Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A First-in-human, Phase 1, Open-label Study of the ATM inhibitor M4076 in Participants with Advanced Solid Tumors
Study Number:	MS201512_0010
Protocol Version:	27 October 2022/Version 4.0
Merck Compound:	M4076
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	Phase 1
Short Title:	First-in-human Study of M4076 in Advanced Solid Tumors
Acronym or Abbreviation:	**DDRi**ver Solid Tumors 410
Coordinating Investigator:	PPD [redacted]
Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 64293 Darmstadt, Germany In the US and Canada: EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA
Regulatory Agency Identifying Numbers:	IND number CCI [redacted]

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	01 Feb 2021
2.0	Global Amendment	07 Apr 2021
3.0	Global Amendment	25 Oct 2021
4.0	Global Amendment	27 Oct 2022

Protocol Version 4.0 (27 October 2022)

Overall Rationale for the Amendment

The overall rationale for this amendment is to update the risk classification in the protocol based on new available clinical data from this study.

Section # and Name	Description of Change	Brief Rationale
Title page	Title page modifications in placement of version reporting and removal of other information.	To follow internal quality standards for clinical study protocols.
1.1 Synopsis	Updated number of participants to 40 in Part 1A	To recruit additional cohorts, if needed.
1.3.1 Part 1A – M4076 Monotherapy Dose Escalation (Daily Dosing) Table 1 Schedule of Activities: M4076 Monotherapy Dose Escalation (Daily Dosing), Part 1A.	Safety Follow-up visit window updated by adding minus 7 days. Physical examination on Day 8 was deleted. Notes for study site visits and fresh paired tumor biopsies was updated.	Updates done for clarity.
1.3.2 Part 1B – Preliminary Food Effect Assessment Table 2 Schedule of Activities: Preliminary Food Effect Assessment, Part 1B	Archival tumor biopsy row was deleted. Note for fresh paired tumor biopsies was updated	For simplicity it was deleted. Updated for clarity.
1.3.3 Parts 1A and 1B – Pharmacokinetic, ECG, and CCI [redacted] Sampling Schedule Table 3 Part 1A M4076 Monotherapy Dose Escalation: Pharmacokinetic, ECG and CCI [redacted]	Visit window on Day 8 was deleted. PK sampling footnote was updated.	For consistency with Table 1.

Section # and Name	Description of Change	Brief Rationale
2.3 Benefit/Risk Assessment	Added new identified and important potential risks (rash and hypersensitivity, respectively). Risk associated with DDI information was updated.	Based on the new available clinical data from this study, new risks have been added. Based on the DDI assessment using in vitro data.
4.1 Overall Design	Flexible wording added for Part 1B of the study.	Updated for clarity and flexibility.
5.2 Exclusion Criteria	Updated prior/concomitant therapy criterion.	Based on the DDI assessment using in vitro data.
6.5.3 Prohibited Medicines	Risk associated with DDI information was updated.	Based on the DDI assessment using in vitro data.
6.6.2.1 Dose Interruptions and Modifications	Added new identified and important potential risks (rash and hypersensitivity, respectively). Table 10 updated with 300 mg related information.	Based on the new available clinical data from this study, new risks have been added. Updated for completeness.
8.2.2 Vital Signs	Semi-supine changed to semi-recumbent.	Updated for consistency with eCRF design.
CCI [redacted]		
9.2 Sample Size Determination	Updated number of participants to 40 in Part 1A.	To recruit additional cohorts, if needed.
9.4.2 Safety Analyses	Deleted interim analysis from Part 1A.	Updated for clarity.
9.4.4 Sequence of Analyses	Primary analysis will be done only for dose escalation part of the study.	Updated for clarity.
Appendix 13 Protocol Amendment History	Update related to V 3.0 copied to this section.	Updated for completeness.
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

DDI = drug-drug interaction; ECG = electrocardiogram; eCRF = electronic case report form.

