian model, and will not formally be replaced.

The MTD is defined by the SMC. An MTD is suggested from the Bayesian logistic regression model with target toxicity of 30%.

6.3 Assignment to Treatment Groups

Once the subject has provided a signed ICF and meets all inclusion criteria and does not meet any exclusion criterion, subjects will be assigned to receive open-label M4112 as a single agent, CCI

Subjects will be assigned sequentially to cohorts of either M4112 as a single agent, CCI . During dose-escalation, 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 Cycle 1.

Subject identifiers will comprise 17 digits, the first 10 digits representing the study number, the following 3 digits representing the site number, and the last 4 digits representing the subject number, which is allocated sequentially starting with PPD .

6.4 Noninvestigational Medicinal Products to be Used

Storage, handling, preparation, and disposal of commercially sourced non IMPs should occur according to the package insert specifications and local institutional guidelines.

The investigator is responsible for ensuring accountability for non IMPs, including reconciliation of drugs and maintenance of drug records in the same manner as described for IMPs in Section 6.8.

Immediate access to an intensive care unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available for use in the treatment of infusion-related reactions CCI

As with all monoclonal antibody therapies, there is a risk of hypersensitivity reaction. Patients should be monitored for signs/symptoms of infusion reactions including but not limited to pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interruption or slow the rate of infusion for mild or moderate infusion-related reactions.

CCI [redacted]

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Guidelines for management of infusion-related reactions and severe hypersensitivity and flu-like symptoms according to the NCI are found in Sections 6.5.5.1 and 6.5.5.2, respectively. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

CCI [redacted]

CCI [redacted]

6.5 Concomitant Medications and Therapies

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

6.5.1 Permitted Medicines

Any medications, therapies or procedures (other than those excluded by the clinical study protocol) that are considered necessary for the subjects' welfare according to local standard of

care and will not interfere with CCI [redacted] may be given at the Investigator's discretion.

Other drugs to be used for prophylaxis, treatment of hypersensitivity reactions, and treatment of fever or flu-like symptoms are described in Section 6.5.5.2.

Hematopoietic growth factors can be used if medically indicated according to standard of care only after the DLT period of 28 days.

Erythropoietin and darbepoetin-alpha are permitted outside the DLT window. Hormonal therapies acting on the hypothalamic-pituitary-gonadal axis are permitted (ie, luteinizing hormone-releasing hormone agonist/antagonists). No other hormonal anticancer therapy is permitted.

Rescue medications may be administered due to anticipated adverse reactions or anticipated emergency situations.

Administration of corticosteroids through a route known to result in a minimal systemic exposure (topical, intranasal, intra-ocular, or inhalation) and anti-infectious drugs are permitted.

6.5.2 Prohibited Medicines

Prohibited medicines are indicated in the exclusion criteria (see Section 5.3.2).

During the study, any other investigational drug, chemotherapy, extensive radiotherapy (involving ≥ 30% of bone marrow) or any other anticancer therapy (cytotoxics, biologics or other targeted therapy) are prohibited.

In vitro assessments indicate that M4112 is a sensitive substrate to CYP3A4 and cannot exclude that it can inhibit or induce CYP3A4 at a clinically relevant extent. Strong inhibitors or inducers of CYP3A4, and drugs with a narrow therapeutic index, which are predominantly metabolized by CYP3A4 should be discontinued 7 days prior to treatment and avoided during treatment. CCI [redacted] An updated list of nonpermitted drugs can be accessed via the following link:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664

Drugs known to have a high risk to prolong QTc as per label or Credible Meds web site (formerly AZCert) are prohibited. For antihistamines only drugs with high risk of QTc prolongation (in the label) or risk mentioned in the label are prohibited (Diphenhydramine is considered of low risk and can be used)

Corticosteroids and immunesuppressants given systemically at therapeutic doses are not permitted throughout treatment other than for treatment of immune-related adverse events and for endocrine replacement therapy (equivalent to < 10 mg prednisone daily).

Concomitant use of warfarin or other Vitamin K antagonists is also prohibited.

The solubility of M4112 is pH dependent; therefore, co-administration of antacid drugs, H2-blocker and proton pump inhibitors (PPIs) are likely to decrease the absorption of M4112. H2-blockers or PPIs should be stopped 5 days prior to the first treatment, and avoided during the entire treatment period with IMP. Antacid drugs should not be taken 1 h before IMP administration until 2 h after IMP administration.

The following treatments must not be administered during the study:

- Immunotherapy including interferon, immunosuppressive drugs (eg, chemotherapy or systemic corticosteroids except for short term treatment of allergic reactions, endocrine replacement therapy at low dose prednisone [≤ 10 mg daily] or equivalent, or for the treatment of irAEs or other appropriate short term steroid use), or other experimental pharmaceutical products. Short term administration of systemic steroid or other immunosuppressant such as infliximab or mycophenolate (ie, for allergic reactions or the management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are allowed. Note: for subjects with glioblastoma, steroid use is allowed
- Adefovir
- Prophylactic use of corticosteroids for infusion related reactions is prohibited
- Any live vaccine therapies for the prevention of infectious disease within 28 days prior to study entry and during study. Administration of inactivated vaccines is allowed (eg, inactivated influenza vaccines)
- Blood transfusions and erythroid growth factors are not allowed during the 28-day DLT window during the escalation phase. These subjects are considered to have had a DLT if the drop in hemoglobin is rated as drug related, or subjects are regarded as not evaluable, if the event is not related to study medication.

If the administration of a nonpermitted concomitant drug becomes necessary during the study, the subject will be withdrawn from study treatment (the Medical Monitor should be contacted to discuss whether the IMP must be discontinued).

6.5.3 Other Interventions

Interventions as indicated in the eligibility criteria in Section 5.3 are applicable.

6.5.4 Special Precautions

Special precautions on Day 1 and Day 15 of every cycle, vital signs (blood pressure, pulse, respiratory rate, temperature,) will be assessed predose (within 15 min of oral dosing and infusion), and then every 15 min CCI [redacted] during infusion and for an additional 2 h post-infusion. If vital signs are not stable after 2 h (either blood pressure > 140/> 90 mmHg or < 90/< 60 mmHg compared to normal blood pressure at start or changes of > 20 reading points between measurements, for heart rate and respiration rate changes of ≥ 20% compared to start) then continue monitoring every 15 min until stable on 2 consecutive

repeated measurements. If vital signs are stable after 2 h, subjects will be monitored for vital signs every 60 min up to 8 h post-infusion on Days 1 and 15 of Cycle 1 only. These monitoring will be performed in an area with resuscitation equipment and emergency agents In addition monitor subjects for signs/symptoms of infusion reactions including but not limited to pyrexia, chills, flushing, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. CCI

Due to possible food effects on the PK of M4112, M4112 should be administered at least 1 h prior to a meal and at least 2 h after a meal.

Subjects will be instructed to avoid any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges and cranberries within 7 days prior to Day 1 of M4112 administration and during M4112 administration. The same applies to herbal supplements which induce or inhibits CYP3A, including but not limited to St. John's wort. For further details, see the Drug Development and Drug Interactions website mentioned in Section 6.5.2.

The treatment recommendations for infusion-related reactions and severe hypersensitivity reactions according to the NCI are as outlined in Sections 6.5.5.1 and 6.5.5.2, respectively.

Investigators should also monitor subjects closely for potential irAEs, which may become manifest earliest after weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of hypothetical irAEs also includes formation of auto-antibodies like anti-nuclear antibodies (ANAs) or anti-neutrophil cytoplasmic antibodies (ANCAs). See Section 6.5.5.3 for details on the management of irAEs.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

Any Grade 4 ADRs require treatment discontinuation except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.

Any Grade ≥ 3 AEs and irAEs require treatment discontinuation with exception of any of ADRs mentioned in Section 6.2.3 and 6.2.4 in the DLT criteria.

6.5.5.1 Infusion-Related Reactions

[redacted]

6.5.5.2 Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf (UK Resuscitation Council). Subjects should be instructed to report any delayed reactions to the investigator immediately.

A. Symptoms

- Impaired airway
- Decreased oxygen saturation (< 92%)
- Confusion
- Lethargy
- Hypotension
- Pale/clammy skin
- Cyanosis.