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A First-in-human, Phase 1, Open-label Study of the ATM inhibitor M4076 in Participants with Advanced Solid Tumors

Short Title: First-in-human Study of M4076 in Advanced Solid Tumors

Rationale: The purpose of this study is to establish the safety, tolerability and pharmacokinetic (PK) profile (with and without food), maximum tolerated dose (MTD; if observed) and recommended dose for expansion (RDE) for M4076 in patients with advanced solid tumors for which no standard therapy is available.

Objectives and Endpoints:

The following table summarizes the objectives and estimands of the study.

Objectives and Estimands: M4076 Monotherapy Dose Escalation (Part 1A) and Preliminary Food Effect Assessment (Part 1B)

Objectives	Estimands attributes
Primary	
To determine dose-toxicity relationship and MTD (if reached) of M4076 monotherapy in patients with advanced solid tumors	**Endpoints**: • Occurrence of Dose Limiting Toxicities (DLTs). • Occurrence of adverse events (AEs) and treatment-related AEs. • Occurrence of clinically significant changes in vital signs, laboratory parameters, and 12-lead electrocardiogram (ECG) findings. **Strategy for handling intercurrent events:** For DLTs: • Discontinuation of treatment (> 20% planned treatment missed during DLT period) to prevent a DLT: composite strategy (to be considered a DLT) • Discontinuation of treatment administrations not due to DLT or preventing a DLT (> 20% of planned treatment missed during DLT period): participant not considered in DLT analysis. For other endpoints: All available data from participants in safety analysis set will be used. **Population:** Patients with advanced solid tumors, who are intolerant or have no effective standard therapies available to them. **Population level summary:** • DLT probability as estimated using BLRM and credibility interval (only applicable for DLTs). • Standard summary statistics.
Secondary	
To determine the recommended dose for expansion (RDE) of M4076 monotherapy in participants with advanced solid tumors	• In addition to safety and tolerability, changes from baseline for the following Pd biomarkers may be considered for determining the RDE: ATM pathway readouts such as, but not limited to, p-ATM, γ–H2AX and p-CHK2 in blood and tumor. • In addition, pharmacokinetic (PK) data will be used to support determination of the RDE.
To characterize the PK profile of M4076 monotherapy in participants with advanced solid tumors	• PK parameters of M4076 in plasma after single dose and multiple doses. • Urine PK parameters (e.g., renal clearance) will be characterized in Part 1B data permitted.

Objectives	Estimands attributes
To evaluate preliminary clinical activity parameters of M4076 monotherapy in participants with advanced solid tumors	**Endpoints** • Objective response (OR) according to RECIST 1.1 assessed by Investigator. • Duration of response (DoR) according to RECIST 1.1 assessed by Investigator. • Progression Free Survival (PFS) according to RECIST 1.1 assessed by Investigator.
To assess the effect of food on the PK of M4076 administered as a single dose under fed/fasting conditions in a cohort of participants with advanced solid tumors at the RDE from Part 1A.	**Endpoints** Fed/fasted ratio of M4076 plasma PK parameters: $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and, C_{max} when administered as a single dose with or without food.
To assess changes in pharmacodynamic markers of M4076 activity in tumor and blood during M4076 monotherapy	**Endpoints** Absolute and relative changes over time from baseline of ATM pathway readouts, such as, but not limited to p-ATM, p-CHK2 and γ-H2AX.

AE = adverse event; ATM = ataxia-telangiectasia mutated; AUC = area under the concentration-time curve; BLRM = Bayesian 2-parameter Logistic Regression Model; DLT = dose limiting toxicity; DoR = duration of response; ECG = electrocardiogram; γ-H2AX = gamma histone family member X; MTD = maximum tolerated dose; OR = objective response; Pd = pharmacodynamics; p-ATM = phosphorylated ataxia-telangiectasia mutated; p-CHK2 = checkpoint kinase 2 protein; PFS = progression free survival; RECIST = Response Evaluation Criteria in Solid Tumors; RDE = recommended dose for expansion.

Overall Design: This is an open-label, Phase 1, clinical study of M4076. Part 1A is a M4076 monotherapy dose escalation designed to determine the safety, tolerability, PK, pharmacodynamics and early signs of efficacy in participants with solid tumors. Once an RDE is declared in Part 1A, a preliminary food effect cohort, Part 1B, may follow and will be conducted at the RDE or a lower dose than RDE determined from Part 1A. Part 1B is a randomized, 2-sequence, 2-period, cross-over design.