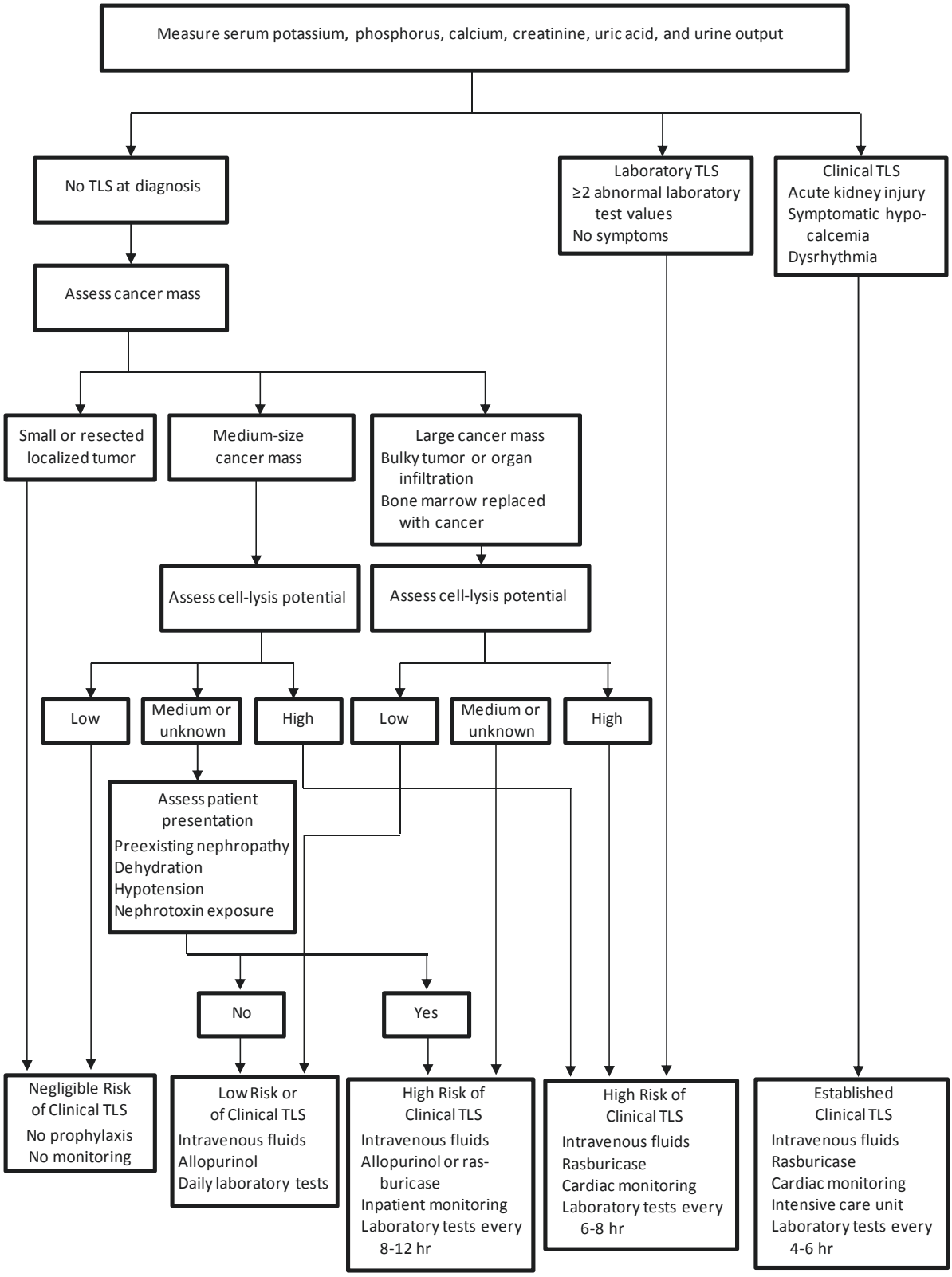
B. Management

- Epinephrine injection and dexamethasone infusion
- Subject should be placed on monitor immediately
- Alert intensive care unit for possible transfer if required

CCI [redacted]

CCI [redacted]

Figure 2 Assessment and Initial Management of Tumor Lysis Syndrome



TLS = tumor lysis syndrome.

6.5.5.3 Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids.

Treatment of irAEs should follow guidelines set forth in Table 9.

Table 9 Management of Immune-Related Adverse Events of CCI [redacted] M4112 as Single Agent CCI [redacted]

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE 4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	CCI [redacted] M4112 therapy Symptomatic treatment (eg, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3, or 4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; iv fluids indicated < 24 h; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay CCI [redacted], or M4112 therapy Symptomatic treatment	If improves to Grade 1: Resume CCI [redacted] or M4112 therapy If persists > 5 to 7 days or recurs: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; iv fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold CCI [redacted] M4112 therapy for Grade 3 Permanently discontinue CCI [redacted] M4112 therapy for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade 1, then taper over at least 1 month, resume CCI [redacted] therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis Permanently discontinue IMP

Dermatological irAEs		
Grade of Rash (NCI-CTCAE 4.03)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue CCI M4112 therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold CCI M4112 therapy Consider skin biopsy CCI If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Covering > 30% body surface area; life threatening consequences	Withhold CCI M4112 therapy for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3 Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections CCI

Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE 4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding CCI, or M4112 therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Withhold CCI M4112 therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and then resume CCI M4112 therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4 Grade 3: Severe new symptoms;	Permanently discontinue CCI r M4112 therapy	If improves to Baseline: Taper steroids over at least 6 weeks

Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE 4.03)	**Initial Management**	**Follow-up Management**
New/worsening hypoxia; Grade 4: life-threatening	Hospitalize Pulmonary and Infectious Disease consults 1.0 to 2.0 mg/kg/day prednisone equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If not improving after 48 h or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, iv immunoglobulin, or mycophenolate mofetil)

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE 4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or total bilirubin > ULN to 1.5 x ULN	Continue CCI [redacted], CCI [redacted] M4112 therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold CCI [redacted], CCI [redacted] M4112 therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Baseline: Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume CCI [redacted] M4112 therapy following steroids taper. If worsens: Treat as Grade 3-4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Discontinue CCI [redacted] M4112 therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone iv or iv equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted (for	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE 4.03)	**Initial Management**	**Follow-up Management**
	study sites in Germany, only MRI is to be used)	

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE 4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue CCI M4112 therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4
Grade 2 Creatinine increased > 1.5 to 6 x ULN	Withhold CCI M4112 therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Baseline: Taper steroids over at least 1 month, and resume CCI M4112 therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 3 to 4 Creatinine increased > 6 x ULN	Permanently discontinue CCI M4112 therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to baseline: Taper steroids over at least 1 month,

Cardiac irAES		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and/or new laboratory CCI or cardiac imaging abnormalities suggestive of myocarditis.	Withhold CCI, CCI M4112 therapy Hospitalize In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management Cardiology consult to	If symptoms improve and immune-mediated etiology is ruled out, re-start CCI CCI CCI M4112 therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.

Cardiac irAES		
Myocarditis	**Initial Management**	**Follow-up Management**
	establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	
Immune-mediated myocarditis	Permanently discontinue CCI [redacted] M4112 therapy. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent.	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A)
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website:http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)		Continue hormone replacement/ suppression and monitoring of endocrine function as appropriate
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold CCI [redacted], CCI [redacted] M4112 therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency), or insulin (for type I diabetes mellitus) as appropriate.	Resume CCI [redacted] M4112 therapy once symptoms and/or laboratory tests improve (with or without hormone replacement/suppression). Continue hormone replacement/ suppression and monitoring of endocrine function as appropriate

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
	Rule-out secondary endocrinopathies (ie, hypopituitarism/hypophysitis)	
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum Free T4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Start hormone replacement/ suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue CCI M4112 therapy if mild or moderate symptoms with normal MRI. Repeat the MRI in 1 month • Withhold CCI 4112 therapy if severe symptoms or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate high-dose corticosteroids (1 to 2 mg/kg/day methylprednisolone iv or equivalent) followed by corticosteroids taper during at least 1 month.	Resume CCI M4112 therapy once symptoms and hormone tests improve (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume CCI M4112 therapy only once shrinkage of the pituitary gland on MRI scan is documented. Continue hormone replacement/ suppression therapy as appropriate.

Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE 4.03)	**Grade of other irAEs (NCI-CTCAE 4.03)**	**Grade of other irAEs (NCI-CTCAE 4.03)**
	Initial Management	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold CCI M4112 therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting CCI M4112 therapy If irAE is confirmed, treat as Grade 2 or 3 irAE
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold CCI M4112 therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade 1: Taper steroids over at least 1 month and resume CCI M4112 therapy following steroids taper
Recurrence of same Grade 3 irAEs	Permanently discontinue CCI M4112 therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade 1: Taper steroids over at least 1 month
Grade 4	Permanently discontinue CCI M4112 therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue CCI M4112 therapy Specialty consult	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; irAE = immune-related adverse event; MRI = magnetic resonance imaging; NCI-CTCAE 4.03 = National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03; T4 = thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

6.6 Packaging and Labeling of the Investigational Medicinal Product

CCI [redacted]

M4112

M4112 will be packaged in child resistant and tamper sealed wallets. Each wallet will contain 1 blister with 4 tablets of 25 mg or 200 mg M4112 tablets.

All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines. All IMPs will be shipped in suitable transport containers according to each IMP's storage and shipping conditions. Shipments are monitored with temperature control devices.

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

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

M4112

M4112 tablets are ready for use and do not require any preparation,

M4112 must be stored at < 25°C and must not be frozen until use, with a temperature log maintained daily. All medication boxes supplied to each study site must be stored carefully, safely, and separately from other drugs.

M4112 must not be used for any purpose other than the study. The administration of M4112 to subjects who have not been enrolled into the study is not covered by the study insurance.

Any unused M4112 should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

Storage, handling, preparation, and disposal of IMP should be according to local institutional guidelines.

6.8 Investigational Medicinal Product Accountability

The Investigator is responsible for ensuring accountability for study drugs, including reconciliation of drugs and maintenance of drug records.

Upon receipt of study drugs, the Investigator (or designee) will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided by the Sponsor and returning it to the Sponsor. A copy will be retained for the Investigator File

The dispensing of the study drugs will be carefully recorded on the appropriate drug accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the Sponsor's Monitor at each monitoring visit.

Study drugs accountability records will include:

- Confirmation of study drugs delivery to the study site;
- The inventory at the site of study drugs provided by the Sponsor and prepared at the site
- The use of each dose by each subject
- The return to the Sponsor or alternative disposition of unused study drugs
- Dates, quantities, batch numbers, expiry dates and (for study drugs prepared at the site) formulation, as well as the subjects' study numbers.

The Investigator should maintain records that adequately document:

- That the subjects were provided the doses specified by the clinical study protocol/amendment(s)
- That all study drugs provided by the Sponsor was fully reconciled.

Unused study drugs must not be discarded or used for any purpose other than the present study. Any study drug that has been dispensed to a subject must not be redispensed to a different subject.

The Sponsor's Monitor will periodically collect the study drugs accountability forms and will check all returns (both unused and used containers) before arranging or authorizing their destruction by the study site.

At the conclusion or termination of this study, study site personnel and the Clinical Study Monitor will conduct a final product supply inventory on the Investigational Drug Accountability Forms and all unused containers will be destroyed. Instructions for destruction of product will be provided to the site. The Clinical Study Monitor will be supplied with a copy for filing of the

Investigational Drug Accountability Forms. This documentation must contain a record of clinical supplies used, unused, and destroyed and shall include information on:

- All administered units
- All unused units
- All destroyed units (during the study)
- All destroyed units at the end of study
- Date of destruction(s)
- Name and signature of the Investigator/Pharmacist.

It must be ensured at each study site that the study drugs are not used in the following instances:

- After the expiry date
- After the retest date unless the study drug is reanalyzed and its retest date extended.

This is to be closely monitored by the Study Monitor.