Disclosure Statement: This is an unblinded sequential treatment study with 2 parts: dose escalation (Part 1A) and food effect study (Part 1B).

Number of Arms: Not applicable.

Blinding: No blinding

Number of Participants: Approximately 40 participants are planned to be assigned to study intervention, including 22 to 28 participants in Part 1A (planned 4 potential dose levels) and 12 participants in Part 1B; the sample size for the MTD and/or RDE dose level needs to be at least 6 participants.

Study Intervention Groups and Duration: It is estimated that participants will be on the study for an approximate duration of 105 days/15 weeks.

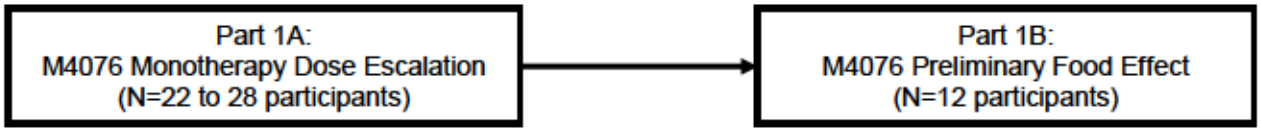
Involvement of Special Committee(s): Safety Monitoring Committee.

1.2 Schema

Figure 1 presents a study schema overview of the study.

- Part 1A: Dose escalation of M4076 monotherapy (Figure 2).
- Part 1B: Preliminary food effect cohort will follow at the recommended dose for expansion (RDE) established in Part 1A.

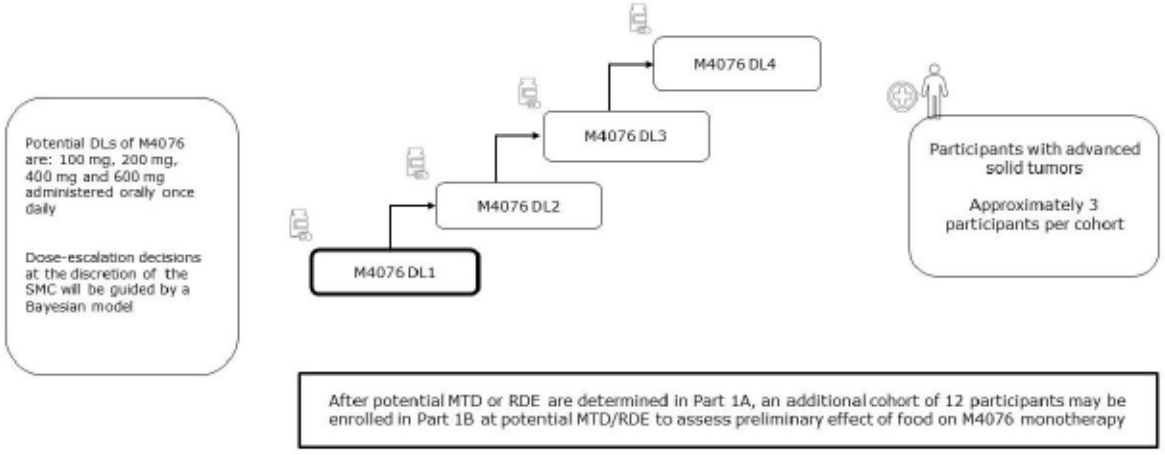
Figure 1 Study Schema Overview



The cohort size planned in Part 1A is 3 participants per Dose Level (DL). The proposed DLs represented in Figure 2 may be adjusted based on Safety Monitoring Committee (SMC) decision to reach exposures associated with preclinical efficacy while balancing safety and tolerability.

After maximum tolerated dose (MTD) and/or RDE have been determined in Part 1A, an additional cohort of 12 participants may be enrolled in Part 1B at this dose to assess preliminary effect of food on M4076 monotherapy.

Figure 2 Part 1A - M4076 Monotherapy Dose Escalation Schema



Note: A DL of 300 mg was also administered orally once daily.