6.9 Assessment of Investigational Medicinal Product Compliance

In this study, subjects will receive study treatment at the investigational site. Well-trained medical staff will monitor and perform the on-site study drug administration. Subjects will be instructed by the Investigator/designee regarding off-site self-administration of M4112, and compliance checks performed at all study visits. The information of each study drug administration (date and dose of study drug) will be recorded on the eCRF. On evenings preceding PK sampling time of drug intake will also be recorded. Subjects will be provided with predosing drug diaries for Days 8 and 15 of Cycle 1 and Day 1 of Cycle 2. The Investigator will ensure that the information entered into the eCRF regarding drug administration is accurate for each subject. Any reason for noncompliance should be documented.

6.10 Blinding

Not applicable

6.11 Emergency Unblinding

Not applicable

6.12 Treatment of Overdose

An overdose is defined as any dose ≥ 10% than the calculated dose for that particular administration. Any overdose must be recorded in the study treatments section of the eCRF.

For monitoring purposes, any case of overdose, whether or not associated with an AE (serious or nonserious), must be reported to Drug Safety in an expedited manner using the SAE Report Form in the eCRF (see Section 7.4.1.5).

There are no known symptoms of overdose with any of the study treatments to date. There is no established treatment for overdose with the study treatments. The Investigator should use his or her clinical judgment when treating an overdose of the study treatments considering the presenting symptoms and standard evaluation results.

6.13 Medical Care of Subjects after End of Study

After a subject has completed the study or has withdrawn early, usual treatment will be administered, if required, in accordance with the study site's medical practice and depending on the subject's individual medical needs.

Upon withdrawal from the study, subjects may receive whatever care they and their physicians agree upon.

7 Study Procedures and Assessments

7.1 Schedule of Assessments

A complete Schedule of Assessments is provided in Table 1, Table 2, and Table 3. Every effort should be made to perform assessments as close as possible to the scheduled time points.

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

7.1.1 Screening and Baseline Procedures and Assessments

The screening procedures and baseline assessments will be completed up to 21 + 7 days before study treatment starts.

Subjects will be asked to sign the ICF at the start of the screening period and before any study-related investigations and assessments are started. The screening procedures and baseline assessments will be completed up to 21 + 7 days of signing the ICF and before receiving treatment. Failure to establish eligibility within 28 days would result in screening failure and the subject will be excluded from the study.

The subjects' information that will be documented during screening includes the demographic information (birth date as permitted by local regulations, sex, and race as permitted by local regulations) and the complete medical history, including the history of malignant disease, history of malignant disease drug therapy/radiotherapy/surgery, previous and ongoing medications, and baseline medical condition (concomitant medications and procedures and AEs will be monitored throughout the study treatment period). Moreover, an Emergency Medical Support card will be handed out at the baseline assessments visit.

During screening, subjects will undergo a complete physical examination, including recording body height and weight, vital signs, chest X-ray, 12-lead ECG, and a determination of the ECOG PS.

The screening laboratory examination includes hematology, coagulation, full serum chemistry, and full urinalysis (dipstick plus microscopic evaluation if indicated), will also be assessed at Screening for all subjects.

During screening, a serum β-human chorionic gonadotropin (βHCG) pregnancy test will be performed for females of childbearing potential, and blood hepatitis B virus and hepatitis C virus tests will be performed (may be analyzed locally) for all screened subjects as these conditions are study entry exclusion criteria (see Section 5.3.2). Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, FSH will be drawn at Screening.

The tumor evaluation (type and staging, etc.) will be performed using computed tomography (CT) scan or magnetic resonance imaging (MRI; if MRI is used, CT of chest is mandatory), as well as histopathological evaluation and tumor markers or any other established methods (see Section 7.2.5 for details).

Free T4 and TSH samples will be collected at time points indicated in the Schedule of Assessments (Table 1, Table 2, and Table 3).

CCI [redacted]

Please see the Schedule of Assessments (Table 1, Table 2, and Table 3) for the full, detailed list of screening and baseline procedures and assessments.

7.1.2 Treatment Period

For this protocol, a treatment cycle is defined as 28 days.

Study treatment will begin within 4 days of treatment assignment. The treatment assignment will be within the 21 + 7 day screening window. While on study treatment, subjects will be asked to visit the study site for assessments according to the Schedule of Assessments (Table 1, Table 2, and Table 3).

The treatment period will begin at the first dose of M4112 in Cycle 1 Day 1 and consist of consecutive 28-day cycles of continuous M4112 BID (or a regimen determined by the SMC), either as monotherapy CCI [redacted] administered as a 1 h infusion every 2 weeks.

On study site visit days, the morning dose of M4112 will be administered at the study site CCI [redacted]

The following instructions should be followed:

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In this study, study treatment will be given until disease progression, significant clinical deterioration (clinical progression), unacceptable toxicity, or any criterion for withdrawal from the study or study treatment is fulfilled (see Section 5.5.1).

A time window of ± 1 day for Cycle 1 and Cycle 2, ± 3 days for ≥ Cycle 3 will be permitted for all study assessment visits.

Assessments to be performed during the treatment period are presented in Table 1, Table 2, and Table 3.

At visits where assessment time points coincide with each other, the following procedure should be followed: perform vital signs assessments and ECG assessments slightly before the specific time point, PK assessments on the specified time point, ADA assessments on the specified time point, and lastly PD assessments. Use of agreed upon time windows will be allowed.

7.1.3 End of Treatment

All subjects who discontinue M4112 treatment or M4112 treatment CCI must undergo the End of Treatment Visit within 7 days and the Safety Follow-up Visit within 30 ± 3 days and CCI

CCI for a full safety evaluation. Subjects who discontinue treatment in the absence of disease progression will not be followed-up after the Safety Follow-up Visits.

7.1.3.1 End of Treatment Visit

All subjects must undergo an End of Treatment Visit after discontinuation of treatment for any reason. This visit should be performed within 7 days of the decision to discontinue treatment but before any new antineoplastic therapy is started (if possible), whichever occurs earlier. Please see Table 1, Table 2, and Table 3 for the specific assessments to be performed.

Any subject who experiences an AE that mandates discontinuation of study treatment should have an End of Treatment Visit as soon as possible after the decision to discontinue study treatment (within 7 days). At the End of Treatment Visit, the assessments indicated in the Schedule of Assessments (Table 1, Table 2, and Table 3) will be performed.

7.1.3.2 Safety Follow-up Visits

The Safety Follow-up Visit is scheduled 30 ± 3 days (monotherapy CCI after the last administration of M4112, CCI until resolution to Grade 1, before the start of any new anticancer therapy, whatever occurs first. Subjects who discontinue treatment must be followed on study until resolution of toxicity or until confirmed disease progression. The Safety Follow-up Visits will include an assessment of safety parameters and other applicable assessments as described the Schedule of Assessments (Table 1, Table 2, and Table 3).

7.2 Demographic and Other Baseline Characteristics

The assessments and procedures described in this section will be performed during the screening period.

7.2.1 Demographic Data

The following demographic data will be collected at Screening: date of birth, sex (gender), race, and ethnicity.

7.2.2 Diagnosis of Tumor

The cancer disease information that will be documented and verified at the Screening Visit for each subject includes:

- Detailed history of the malignancy, including histopathological diagnosis, grading, and staging in accordance with the American Joint Committee on Cancer (AJCC)/International Union Against Cancer Tumor Node Metastasis Classification of Malignant Tumors (UICC) at diagnosis
- All therapy used for prior treatment of the malignancy (including surgery, radiotherapy and chemotherapy, immunotherapy)
- Any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy
- Current signs and symptoms of the malignancy and AEs from current and previous anticancer treatments
- Current disease status.

7.2.3 Medical History

In order to determine the subject's eligibility to the study, a complete medical history of each subject will be collected and documented during screening, which will include, but may not be limited to, the following:

- Past and concomitant nonmalignant diseases and treatments
- All medications taken and procedures carried out within 4 weeks prior to Screening.

7.2.4 Vital Signs and Physical Examination

Vital signs and physical examinations will be recorded at Screening, study entry, and subsequent visits as indicated in the Schedule of Assessments (Table 1, Table 2, and Table 3).

Vital signs including oral temperature, respiratory rate, heart rate, and blood pressure will be recorded after 3 to 5 min rest in the semi-recumbent position. The resting time will have to be reported in the eCRF.

A complete physical examination (including, general appearance, skin, pulmonary, cardiovascular, gastrointestinal, external genitourinary only as medically relevant, lymphatic, neurologic and musculoskeletal systems, head/neck, extremities, eyes, ears, nose, throat, and cognitive status) will be performed and the results documented.

The ECOG PS as well as the height and body weight will be documented in the eCRF.

7.2.5 Computed Tomography or Magnetic Resonance Imaging Scans for Tumor Assessment at Baseline

Baseline imaging will be performed up to 21 + 7 days prior to the first M4112 administration in order to establish baseline disease status of target and nontarget lesions according to RECIST 1.1 (Appendix III). A chest X-ray should be performed before a CT or MRI scan to exclude prohibitive entry criteria.

In addition to a baseline assessment prior to start of treatment, during treatment, CT scans (with contrast media, unless contraindicated) will be done for tumor assessments within 7 days prior to Day 1 of Cycles 3, 5, and 7 and thereafter every 3 cycles until progressive disease. These assessments can also be done by MRI (if MRI is used, CT of chest is mandatory), using the same method at all subsequent assessment time points. Imaging should be performed of the chest/abdomen/pelvis (plus other regions as specifically required for specific tumor types), and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual subject. A brain CT/MRI scan should be performed, if clinically indicated by development of new specific symptoms. Skin metastasis can be used as target lesions according to RECIST 1.1 (Appendix III) using measurements by caliper, if they fulfill RECIST 1.1 for target lesions. All the scans performed at baseline need to be repeated at subsequent visits for tumor assessment. In general, lesions detected at Baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

7.2.6 Cardiac Assessments

Triplicate digital 12-lead ECGs will be recorded at baseline and at subsequent visits as indicated in the Schedule of Assessments (Table 1, Table 2, and Table 3) immediately after measurement of vital signs and after the subject has rested in a semi-recumbent position for at least 5 min. The ECG results will be used to evaluate the heart rate, atrial ventricular conduction, QR and QT intervals, and possible arrhythmias.