DL = dose level; MTD = maximum tolerated dose; RDE = recommended dose for expansion; SMC = safety monitoring committee.

1.3 Schedule of Activities

The Schedule of Activities for Part 1A (M4076 Monotherapy Dose Escalation) daily dosing schedule of this study is provided in Table 1. Additional assessments may be performed at unscheduled time points if clinically indicated at the Investigator's discretion. To facilitate timely administration of study intervention, safety laboratory samples may be obtained up to 3 days before dosing. If laboratory samples are drawn before the day of dosing, they should be recorded in the case report forms (CRF) corresponding to the day of planned M4076 administration. The Part 1A pharmacokinetic (PK), electrocardiogram (ECG) and pharmacodynamic (Pd) biomarker assessments schedule is detailed in Table 3.

The Schedule of Activities for Part 1B (preliminary Food Effect Assessment) is provided in Table 2. The Part 1B PK, ECG, and Pd biomarker assessments schedule is detailed in Table 4.

For Part 1A, potential variations in study intervention schedules and schedule of activities due to alternative dosing schedules are found Appendix 7. Please see Sections 4.1.1 and 4.1.2, and Appendix 12 for details on model for Bayesian dose escalation.

1.3.1 Part 1A – M4076 Monotherapy Dose Escalation (Daily Dosing)

The schedule of events for Part 1A are provided in Table 1.

The Part 1A fasting window is defined as: 2 hours predose to 1-hour postdose in general, and [redacted] hours predose to 4 hours postdose on days where PK-time matched triplicate ECGs are collected.

Table 1 Schedule of Activities: M4076 Monotherapy Dose Escalation (Daily Dosing), Part 1A

Assessments and Procedures	Screen (D -28 to -1)	DLT Period (21 days)					Subsequent 3-week Periods (21 days)			End of Study Intervention Visit	Safety Follow up/ Discontinuation Visit	Notes
Day		1	2	8	9	15	1	8	15	Within 7 days after last dose	30 days after last dose	
Visit Window (days)		-1								+7	+/- 7	Day 1 assessments that could be completed on Day -1 are limited to physical examination, height/weight, and ECOG performance status.
Study Site Visits	X	X	X	X	X	X	X	X	X	X	X	Starting Cycle 4, visits at Day 8 and Day 15 are optional
Written informed consent	X											
Inclusion / Exclusion Criteria	X											
Medical History (includes substance usage); Demography	X											Substances: tobacco use only.
Hepatitis B and C tests	X											To rule out active infection, performed at the Investigator's discretion. See Appendix 6 for details.
Optional HIV Screening	X											HIV testing is optional at the Investigator's discretion unless required locally.

Assessments and Procedures	Screen (D -28 to -1)	DLT Period (21 days)					Subsequent 3-week Periods (21 days)			End of Study Intervention Visit	Safety Follow up/ Discontinuation Visit	Notes
Day		**1**	**2**	**8**	**9**	**15**	**1**	**8**	**15**	**Within 7 days after last dose**	**30 days after last dose**	
Visit Window (days)		-1								+7	+/- 7	Day 1 assessments that could be completed on Day -1 are limited to physical examination, height/weight, and ECOG performance status.
Serum Pregnancy Test (WOCBP only)	X									X		See Section 8.3.5.
Urine Pregnancy Test (WOCBP only)		X					X					Urine β-hCG results must be available prior to M4076 dosing.
Physical Examination	X	X			X	X	X			X	X	See Section 8.2.1.
Height and Weight	X	X					X			X	X	Collect height at Screening only.
Imaging Disease Assessment (CT/MRI)	X	X (at the end of every 6 weeks for the first 24 weeks, then every 12 weeks)								X		Tumor assessment according to RECIST 1.1 until disease progression, end of study, or death, whichever is earlier. See Section 8.1 for details of imaging.
Vital signs	X	X		X		X	X			X	X	In the first 6 weeks on study treatment, vital signs are measured as follows: • Predose (within approximately 30 to 60 minutes prior) • 4 hours (±1 hour) postdose on Day 1 and Day 8. After 6 weeks, vital signs to be measured predose.
Standard 12-lead ECG	X						X post dosing			X	X	
Triplicate digital ECG		X	X	X								See Table 3 for triplicate ECG details.

Assessments and Procedures	Screen (D -28 to -1)	DLT Period (21 days)					Subsequent 3-week Periods (21 days)			End of Study Intervention Visit	Safety Follow up/ Discontinuation Visit	Notes
Day		1	2	8	9	15	1	8	15	Within 7 days after last dose	30 days after last dose	
Visit Window (days)		-1								+7	+/- 7	Day 1 assessments that could be completed on Day -1 are limited to physical examination, height/weight, and ECOG performance status.
ECOG performance status	X	X					X			X	X	See Appendix 10.
AE, AESI and SAE assessment	Continuous											From time of signing the ICF through the Safety Follow-up Visit, and until completion of the study. SAEs and AESIs should be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (see Section 8.3.3).
Concomitant medications and procedures (including collection of subsequent anticancer therapy)												
Serum Chemistry	X	X	X	X		X	X	X	X	X	X	For Visit 1/D1, sample can be collected up to 72 hours prior to dosing. D8 and D15 assessments are optional after Week 9. See Appendix 6 for details.
Hematology and Coagulation (PT, aPTT, INR)	X	X	X	X		X	X	X	X	X	X	For Visit 1/D1, sample can be collected up to 72 hours prior to dosing. D8 and D15 assessments are optional after Week 9. See Appendix 6 for details.
Urinalysis	X	X				X	X			X		See Appendix 6 for details.

Assessments and Procedures	Screen (D -28 to -1)	DLT Period (21 days)					Subsequent 3-week Periods (21 days)			End of Study Intervention Visit	Safety Follow up/ Discontinuation Visit	Notes
Day		**1**	**2**	**8**	**9**	**15**	**1**	**8**	**15**	**Within 7 days after last dose**	**30 days after last dose**	
Visit Window (days)		-1								+7	+/- 7	Day 1 assessments that could be completed on Day -1 are limited to physical examination, height/weight, and ECOG performance status.
Archival tumor biopsy collection	X											If insufficient tissue is available from an archived specimen, or if the biopsy was obtained > 12 months before Screening, a fresh biopsy sample may be requested during screening (prior to D1) unless contraindicated for medical reasons.
Study Intervention Administration												
M4076 Monotherapy		Daily dosing. (Fasting window: 2 hrs predose to 1 hr postdose in general, and 2 hrs predose to 4 hrs postdose on days where PK-time matched triplicate ECGs are collected.)										See additional potential treatment schedules in Appendix 7.
Pharmacokinetic Assessments												
Blood - PK blood samples M4076		X	X	X	X		X					See Table 3 for PK sample details.
Biomarker Assessments												
[redacted]		[redacted]	[redacted]				[redacted]					[redacted]

Assessments and Procedures	Screen (D -28 to -1)	DLT Period (21 days)					Subsequent 3-week Periods (21 days)			End of Study Intervention Visit	Safety Follow up/ Discontinuation Visit	Notes
Day		**1**	**2**	**8**	**9**	**15**	**1**	**8**	**15**	**Within 7 days after last dose**	**30 days after last dose**	
Visit Window (days)		**-1**								**+7**	**+/- 7**	Day 1 assessments that could be completed on Day -1 are limited to physical examination, height/weight, and ECOG performance status.
Fresh Paired tumor biopsies	X		X									Optional. The first of two paired biopsies should be collected anytime during screening. The second biopsy should be collected on D2 from 2 to 4 hours after study intervention administration. No bone biopsies are allowed. The first biopsy can replace the archival tumor biopsy.
Plasma – Circulating Tumor DNA Sample		X					X			X		Collect predose on dosing days.
Blood – Immuno-phenotyping		X					X D22 only					Collect predose.
Serum/plasma – Circulating factors (cytokines)		X					X D22 only					Collect predose.
CCI [redacted]												

AE = adverse event; aPTT = activated partial thromboplastin time; β-hCG = beta human chorionic gonadotropin; CT = computed tomography; D = Day; DLT = dose limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; γ–H2AX = gamma histone family member X; HIV = human immunodeficiency virus; ICF = informed consent form; INR = international normalized ratio; MRI = magnetic resonance imaging; Pd = pharmacodynamics; PK = pharmacokinetic; PT = prothrombin time; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; WOCBP = woman of childbearing potential.