Triplicate digital 12-lead ECG will be recorded at Screening, predose and 2, 3, 4 and 8 h postdose just prior PK sample collections during Days 1 and 15 of Cycle 1, predose Day 8 of Cycle 1 and predose and at least 60 min postdose on Day 1 Cycle 2, Day 1 Cycle 4, Day 1 Cycle 6 and then every second cycle thereafter and during the End of Treatment Visit and first Safety Follow-up Visit (Table 4 to Table 6). These ECGs will be approximately 2 min apart to determine mean QTc (average of triplicates) and will be read locally first. For Part IB and IC, Cycle 1 Day 1 and Day 15 triplicate digital ECGs will be also be read centrally for central tendency, outlier and exposure-QTc analyses.

For Part IA only, replicate ECGs (Holter) will also be collected on Days 1 and 15 of Cycle 1 for concentration-QTc analysis (Part IA only) as indicated in Table 4.

ECG recordings must be performed before PK sampling time points. Time points may change if C_{max} is different from predicted, ECG time points may be changed.

To assess the safety and tolerability of the IMP, an ECG can be repeated at the Investigator's discretion at unscheduled visits.

The start of the resting time, ECG time, and PK sampling time will be recorded in the eCRF.

7.2.7 Clinical Laboratory Tests

Blood samples will be collected at Screening for clinical laboratory parameter evaluations. These clinical laboratory test results will serve not only as the baseline values for subsequent safety clinical laboratory evaluations during the study, but also help to make sure that each enrolled subject fulfills all the study entry criteria and does not meet any of the study exclusion criteria for laboratory parameters as listed in Section 5.3. Detailed description of laboratory assessments is provided in Section 7.4.3.

7.3 Efficacy Assessments

The tumor response assessments will be performed at time points indicated in the Schedule of Assessments (Table 1, Table 2, and Table 3) and as discussed in Section 7.2.5.

- **Clinical endpoints:** Time to tumor response, objective response, best overall response (BOR), DCR, duration of response (DOR), and progression-free survival per Investigator according to RECIST 1.1 (Appendix III). A CT or MRI scan is mandatory for confirming any CR and partial response (PR) after at least 4 weeks following first assessment.
- **Progression Free Survival (PFS)** time is defined as the time from start date to the date of the first documentation of objective progression of disease or death due to any cause, whichever occurs first. PFS data will be censored on the date of the last adequate tumor assessment for subjects who do not have an event (progressive disease or death), for subjects who start a new anticancer therapy prior to an event or for subjects with an event after 2 or more missing tumor assessments. Subjects who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the treatment start date unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.
- **Best Overall Response (BOR)** will be determined according to RECIST 1.1 (Appendix III). It is defined as the best response obtained among all tumor assessment visits after the date of first study drug administration until documented disease progression. The BOR rate is defined as the number of subjects with BOR was either confirmed CR or PR, relative to the number of subjects belonging to the study of interest.
- Only tumor assessments performed before the start of any further anticancer treatment will be considered in the assessment of BOR. Clinical deterioration will not be considered as documented disease progression.
- **Disease Control Rate (DCR)** is defined as a BOR of complete response (CR), PR or stable disease. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. DCR is the proportion of subjects with disease control.

- **Duration of Response (DOR)** is defined, for subjects with an objective response, as the time from first documentation of objective response (CR or PR) to the date of first documentation of objective progression of disease or death due to any cause whichever occurs first. If a subject has not had an event (progressive disease or death), DOR is censored at the date of last adequate tumor assessment.
- **Follow-up:** See Schedule of Assessments (Table 1, Table 2, and Table 3). Subjects without progressive disease according to RECIST 1.1 (Appendix III) at the End of Treatment Visit will not be followed up for disease progression.

At baseline, tumor lesions will be categorized in target and nontarget lesions as described in RECIST 1.1 (Appendix III).

Results for these evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluating tumor response.

The Investigator may perform scans in addition to a scheduled study scan for medical reasons or if the Investigator suspects progressive disease. Subjects who withdraw from the study for clinical or symptomatic deterioration before objective documentation of progressive disease will be requested to undergo appropriate imaging to confirm progressive disease. Every effort should be made to confirm a clinical diagnosis of progressive disease by imaging.

7.4 Assessment of Safety

The safety profile of M4112 will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, AESIs, DLTs, physical examination findings including vital signs, laboratory tests (chemistry, hematology, and coagulation), ECOG PS and a 12-lead ECG in triplicate from the date of signature of first informed consent either until the 30 ± 3 days or until the 90 ± 6 days Safety Follow-up Visit (for Part IB and Part IC). Severity of AEs will be graded using the NCI-CTCAE 4.03 (publication date: 14 June 2010) toxicity grades. AEs related to study medication will be defined as any AE considered related to M4112 CCI [redacted]

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the study, from the time of the subject's signature of informed consent. Study site personnel will report any AE, 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.

The safety assessments will be performed according to the Schedules of Assessments (Table 1, Table 2, and Table 3).

On Day 1 and Day 15 of every cycle, vital signs (blood pressure, pulse, respiratory rate, temperature) will be assessed predose (within 15 min of oral dosing and infusion), and then every 15 min CCI [redacted], during infusion and for an additional 2 h post-infusion. If vital signs are not stable after 2 h (either blood pressure

> 140/> 90 mmHg or < 90/< 60 mmHg compared to normal blood pressure at start or changes of > 20 reading points between measurements, for heart rate and respiration rate changes of ≥ 20% compared to start) then continue monitoring every 15 min until stable on 2 consecutive repeated measurements. If vital signs are stable after 2 h, subjects will be monitored for vital signs every 60 min up to 8 h post-infusion on Days 1 and 15 of Cycle 1 only. These monitoring will be performed in an area with resuscitation equipment and emergency agents. In addition monitor subjects for signs/symptoms of infusion reactions including but not limited to pyrexia, chills, flushing, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. CCI [redacted] In order to treat possible hypersensitivity reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation. CCI [redacted]

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 4.03 (publication date: 14 June 2010), 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 study treatment (M4112, CCI [redacted] using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study treatment include, but may not be limited to, temporal relationship between the AE and the study treatment, known side effects of study treatment, medical history, concomitant medication, course of the underlying disease, study procedures.

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

Related: Reasonably related to the IMP. The AE could medically (pharmacologically/clinically) be attributed to the study treatment under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the 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.

Adverse Drug Reaction (ADR)

ADRs are defined in this study as any AEs suspected to be related to study treatment by the Investigator and/or Sponsor.

SAE

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 7.4.1.5.

Events that Do Not Meet the Definition of an SAE

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

Events Not to Be Considered as AEs/SAEs

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

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 (S)AE, 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).

Predefined AESIs for Safety Monitoring

Any AE that is suspected to be a potential irAE and infusion related reactions will be considered an AESI.

7.4.1.2 Methods of Recording and Assessing Adverse Events

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

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 SAE eCRF page as described in Section 7.4.1.5.

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 study treatment, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study treatment, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion Guidelines.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the study (date of first signature of informed consent) and continues through the 30 ± 3 days Safety Follow-up Visit or 90 ± 6 days Safety Follow-up Visit (for Part IB and Part IC; as a phone call). After the Safety Follow-up Visit all SAEs and treatment-related nonserious AEs need to be documented up until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up".

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

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

SAEs

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

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an SAE Report Form in the eCRF must be completed immediately thereafter. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the study‑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).

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 Drug Safety department of the Sponsor may contact the Investigator directly to obtain clarification or to obtain further information or to discuss the event.

AESIs

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the study. The Investigator will report any AESI, whether observed by the Investigator or reported by the subject. The AESI reporting period for safety surveillance begins when the subject is initially included in the study (date of first signature of informed consent) and continues until last Safety Follow-up Visit defined as 30 ± 3 days or 90 ± 6 days (as a phone call) after the last dose of M4112, CCI CCI or before start of any anticancer therapy, whatever comes first.

DLTs

Each DLT has to be immediately recorded in the eCRF.

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 study subjects to the IEC/IRB that approved the study.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study." In particular and in line with

respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" 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 studies 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

Any AE that occurs during the course of a clinical study must be monitored and followed up and are assessed for final outcome at the last Safety Follow-up Visit.

All SAEs ongoing at the Safety Follow-up Visits 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.

Monitoring of Specific Adverse Events

In addition to the standard AE and SAE monitoring, precautions to be taken in subjects exposed to[redacted] M4112 and management of specific AEs or ADRs are provided in Section 6.5.4 and Section 6.5.5.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to study 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 CRF. 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 paper Pregnancy Report Form, which must be transmitted according to the same timeline as described for SAE reporting in Section 7.4.1.5.

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

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form in the eCRF 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 7.4.1.5, 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 study, the subject must be discontinued from study treatment immediately. The Sponsor/designee must be notified without delay and the subject must be followed as mentioned above.

7.4.3 Clinical Laboratory Safety Assessments

Blood and urine samples will be collected for the following clinical laboratory safety tests (Table 10), following the timing noted in the Schedule of Assessments (Table 1, Table 2, and Table 3). All samples should be clearly identified.

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

All clinical laboratory samples for the assessment of the relevant safety parameters, will be collected and analyzed locally. Local laboratory samples and results will be recorded in the eCRFs according to the eCRF completion guidelines. The report of the results must be retained as a part of the subject's medical record or source documents. Blood samples for the full safety tests will be taken from fasted subjects. If confirmation of a subject's postmenopausal status is necessary, an FSH level will also be performed at Screening.