1.3.2 Part 1B – Preliminary Food Effect Assessment

Part 1B (the preliminary food effect assessment) will be assessed by a predefined schedule in Table 2 from Day -7 until Day 3. The fasting window is defined in Part 1B as 10 hours predose to 4 hours postdose. For assessments after Day 4 see Part 1A Schedule of Activities (Table 1).

Note: After M4076 PK is established, the minimum required time interval (washout) between the first 2 administrations of M4076 may be adjusted (minimum of 5 times the half-life of M4076, but at least 1 day and not > 6 days). Additionally, if the half-life of M4076 is substantially longer than originally predicted, an additional PK time point on Day -5 may be added and earlier time point(s) removed so that the total number of blood draws is not increased.

Table 2 Schedule of Activities: Preliminary Food Effect Assessment, Part 1B

Assessment and Procedures	Screen	Food Effect Assessment								Treatment	Notes
Day	D-28 to -8	-7	-6	-5	-4	-3 to -1	1	2	3	4	
Visit Window (days)							-1				Day 1 assessments that could be completed on Day -1 are limited to physical examination, height/weight, and ECOG performance status.
Study Site Visits	X	X	X	X	X	Wash out days	X	X	X	See Table 1	After Day 4 participants will continue to be treated as per Table 1 (Schedule of Activities for Part 1A).
Written informed consent	X										
Inclusion/Exclusion Criteria	X										
Medical history (includes substance usage); Demography	X										Substances: tobacco use only.

Assessment and Procedures	Screen	Food Effect Assessment								Treatment	Notes
Day	D-28 to -8	-7	-6	-5	-4	-3 to -1	1	2	3	4	
Visit Window (days)							-1				Day 1 assessments that could be completed on Day -1 are limited to physical examination, height/weight, and ECOG performance status.
Hepatitis B and C tests	X										To rule out active infection, performed at the Investigator's discretion.
Optional HIV Screening	X										HIV testing is optional at the Investigator's discretion.
Pregnancy Test (WOCBP only)	X	X					X				Serum test at Screening, urine test otherwise. Urine pregnancy results must be available prior to M4076 dosing.
ECOG performance status	X	X					X				See Appendix 10.
Safety Assessments											
Physical Examination	X						X				Refer to Section 8.2.1.
Height and Weight	X						X				Collect height at screening only.
Imaging Disease Assessment (CT/MRI)	X										
Vital Signs	X	X					X				Vital signs are to be measured as follows: • Day -7 and Day 1, at predose (within approximately 30 to 60 minutes prior) and

Assessment and Procedures	Screen	Food Effect Assessment								Treatment	Notes
Day	D-28 to -8	-7	-6	-5	-4	-3 to -1	1	2	3	4	
Visit Window (days)							-1				Day 1 assessments that could be completed on Day -1 are limited to physical examination, height/weight, and ECOG performance status.
											• 4 hours (±1 hour) postdose
Serum Chemistry	X	X					X				See Appendix 6 for details.
Hematology and Coagulation (PT, aPTT, INR)	X	X					X				See Appendix 6 for details.
Urinalysis	X	X					X				See Appendix 6 for details.
Standard 12-lead ECG	X										
Triplicate digital ECG		X					X				ECG should only be collected for participants dosed in the fasted state. See Table 4 for triplicate ECG details.
AE and SAE assessment	Continuous										
Concomitant medications and procedures review											