Table 10 Clinical Laboratory Safety Assessments

Serum Chemistry	Hematology	Coagulation
Albumin	Absolute lymphocyte count	Activated partial thromboplastin time
Alkaline phosphatase[a]	Absolute neutrophil count	Prothrombin time/International normalized ratio (Quick, INR)
Alanine aminotransferase[a]	Hematocrit	
Amylase	Hemoglobin	
Aspartate aminotransferase[a]	Platelet count	**Basic Urinalysis** (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen)
Gamma glutamyltransferase	Red blood cell count	
Blood urea nitrogen/total urea[a]	White blood cell count and differential count	
Calcium[a]	Red blood cell morphology	Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the Screening and End of Treatment Visit.
Chloride[a]	Reticulocytes	
Creatine kinase	Mean corpuscular hemoglobin	
Creatinine[a]	Mean corpuscular volume	**Hormones**
C-reactive protein	Mean corpuscular hemoglobin concentration	Follicle-stimulating hormone (if applicable) Serum/urine β-human chorionic gonadotropin (if applicable)
Glucose[a]		T4 and TSH
Lactate dehydrogenase		
Lipase		
Phosphorus/phosphates[a]		
Magnesium[a]		
Potassium[a]		
Sodium[a]	**Serology**	
Total bilirubin/indirect bilirubin[a]	HBsAg, HBcAb	
Total protein	HBV DNA (quantitative PCR)	
Troponin-T	HCVAb, HCV RNA (quantitative PCR)	
Uric acid		

HBcAb = Hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HCVAb = hepatitis C virus antibody; T4 = thyroxine; TSH = thyroid-stimulating hormone.

a Core serum chemistries. Blood samples for serum chemistry profile will be obtained prior to the administration of the study drugs. Full serum chemistry will be performed at Screening and in Cycle 1 on Day 1 and Day 15; core chemistry in Cycle 1 on Day 8 and Day 22. In Cycle 2 to 6 thereafter, full chemistry will be performed on Day 1 and core chemistry on Day 15. From Cycle 7 onwards, full chemistry will be performed on Day 1 of every cycle and at the End of Treatment and Safety Follow-up Visits

If a subject has a clinically significant abnormal laboratory test value that is not present at Baseline, the test will be repeated weekly and the subject will be followed until the test value has returned to the normal range or the Investigator has determined that the abnormality is chronic or stable.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

Vital signs, (blood pressure, pulse, respiratory rate, temperature,) should be assessed predose (within 15 min of oral dosing and infusion), and then every 15 min CCI [redacted], during infusion and for an additional 2 h post-infusion. If vital signs are not stable after 2 h (either blood pressure > 140/> 90 mmHg or < 90/< 60 mmHg compared to normal blood pressure at start or changes of > 20 reading points between measurements, for heart rate and respiration rate changes of ≥ 20% compared to start) then continue monitoring every 15 min until stable on 2 consecutive repeated measurements. Consider hospital observation for prolonged vital sign changes or instability. As a routine precaution, subjects enrolled in this study must be observed for at least 8 h after infusion during Day 1 and Day 15 (continue vital signs every 60 min) of Cycle 1 and 2 h post infusion in follow-on cycles, in an area with resuscitation equipment and emergency agents (see Table 1, Table 2, Table 3).

ECOG PS, and 12-lead ECG (see Section 7.2.6 for 12-lead ECG details) will be assessed at time points indicated in the Schedule of Assessments (Table 1, Table 2, and Table 3).

A physical examination will be conducted at Screening and at subsequent visits as indicated in the Schedules of Assessments (Table 1, Table 2, and Table 3) and documented in the eCRF. Abnormal findings are to be reassessed at subsequent visits.

Body weight will be recorded at Screening and at subsequent visits as indicated in the Schedules of Assessments (Table 1, Table 2, and Table 3) and documented in the eCRF. Height will be measured at Screening only.

All newly diagnosed or worsening conditions, signs, and symptoms observed from screening, whether related to study treatment or not, are to be reported as AEs.

For female subjects of childbearing potential, a serum βHCG pregnancy test will be carried out during the Screening phase and a urine βHCG pregnancy test at the subsequent visits and at the Safety Follow-up visit of 30 ± 3 days as indicated in the Schedules of Assessments (Table 1, Table 2, and Table 3). Results of the most recent pregnancy test (within the last 28 days) should be available prior to the next dosing of the study treatment. Subjects who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months or FSH > 40 mIU/mL), or who had undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

Total volume of blood to be collected per subject will be approximately 20 mL for Screening and approximately 220 to 250 mL per cycle.

7.5 Pharmacokinetics

Venous blood samples (4mL each) will be collected for analysis of M4112 in plasma by a validated LC-MS/MS assay. Full details of the bioanalytical method used will be described in a separate bioanalytical report.

The schedules for PK blood sampling are shown for M4112 administered as single agent (Table 4), CCI PK parameters for M4112 will be calculated predose and over 8 h postdosing on Day 1 and Day 15, with a predose sample collected on Day 8 and predose and 2 h postdosing samples collected on Day 1 of Cycle 2.

Following analysis of M4112 concentrations, remaining plasma may be used for evaluation of potential metabolites.

CCI

The exact date/time of sample collection will be recorded in the eCRF. Although every effort should be made to collect PK blood samples according to the schedule, blood samples collected outside of the planned window are not to be considered protocol deviations as long as the actual collection time is recorded, with the exception of the predose samples, which will be considered a deviation if not collected predose.

The PK sample should be collected after ECG and vital signs are collected when scheduled at the same time.

Details of blood sample labeling, processing, storage, and shipment requirements will be described in a separate laboratory manual.

For each subject participating in the M4112 single agent dose escalation phase, a total of approximately 76 mL of blood (4 mL/sample; 19 samples over Cycle 1 and Cycle 2, Day 1) will be collected for determination of the M4112 plasma concentration.

CCI

CCI

7.5.1 Body Fluid(s)

Further details will be summarized in the Laboratory Manual.

7.5.2 Pharmacokinetic Calculations

The software to be used and PK calculations and parameters will be specified in the integrated analysis plan (iAP).

For M4112, PK calculations using standard noncompartmental analysis methods will be performed, if appropriate, using commercial software such as Phoenix® WinNonlin® (Version 6.3 or higher) at PPD by standard methods. Actual dates and times as recorded on the eCRF will be utilized for final analyses, however, nominal times may be used for PK determinations in support of the SMC review (See Section 8.6).

All other data handling procedures will be detailed in the iAP.

Pharmacokinetic parameters to be calculated for M4112 are specified in Table 11.

Table 11 Pharmacokinetic Parameters for M4112

AUC_{0-8}	Area under the plasma concentration-time curve from time zero to 8 h postdose
C_{max}	Maximum plasma concentration observed postdose
t_{max}	Time to reach maximum plasma concentration
C_{min}	Minimum observed postdose (trough) plasma concentration
$AUC_{0-8/dose}$	Area under the plasma concentration-time curve from time zero to 8 h postdose/dose
$C_{max/dose}$	Maximum observed plasma concentration/dose
$C_{min/dose}$	Minimum observed postdose (trough) plasma concentration/dose
$R_{acc(AUC0-8)}$	Accumulation of the M4112 AUC_{0-8} (Day 15/Day 1)
$R_{acc(Cmax)}$	Accumulation of the M4112 C_{max} (Day 15/Day 1)

Final PK parameters reported will be detailed in the iAP.

A population pharmacokinetic (PopPK) model will be constructed to allow for calculation of PopPK parameters for M4112 and the analysis of selected covariates. PopPK analyses will be detailed in a separate analysis plan.

Serum concentrations for CCI [redacted] will be summarized and may be included in population PK analyses models constructed for each analyte, respectively.

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]


CCI


CCI

CCI [redacted]

[redacted]

[redacted]

7.7 Other Assessments

7.7.1 Anti-Drug Antibody

CCI [redacted]

[redacted]

.

CCI [redacted]

[redacted]

[redacted]

8 Statistics

8.1 Sample Size

A Bayesian model is applied to assist the SMC in dosing recommendations. Bayesian models will be set up for IDO monotherapy and CCI [redacted] separately.

For this sample size assessment, it is assumed that it is not necessary to enroll additional subjects at RP2D or MTD and no additional levels are tested (see Section 5.1).

It is anticipated that 24 to 30 evaluable subjects (6 projected dose levels with 3 to 12 subjects each) may be needed in order to test the planned dose range of IDO monotherapy. As it is not anticipated that MTD occurs in the planned dose range, DLTs are not expected to occur frequently. Therefore, the following scenario could be anticipated, assuming 2 DLTs:

- For single agent escalation: 4 dose levels with 3 subjects each and 2 dose levels with 6 subjects each.

[redacted]

As inherent in dose escalation studies, the sample size cannot be prespecified. The SMC will recommend doses. Dose regimens are not prespecified as it is dependent on DLTs, PK, and PD observed.

8.2 Randomization

Not applicable

8.3 Endpoints

8.3.1 Primary Endpoints

Part IA (Dose Escalation – M4112 as Single Agent)

- DLTs in subjects receiving M4112 as single agent during the first 4 weeks (Day 1 to Day 28 of Cycle 1) of treatment
- TEAEs and TRAEs according to NCI-CTCAE 4.03 (including deaths) in subjects receiving M4112 as single agent from start of treatment up to the last Safety Follow-up Visit
- Treatment-emergent changes from baseline in clinical laboratory measures, vital signs, ECOG PS, and physical examination findings in subjects receiving M4112 as single agent up to the last Safety Follow-up Visit.

CCI [redacted]

[redacted]

8.3.2 Secondary Endpoints

Part IA (Dose Escalation – M4112 as Single Agent)

- Plasma PK parameters for M4112: $AUC_{0\text{-}8}$, C_{max}, t_{max}, $AUC_{0\text{-}8/dose}$, $C_{max/dose}$, (Days 1 and 15), $R_{acc(AUC0\text{-}8)}$ and $R_{acc(Cmax)}$ (Day 15), C_{min}, and $C_{min/dose}$ (Days 8 and 15 of Cycle 1 and Day 1 of Cycle 2)
- Slope of concentration-QTc (cQTc) regression based on time-matched ECG readings (3 or more replicates) and PK samples during Cycle 1 at Day 1 and Day 15, central tendency and outlier analyses for absolute QTcF, and delta QTc
- BOR, DOR, DCR, time to tumor response, and PFS using RECIST 1.1, up to confirmed tumor progression.

[redacted]

CCI

8.3.3 Other Endpoints

CCI

8.4 Analysis Sets

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

Table 13 Analysis Sets

Population	Description
Screening	All participants who sign informed consent.
Dose Escalation	All subjects treated in dose escalation cohorts who do not miss > 5 planned total daily doses of M4112 CCI in the first cycle (first 28 days) of the dose escalation part for other than DLT. CCI
Safety	The Safety Analysis Set will include all subjects who receive at least 1 dose of study treatment. CCI
Concentration-QTc Analysis Set	The cQTc Analysis Set will include all subjects with at least baseline and one on treatment measurement of time-matched ECG and M4112 plasma concentration collected during the dose-escalation phase. The cQTc analysis set will be used for slope analysis of exposure response in QTc analysis.
M4112 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 M4112 and must have sufficient M4112 plasma concentration data to enable the calculation of at least 1 PK parameter. Sufficient concentration data is defined as at least 3 valid, postdose concentration points in the PK profile to obtain any PK parameter.
CCI	
Pharmacodynamics	All subjects who received at least 1 dose of M4112 and provide the predose and at least 1 postdose sample for PD assessment.

ADA = anti-drug antibody; cQTc = concentration-corrected QT interval (QTc); DLT = dose-limiting toxicities; ECG = electrocardiogram; PD = pharmacodynamics; PK = pharmacokinetic.

8.5 Description of Statistical Analysis

8.5.1 General Considerations

All analyses will be prepared by study part (eg, monotherapy escalation, CCI and dose level and will be described in detail in the iAP.

There is no formal significance level for this study and all analyses are considered descriptive.

In general, continuous variables will be summarized using number of subjects (n); mean, standard deviation; median, 25th Percentile to 75th Percentile (Q1-Q3), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

The calculation of proportions will be based on the number of subjects in the analysis set of interest, unless otherwise specified in the study iAP.

Baseline

In general, the last nonmissing measurement prior to the first study treatment will serve as the baseline measurement.

8.5.2 Analysis of Primary Endpoints

For the dose escalation parts the analysis will focus on the number of subjects experiencing a DLT. The SMC will receive results of a Bayesian 2-parameter logistic model with overdose control updated with the observed DLT data for SMCs dedicated to dose escalation decisions (1, 30). A separate model will be set up for monotherapy CCI CCI

Recommendation on next dose of the model is based on a loss function (probabilities of being in 1 of the 4 toxicity probability intervals) will be multiplied with a loss term as follows:

0 × P (target dosing [0.17-0.35]) + 1 × P (for over [0.35-0.67] or under dosing [0-0.17]) + 2

× P (excessive dosing [0.67-1]).

In addition, only doses that have a corresponding probability of less than 25% that the true DLT rate is more than 35% (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. This Bayesian escalation approach will be used to assist the SMC to select the next dose from a predicted set of acceptable doses (eg, 100, 200, 400, 600, 800 and 900 mg BID). The SMC may choose a different dose or dosing regimen than suggested by the Bayesian escalation approach.

CCI CCI

If the SMC decides to change the dosing regimen, a separate model will be set up or the model extended to a partial order Continual Reassessment Method.

All subjects treated in dose escalation cohorts who miss > 5 planned total daily doses of M4112 CCI in the first cycle (first 28 days) of the dose escalation part for other than safety reasons are not eligible for DLT assessment, will not be considered in the Bayesian model and will not formally be replaced. The SMC can still be adjourned and the Bayesian model will be updated with the data from the evaluable subjects.

The target probability for the MTD suggested by the model will be 30%. If the DLT probability of a potential MTD reaches sufficient precision, the SMC will be informed.

The 2-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 dj ε{100 mg, 200 mg, 400 mg, 600 mg, 800 mg, 900 mg} (BID dosing) and (α, β) are bivariate normally distributed and the reference dose (d_{ref}) is 900 mg.

The following parametrization is chosen for the monotherapy prior:

E(α) = -0.8001

E(β) = 0.4647

Var(α) = 1.5², Var(β) = 1.5², Cov(α, β) = 0

This would correspond to:

Dose	100 mg	200 mg	400 mg	600 mg	800 mg	900 mg
Prior mean DLT rate	9%	12%	17%	22%	29%	36%
Prior median DLT rate	1%	3%	7%	13%	22%	30%

DLT = Dose-limiting toxicity.

For more information on operating characteristics of the prior, see Appendix V.

Posterior distribution and the recommended next dose level will be calculated using R version 3.1.2 or higher with library package bcrm (38) or package CRMpack or EAST version 6.4 or higher.

At interim analysis, after end of dose escalation, and main analysis, 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) will be estimated.

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

8.5.3 Analysis of Secondary Endpoints

Efficacy Endpoints

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 (CIs) will be used for binary endpoints.

Posterior probabilities assuming a beta (1,1) prior for the binary efficacy endpoints will also 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-month survival rate estimates and estimates for every 6 months thereafter if applicable) including the corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (7) and CIs for the survival function estimates at above defined time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (20). The estimate of the standard error will be computed using Greenwood's formula.

The Safety Analysis Set will be used for the efficacy analyses in Part I of the study.

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8.5.4 Pharmacokinetic Calculations

M4112 plasma concentrations will be listed, summarized, and graphically displayed by treatment and time point. Derived PK parameters will be listed and summarized by treatment. Descriptive summaries of plasma concentrations and derived PK parameters of M4112 will be presented for the PK analysis set. The PK variables will be summarized by the number of observations, mean, geometric mean, median, SD, standard error of mean, minimum, maximum, and/or coefficient of variation. Concentration values below the lower limit of quantification will be taken as zero for descriptive statistics.

Individual plasma and mean (±SD) concentration time plots will be provided for each treatment using a linear and semi-logarithmic scale.

Graphical displays will be given, where appropriate. Details of the statistical analysis, including evaluation of dose proportionality and comparison of parameters between single agent treatment CCI will be described further in the iAP.

A PopPK model will be constructed to allow for calculation of population pharmacokinetic parameters for M4112 and the analysis of selected covariates. PopPK analyses will be detailed in a separate analysis plan.

CCI

8.5.5 Concentration-QTc analysis

Time-matched, replicate ECGs and PK samples collected in the dose-escalation phase will be used to analyze for cQTc responses using slope analysis of exposure/response. Analyses will be further detailed in a separate analysis plan.

8.5.6 Analysis of Safety and Other Endpoints

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

Adverse Events

All AEs will be coded according to MedDRA. Severity of AEs will be graded using the NCI-CTCAE 4.03 toxicity grading scale.

AEs will be summarized according to MedDRA System Organ Classes (SOCs) and Preferred Terms. The incidence of the following will be analyzed:

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

AESIs will be summarized according to MedDRA SOCs and Preferred Terms.

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

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

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

Laboratory Values

Laboratory results will be classified by grade according to NCI-CTCAE 4.03. The worst on-treatment grades for chemistry and hematology laboratory results will be summarized. Shifts in toxicity grading from baseline to highest grade during the on-treatment period will be displayed. For laboratory tests without an NCI-CTCAE grade definition, results will be presented categorically (eg, below, within, or above normal limits).

Physical Examination Results and Electrocardiograms

Physical examination, including vital signs (body temperature, respiratory rate, heart rate, and blood pressure) and ECG, recorded at baseline and after drug administration will be presented. The ECG parameters will be summarized by descriptive statistics per time point, and changes from baseline will be calculated. Data will be further analyzed using concentration effect modeling for baseline corrected QTcF values. Time-matched replicate ECGs will be analyzed along with M4112 plasma concentrations in a cQTc analysis as described in Section 8.5.3.

CCI [redacted]

[redacted]

8.6 Interim and Additional Planned Analyses

This is an exploratory study. Available data will be evaluated during the study by the SMC.

The SMC will review the data during the conduct of the study. The cut off for dose escalation assessments by the SMC will usually be triggered by the completion of Cycle 1 (or dropout) of the last subject in the respective dose escalation cohort of usually 3 subjects. In cases where enrollment of 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 Cycle 1. The Bayesian model will then be updated with the available data, and the data from the subject not having completed Cycle 1 at time of SMC will be considered in the next SMC.

The cut off for an exploratory interim analysis of the safety and preliminary antitumor activity data from the complete single agent dose escalation will be triggered when the last subject enrolled in monotherapy dose escalation reaches the first on-treatment tumor assessment or experiences death or premature withdrawal for any reason, whichever comes first.

CCI [redacted]

The main analysis of the study is planned to occur after the objectives of the study can be answered.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

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

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

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject’s participation in the study is his/her written informed consent. The subject’s written informed consent to participate in the study must be given before any study-related activities are carried out. CCI [redacted]

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

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

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

After the information is provided by the Investigator, the ICF must be signed and dated by the subject and the Investigator.

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

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor or designee and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be provided to each subject in the study for signing and dating. The Investigator will explain the changes to the previous version. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

9.3 Subject Identification and Privacy

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

CCI [redacted] During this time, the samples may be reanalyzed for newly identified markers or with new or improved technology. After 10 years, the samples will be destroyed or fully anonymized or a new IEC/IRB approval and informed consent will be requested to keep the samples for an additional period. If tumor tissue remains, the site will be notified and the tumor tissue will be returned to the site upon request. If the site does not request the return of the tumor tissue, it will be destroyed.

9.4 Emergency Medical Support and Subject Card

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

The first point of contact for all emergencies will be the clinical study 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 or designated CRO will provide the appropriate means to contact a Sponsor/CRO physician. This includes the provision of a 24 h contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor/CRO physician to assist with the medical emergency.

9.5 Clinical Study Insurance and Compensation to Subjects

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

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the study at a given site, this clinical study protocol will be submitted together with its associated documents (eg, ICF) 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 study, the clinical study protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical study 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 study in accordance with national regulations and requirements.

9.7 Health Authorities

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

10 Study Management

10.1 Case Report Form Handling

Refer to the Manual of Operations for eCRF handling guidelines.

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

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

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

10.2 Source Data and Subject Files

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

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the study)
- Study identification, that is, the Sponsor study number for this clinical study, and subject number

- Dates for entry into the study (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical study protocol
- All AEs
- Date that the subject left the study including any reason for early withdrawal from the study or IMP (if applicable).

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

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

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

10.4 Monitoring, Quality Assurance, and Inspection by Health Authorities

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

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

CRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Study Protocol

Changes to the clinical study protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant 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 study requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Study Report and Publication Policy

10.6.1 Clinical Study Report

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

Posting of data on ClinicalTrials.gov is planned and will occur 12 months after the last study site visit of the final study subject or another appropriate date to meet applicable requirements.