Assessment and Procedures	Screen	Food Effect Assessment								Treatment	Notes
Day	D-28 to -8	-7	-6	-5	-4	-3 to -1	1	2	3	4	
Visit Window (days)							-1				Day 1 assessments that could be completed on Day -1 are limited to physical examination, height/weight, and ECOG performance status.
Study Intervention and Treatment											
Low-fat Meal or Overnight Fasting (Fasting window: 10 hours predose to 4 hours postdose)		X	X				X				Participants in Part 1B will be randomly assigned on a 1:1 basis to 1 of 2 study intervention sequences: (1) fasted followed by fed, or (2) fed followed by fasted. After completion of food effect assessments, participants may continue to receive study intervention at RDE from D4 onward (on an empty stomach) and follow assessments as per Table 1 from D8 onwards.
M4076 Administration (single dose)		X					X			X	After D4, M4076 dosing should continue at the RDE and thereafter follow assessments as per Table 1.
Pharmacokinetic Assessments:											
Blood – PK blood samples M4076		X	X	X	X		X	X	X	X	See Table 4 for PK sample details.
Urine PK Collection		X	X	X	X		X	X	X	X	See Table 4 for urine PK sample details.
CCI [redacted]											

Assessment and Procedures	Screen	Food Effect Assessment								Treatment	Notes
Day	D-28 to -8	-7	-6	-5	-4	-3 to -1	1	2	3	4	
Visit Window (days)							-1				Day 1 assessments that could be completed on Day -1 are limited to physical examination, height/weight, and ECOG performance status.
CCI [redacted]											
Plasma – Circulating Tumor DNA Sample		X									Collect predose.
Fresh Paired Tumor Biopsies	X									X	Mandatory collection, if not contraindicated for medical reasons. The first of two paired biopsies must be collected anytime during screening. The second biopsy must be collected on D4 from 2 to 4 hours after study intervention. No bone biopsies are allowed.
Blood - Immune Phenotyping		X									Collect predose.
Serum/plasma – Circulating Factors		X									Collect predose.

AE = adverse event; aPTT = activated partial thromboplastin time; CT = computed tomography; D = Day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; INR = international normalized ratio; MRI = magnetic resonance imaging; Pd = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; RDE = recommended dose for expansion; SAE = serious adverse event; WOCBP = woman of childbearing potential.

1.3.3 Parts 1A and 1B – Pharmacokinetic, ECG, and CCI ampling Schedule

Table 3 Part 1A M4076 Monotherapy Dose Escalation: Pharmacokinetic, ECG and CCI Assessments

Study Day	M4076 Dosing	PK Sampling Time	ECG[b]	Paired Biopsies	CCI
Screening (D –28 to -1)				X	
Day 1	X	Predose[a]	X		
		0.5 hour ± 10 minutes postdose			
		1 hour ± 10 minutes postdose			
		2 hours ± 10 minutes postdose	X		
		3 hours ± 20 minutes postdose	X		
		4 hours ± 20 minutes postdose	X		
		6 hours ± 20 minutes postdose	X		
		8 hours ± 20 minutes postdose	X		
Day 2	X	Predose[a]	X		
		2 hours -4 hours postdose[c]		X[c]	
Day 8	X	Predose[a]	X		
		1 hour ± 10 minutes postdose	X		
		2 hours ± 10 minutes postdose	X		
		3 hours ± 20 minutes postdose	X		

Study Day	M4076 Dosing	PK Sampling Time	ECG[b]	Paired Biopsies	CCI [redacted]
		4 hours ± 20 minutes postdose	X		
		6 hours ± 20 minutes postdose			
		8 hours ± 20 minutes postdose	X		
Day 9	X	Predose[a]			
Day 22	X	Predose[a]			X
		2 hours ± 10 minutes postdose			X
		4 hours ± 20 minutes postdose			X
All subsequent Day 1 of every 3 week treatment period	X	Predose[a]			

Note: The fasting window in Part 1A is defined as: 2 hours predose to 1-hour postdose in general, and 2 hours predose to 4 hours postdose on days where PK-time matched triplicate ECG will be collected.

ECG = electrocardiogram; γ-H2AX = gamma histone family member X; CCI [redacted]; PK = pharmacokinetic.

[a] All predose samples have a window of -60 minutes prior to dosing.
[b] The window period for ECG is the same as noted for PK sampling.
[c] Efforts should be made to collect blood for PK and C CI and biopsy samples around similar time points (± 20 minutes).