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

Contraceptive Guidance

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

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

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

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
• Vasectomized partner (A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized 30 days prior to the first study treatment administration, during the treatment period and for at least 60 days after the last dose of study treatment

Appendix II: Strong Inhibitors and Inducers of CYP3A4 or Substrates with a Narrow Therapeutic Range and Drugs Causing QTc Prolongation

Table with Examples of Inhibitors or Inducers of CYP3A4 Enzymes or Substrates with a Narrow Therapeutic Range

Strong Inhibitors
Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole
Strong Inducers
Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort
Substrates With a Narrow Therapeutic Range
Alfentanil, astemizole[a], cisapride[a], cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[a]

CYP = cytochrome P450.

a Withdrawn from the US and certain other markets because of safety reasons.

Note: This is not an exhaustive list. For an updated list, see Tables 5, 6, and 7 in the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Note: A strong inhibitor is defined as an inhibitor that increases the AUC of a substrate sensitive for that CYP ≥ 5-fold or decreases clearance by > 80%, and a strong inducer decreases AUC of a substrate by ≥ 80%.

Note: CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de pointes).

Table with Examples of Drugs Causing QTc Prolongation

Antipsychotics	Type IA Antiarrhythmics	Type IC Antiarrhythmics	Class III Antiarrhythmics
Chlorpromazine	Quinidine	Flecainide	Sotalol
Haloperidol	Procainamide	Encainide	Amiodarone
Droperidol	Disopyramide		
Quetiapine			
Olanzapine			
Amisulpride			
Thioridazine			
Tricyclic antidepressants	**Other antidepressants**	**Antihistamines**	**Other**
Amitriptyline	Mianserin	Astemizole	Chloroquine
Doxepin	Citalopram	Loratidine	Hydroxychloroquine
Imipramine	Escitalopram	Terfanadine	Quinine
Nortriptyline	Venlafaxine		Macrolides
Desipramine	Bupropion		Erythromycin
	Moclobemide		Clarithromycin

Note: This is not an exhaustive list.

Appendix III: Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

For details, see Eisenhauer et al. 2009 (10).

Definitions

At baseline (within 4 weeks of initiation of treatment), tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable:

- *Tumor lesions*: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
- 10 mm by CT scan (CT scan slice thickness ≤ 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- *Malignant lymph nodes*: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

Non-measurable

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, positron emission tomography scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT, MRI, or other established

methods can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area or other loco-regional therapy area are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Methods of measurement

- Measurement of lesions

  All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

- Method of assessment

  The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

- *Chest X-ray*: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- *CT, MRI:* CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have

slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. An MRI is also acceptable in certain situations (eg, for body scans).

- *Ultrasound*: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.
- *Endoscopy, laparoscopy:* The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following CR or surgical resection is an endpoint.
- *Tumor markers:* Tumor markers alone cannot be used to assess objective tumor response.
- *Cytology, histology:* These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor response evaluation

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. Response criteria are listed in Table A and Table B.

Response Criteria

Table A

Evaluation of target lesions	
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study

Table B

Evaluation of non-target lesions	
Complete Response (CR)	Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
Stable Disease	Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease	Unequivocal progression (see comments below) of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression).

Note: Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

It is assumed that at each protocol specified time point, a response assessment occurs. Table C below provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Table C

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-progressive disease	No	PR
CR	Not evaluated	No	PR
PR	Non- progressive disease or not all evaluated	No	PR
Stable disease	Non- progressive disease or not all evaluated	No	Stable disease
Not all evaluated	Non progressive disease	No	Not evaluable
Progressive disease	Any	Yes or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease

CR = complete response, PR =partial response.

The best overall response is determined once all the data for the subject is known.

Best response determination in studies where confirmation of CR or PR IS NOT required: Best response in these studies is defined as the best response across all time points (for example, a subject who has stable disease at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response of PR). When stable disease is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when stable disease is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has stable disease at first assessment, progressive disease at second and does not meet minimum duration for stable disease, will have a best response of progressive disease. The same subject lost to follow-up after the first stable disease assessment would be considered not evaluable.

Best response determination in studies where confirmation of CR or PR is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (at least 4 weeks apart). In this circumstance, the best overall response can be interpreted as in Table D.

Table D

Overall response	Overall response	BEST overall response
First time point	**Subsequent time point**	
CR	CR	CR
CR	PR	Stable disease, progressive disease, or PR[a]
CR	Stable disease	Stable disease provided minimum criteria for stable disease duration met, otherwise, progressive disease
CR	Progressive disease	Stable disease provided minimum criteria for stable disease duration met, otherwise, progressive disease
CR	NE	Stable disease provided minimum criteria for stable disease duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	Stable disease	Stable disease
PR	Progressive disease	Stable disease provided minimum criteria for stable disease duration met, otherwise, progressive disease
PR	NE	Stable disease provided minimum criteria for stable disease duration met, otherwise NE
NE	NE	NE

CR = complete response, NE = not evaluable, PR = partial response.

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease progressive disease at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for stable disease was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Appendix IV: Immune-Related Response Criteria

Below is a summary of irRECIST (Bohnsack 2014 [4]):

1. Total measured tumor burden (TMTB): Baseline-selected target lesions and new measurable lesions should NOT be assessed separately. Measurements of those lesions should be combined into the TMTB, and one combined assessment provided.

2. New Measurable Lesions: In irRECIST, criteria for unidimensional lesion measurement apply to both target and new measurable lesions: a minimum 10 mm in the longest diameter for non-nodal lesions, and a minimum 15 mm in short axis for lymph nodes. Smaller lesions contribute to the non-target or new non-measurable tumor burden, but do not get measured.

3. irPR if no Target Lesions: If new measurable lesions appear in subjects with no target lesions at Baseline, irPD will be assessed. That irPD time point will be considered a new Baseline, and all subsequent time points will be compared with it for response assessment. An assessment of irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared with the first irPD documentation.

4. Non-Target Lesions: In alignment with RECIST 1.1, Baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent time points and become measurable. Only true new lesions can be measured and contribute to the TMTB.

Example: A subject has multiple lung metastases, all smaller than 10 mm and selected as no-target lesions at Baseline. If, at a subsequent time point some of these non-target lesions increase and become > 10 mm, and 1 new lesion > 10 mm appears, only the new measurable lesion will contribute to the TMTB, and not the Baseline selected non-target lesion that increased in size. Otherwise such an increase would make persisting non-target lesions switch into the new measurable lesion category, which would be inaccurate, as the lesion existed at Baseline.

5. irPD Based on Non-Target Lesions: In irRECIST, a substantial and unequivocal increase of non-target lesions is indicative of progression.

6. irPD Based on New Non-Measurable Lesions: According to irRECIST, the reviewer may assign irPD for the subject with multiple new lesions of 9 mm if they are considered to be a sign of unequivocal, massive worsening.

7. irPD Confirmation: Progression confirmation no less than 4 weeks after the initial irPD assessment is recommended, especially in case of marginal disease growth and if the first irPD assessment is within the compound-specific tumor flare window.

Appendix V: Operating Characteristics of Bayesian Dose Escalation 2-Parameter Logistic Regression Model with Selected Prior and Overdose Control Boundary at 35%

The following table shows the operating characteristics of the Bayesian logistic regression dose escalation model. It shows potential scenarios for dose escalation and associated estimated posterior probabilities of estimated DLT probability being in one of the toxicity intervals.

			Prior Specifications: E(α)=-0.800119, E(β)=0.464697, Var(α) = 1.5², Var(β) = 1.5², Cov(α, β) = 0						
			Recommended Dose Considering			Posterior Probability of DLT Probability of Recommended Dose (Model and Overdose Control) being in Toxicity Interval			
Scenario	Doses Tested	Dose-Limiting Toxicities/ Number of Subjects	Loss Function	Overdose Control	Model and Overdose Control	[0,0.17] "Under Dosing"	(0.17,0.35] "Target Dosing"	(0.35,0.67] "Over Dosing"	(0.67,1] "Excessive Dosing"
1	100 mg	0/3	800 mg	600 mg	600 mg	0.67	0.19	0.12	0.02
1a	100 mg	1/3	100 mg	100 mg	100 mg	0.43	0.32	0.22	0.02
1b	100 mg	1/6	200 mg	200 mg	200 mg	0.49	0.36	0.15	<0.01
2	100 mg 200 mg	0/3 0/3	800 mg	800 mg	800 mg	0.54	0.24	0.18	0.04
2a	100 mg 200 mg	0/3 1/3	400 mg	200 mg	200 mg	0.59	0.31	0.10	<0.01
2b	100 mg 200 mg	0/3 1/6	400 mg	400 mg	400 mg	0.48	0.37	0.15	<0.01
3	100 mg 200 mg 400 mg	0/3 0/3 0/3	800 mg	800 mg	800 mg	0.61	0.23	0.14	0.02
3a	100 mg 200 mg 400 mg	0/3 0/3 1/3	600 mg	400 mg	400 mg	0.60	0.31	0.09	<0.01
3b	100 mg 200 mg	0/3 0/3	600 mg	600 mg	600 mg	0.48	0.36	0.15	<0.01

			Prior Specifications: E(α)=-0.800119, E(β)=0.464697, Var(α) = 1.5², Var(β) = 1.5², Cov(α, β) = 0						
			Recommended Dose Considering			Posterior Probability of DLT Probability of Recommended Dose (Model and Overdose Control) being in Toxicity Interval			
Scenario	Doses Tested	Dose-Limiting Toxicities/ Number of Subjects	Loss Function	Overdose Control	Model and Overdose Control	[0,0.17] "Under Dosing"	(0.17,0.35] "Target Dosing"	(0.35,0.67] "Over Dosing"	(0.67,1] "Excessive Dosing"
	400 mg	1/6							
4	100 mg 200 mg 400 mg 600 mg	0/3 0/3 0/3 0/3	900 mg	800 mg	800 mg	0.70	0.20	0.09	<0.01
4a	100 mg 200 mg 400 mg 600 mg	0/3 0/3 0/3 1/3	600 mg	600 mg	600 mg	0.57	0.33	0.10	<0.01
4b	100 mg 200 mg 400 mg 600 mg	0/3 0/3 0/3 1/6	800 mg	800 mg	800 mg	0.42	0.36	0.21	0.02
5	100 mg 200 mg 400 mg 600 mg 800 mg	0/3 0/3 0/3 0/3 0/3	900 mg	900 mg	900 mg	0.61	0.24	0.13	0.03
5a	100 mg 200 mg 400 mg 600 mg 800 mg	0/3 0/3 0/3 0/3 1/3	800 mg	800 mg	800 mg	0.49	0.36	0.15	<0.01
5b	100 mg 200 mg 400 mg	0/3 0/3 0/3	900 mg	900 mg	900 mg	0.42	0.34	0.20	0.03

			Prior Specifications: E(α)=-0.800119, E(β)=0.464697, Var(α) = 1.5², Var(β) = 1.5², Cov(α, β) = 0						
			Recommended Dose Considering			Posterior Probability of DLT Probability of Recommended Dose (Model and Overdose Control) being in Toxicity Interval			
Scenario	**Doses Tested**	**Dose-Limiting Toxicities/ Number of Subjects**	**Loss Function**	**Overdose Control**	**Model and Overdose Control**	**[0,0.17] "Under Dosing"**	**(0.17,0.35] "Target Dosing"**	**(0.35,0.67] "Over Dosing"**	**(0.67,1] "Excessive Dosing"**
	600 mg 800 mg	0/3 1/6							
6[a]	100 mg 200 mg 400 mg 600 mg 800 mg 900 mg	0/3 0/3 0/3 0/3 0/3 0/3	900 mg	1,000 mg	900 mg	0.79	0.17	0.03	<0.01
6a[a]	100 mg 200 mg 400 mg 600 mg 800 mg 900 mg	0/3 0/3 0/3 0/3 0/3 1/3	900 mg	900 mg	900 mg	0.43	0.37	0.19	0.01
6b[a]	100 mg 200 mg 400 mg 600 mg 800 mg 900 mg	0/3 0/3 0/3 0/3 0/3 1/6	900 mg	900 mg	900 mg	0.62	0.31	0.06	<0.01

a Maximum of preplanned doses reached. Potential higher doses offered to the model are 1,000 mg and 1,200 mg.

Appendix VI: Signature Pages and Responsible Persons for the Study

Signature Page – Protocol Lead

Study Title:	Phase I, First-in-Human, Open-Label, Multiple-Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M4112 an IDO1/TDO2 Inhibitor as Single Agent CCI CCI CCI in Subjects with Metastatic or Locally Advanced Unresectable Solid Tumors
IND Number:	CCI
EudraCT Number:	To be determined
Clinical Study Protocol Date / Version:	08 September 2017 / Version 2.0

Protocol Lead:

I approve the design of the clinical study:

PPD

PPD

Signature PPD

Date of Signature

Name, academic degree: PPD

Function/Title: Medical Responsible/PPD

Institution: Merck KGaA

Address: Frankfurter Strasse 250, 64293 Darmstadt, Germany

Telephone number: PPD

Mobile number:

E-mail address:

Signature Page – Coordinating Investigator

Study Title	Phase I, First-in-Human, Open-Label, Multiple-Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M4112 an IDO1/TDO2 Inhibitor as Single Agent CCI CCI CCI n Subjects with Metastatic or Locally Advanced Unresectable Solid Tumors
IND Number	CCI
EudraCT Number	To be determined
Clinical Study Protocol Date / Version	08 September 2017 / Version 2.0

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

PPD

Signature

PPD

Date of Signature

Name, academic degree: PPD

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Signature Page – Principal Investigator

Study Title	Phase I, First-in-Human, Open-Label, Multiple-Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M4112 an IDO1/TDO2 Inhibitor as Single Agent CCI [redacted] n Subjects with Metastatic or Locally Advanced Unresectable Solid Tumors
IND Number	CCI [redacted]
EudraCT Number	To be determined
Clinical Study Protocol Date / Version	08 September 2017 / Version 2.0
Center Number	

Principal Investigator

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

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

_____ _____

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:	Clinical Trial Lead
Institution:	EMD Serono, Inc.
Address:	45A Middlesex Turnpike, Billerica, MA 01821, US
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Function/Title:	Biostatistician
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Appendix VII: Protocol Amendments and List of Changes

Previous Protocol Amendments

Table of Amendments

Amendment Number	Substantial (Y/N)	Date	Region or Country	Included in the current document (Y/N)
1	Yes	08 September 2017	Global	Yes

Amendment 1, 08 September 2017, Global Amendment

Rationale

The purpose of this amendment is to amend the protocol following the FDA's requests: received by 01 September 2017 (see major scientific changes).

This amendment also includes changes in schedule of assessments tables with the intent to:

- Align and provide consistency between treatment arms
- Resolve discrepancies between tables and their footnotes for triplicate electrocardiogram (ECG) at Day 1 Cycle 2.

Administrative and Editorial Changes

The name of the Clinical Trial Lead was updated to reflect the recent transition in this role. Additional clarifications and minor editorial changes to correct, eg, typographical errors were implemented.

Comparison with Clinical Study Protocol Version 1.0, 28 July 2017 (Amendment No. 1)

Addition of text is indicated in **bold** in below table. If the original text was bold, additional text is indicated in **bold and underlined**. Deleted text is indicated by ~~strikethrough~~.

Change	Section	Previous Wording	New Wording
Safety monitoring of IRRs and cytokine release wording was added to the protocol	Schedule of Assessments Table 1 to Table 3, footnote g	Table 1: Vital signs (blood pressure, pulse, respiratory rate, and oral temperature) will be assessed after the subject has rested in the semi-recumbent position for 3 to 5 min. Height and weight at Screening only. Table 2 and Table 3: Vital signs (blood pressure, pulse, respiratory rate, and oral temperature) will be assessed after the subject has rested in semi-recumbent position for 3 to 5 min. Vital signs should be assessed predose (within 15 min of start of infusion), then every 15 (± 5) min after the start of infusion (15, 30, 45, 60 [end infusion] and 30 (± 10), 60 (± 10) min after the end of infusion. Height at Screening only. CCI [redacted]	Table 1: ~~Vital~~ **On Day 1 and Day 15 of every cycle, vital** signs (blood pressure, pulse, respiratory rate, ~~and oral~~ temperature) will be assessed **predose (within 15 min of oral dosing** after the subject has rested in the semi-recumbent position for 3 to 5 min)**, and then every 15 min from dosing of M4112 for an additional 2 h. Observation can be extended per investigator's discretion.** Height and weight at Screening only. Table 2 and Table 3: Vital signs (blood pressure, pulse, respiratory rate, and oral temperature) will be assessed after the subject has rested in semi-recumbent position for 3 to 5 min. CCI [redacted]

Change	Section	Previous Wording	New Wording
			CCI [redacted]
	Table 4 footnote a, Table 5 and table 6 footnote b	Table 4 to Table 6 Including optional metabolite analysis from samples.	Table 4 to Table 6: **For all study medication administration, a physician must be present at the site or immediately available to respond to emergencies during all administrations. Critical care and resuscitation facilities should be available immediately.** Including optional metabolite analysis from samples.
	Section 6.4 Noninvestigational Medicinal Products to be used	As with all monoclonal antibody therapies, there is a risk of allergic reaction. CCI [redacted]	As with all monoclonal antibody therapies, there is a risk of ~~for~~ **hypersensitivity reaction.** CCI [redacted]
	Section 6.5.4 Special Precautions, Section 7.1.2 Treatment Sequence for Dose escalation, Section 7.4 Assessment of Safety, Section 7.4.4 Vital signs and physical examinations.	CCI [redacted]	All or some of below new wording has been included in the mentioned sections: CCI [redacted] CCI [redacted]

Change	Section	Previous Wording	New Wording
			CCI
CCI	Synopsis – Study centers/countries, Objectives, Methodology, Treatment Period, Planned number of subjects, Endpoints, IMP dose/mode of administration/dosing schedule	CCI Figure 1: Study design for Part I (dose escalation) CCI)	CCI

Change	Section	Previous Wording	New Wording
	Protocol – Section 2 and 2.1, Section 4.1 to 4.3, Section 5.1 (including Figure 1), Section 5.2.2, Section 5.3.1 and 5.3.2, Section 6.2.2, Section 7.6.1, Section 8.1, Section 8.3.1 to 8.3.3, Section 8.4, Section 8.5.1		
Schedule of Assessments tables (Table 1 to Table 6) and the text in the footnotes updated for consistency and alignment between the different treatment arms	Table 2 and Table 3	Cycle 7	CCI
	Table 1 and Table 2	Missing pregnancy test at Safety Follow-up (30 ± 3 days) visit Incorrect PD blood sample at 7+n×3 Until Progression	Added serum pregnancy test at Safety Follow-up (30 ± 3 days) visit Deleted PD blood sample at 7+n×3 Until Progression visits and added it to End of Treatment visit
	Table 3	Coagulation sample on Day 8 and Day 22 of Cycle 1 and Day 1 of Cycle 5	Deleted coagulation sample on Day 8 and 22 of Cycle 1 and on Day 1 of Cycle 5
	Table 1 and Table 3	Missing T4 and TSH samples on Day 1 of Cycle 7	Added T4 and TSH samples on Day 1 of Cycle 7
	CCI		
	Table 1 to Table 3 footnote h Table 4 footnote f Table 5 footnote c Table 6 footnote c	Missing text in footnotes on triplicate ECG at predose and + 2 h postdose on Cycle 2 Day 1	Included text in footnote: triplicate ECG at predose and + 2 h postdose on Cycle 2 Day 1

Change	Section	Previous Wording	New Wording
Additional information and specification of anti-drug antibodies added	Section 7.7.1		CCI

Change	Section	Previous Wording	New Wording
Addition of PK and ADA analysis sets CCI [redacted]	Table 13	**Pharmacokinetic**	**M4112 Pharmacokinetic** CCI [redacted]
CCI [redacted]			CCI [redacted]

Table 14 Subject Characterization Based on ADA Results

Category	Definition	Subject at Risk (Denominator for Incidence)
Never-positive	No positive results at any time point	Number of subjects with at least one valid ADA result at any time point
Ever-positive	At least one positive result at any time point	Number of subjects with at least one valid ADA result at any time point
[redacted]		
Transient positive	If treatment emergent subjects have (a single positive evaluation, or duration between first and last positive result < 16 weeks) and last assessment not positive.	Number of subjects with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)
Persistent positive	If treatment emergent subjects have duration between first and last positive result ≥ 16 weeks or a positive evaluation at the last assessment	Number of subjects with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)