Period 1 Day 8/9 PK sampling may be conducted on Day 15/16, or Period 2 Day 1/2, if required for logistical reasons and/or in case study intervention was interrupted and resumed. In this case, timing of associated triplicate ECG measurements should be rescheduled accordingly, and the Sponsor notified in advance.

Table 4 **Part 1B Preliminary Food Effect Assessment: Pharmacokinetic, ECG and CCI Assessments**

Study Day	M4076 Dosing	PK Sampling Time	Urine Collection for PK	ECG[b]	Paired Biopsies	CCI
Screening (D -28 to -8)					X	
-7	X	Predose[a]	X (1 hour, 0)	X		
		0.5 hour ± 10 minutes postdose	X (0 to 4 hours)			
		1 hour ± 10 minutes postdose		X		
		2 hours ± 10 minutes postdose		X		
		3 hours ± 20 minutes postdose		X		
		4 hours ± 20 minutes postdose	X (4 to 8 hours)	X		
		6 hours ± 20 minutes postdose		X		
		8 hours ± 20 minutes postdose	X (8 to 24 hours)	X		
		10 hours ± 20 minutes postdose				
-6		24 hours ± 2 hours postdose	X (24 to 48 hours)			
-5		48 hours ± 2 hours postdose	X (48 to 72 hours)			
-4		72 hours ± 2 hours postdose				
Day -3 to -1 Washout						

Study Day	M4076 Dosing	PK Sampling Time	Urine Collection for PK	ECG[b]	Paired Biopsies	CCI
Day 1	X	Predose[a]		X		
		0.5 hour ± 10 minutes postdose	X (0 to 4 hours)			
		1 hour ± 10 minutes postdose				
		2 hours ± 10 minutes postdose		X		
		3 hours ± 20 minutes postdose		X		
		4 hours ± 20 minutes postdose	X (4 to 8 hours)	X		
		6 hours ± 20 minutes postdose		X		
		8 hours ± 20 minutes postdose	X (8 to 24 hours)	X		
		10 hours ± 20 minutes postdose				
Day 2		24 hours ± 2 hours postdose	X (24 to 48 hours)			
Day 3		48 hours ± 2 hours postdose	X (48 to 72 hours)			
Day 4[d]	X	Predose[a]				
		1 hours ± 10 minutes postdose				
		3 hours ± 60 minutes postdose			X[c]	
		6 hours ± 20 minutes postdose				
		8 hours ± 20 minutes postdose				

ECG = electrocardiogram; γ-H2AX = gamma histone family member X; Pd = pharmacodynamic; PK = pharmacokinetic; RDE = recommended dose for evaluation.

[a] All predose samples have a window of – 60 minutes prior to next dosing.

[b] Triplicate ECG collection is only applicable to participants dosed in the fasted state. The fasting window in Part 1B is defined as 10 hours predose to 4 hours postdose.

[c] The biopsy can be collected anytime between 2 and 4 hours after treatment administration. Efforts should be made to collect PK ad Pd blood and biopsy samples around similar time points (± 20 minutes).

[d] After completion of Part 1B assessments, participants may continue to receive study intervention at RDE from D4 onward (on an empty stomach) and follow assessments as per Table 3 from D8 onwards.

2 Introduction

M4076 (MSC2585823A) is a potent, selective and orally bioavailable adenosine triphosphate competitive inhibitor of ataxia-telangiectasia mutated (ATM) kinase. ATM plays a central role in the deoxyribonucleic acid (DNA) damage response and ATM inhibitors enhance the cytotoxic effects of DNA damaging therapies such as radiotherapy and DNA double-strand break (DSB)-inducing chemotherapies. M4076 also has monotherapy antitumor activities in a subset of cancer cell models.

Detailed information on the chemistry, pharmacology, efficacy, and safety of M4076 is in the M4076 Investigator's Brochure (IB).

2.1 Study Rationale

The purpose of this study is to establish the safety, tolerability and PK profile (with and without food), MTD (if observed) and RDE for M4076 in participants with advanced solid tumors for which no standard therapy is available.

The following sections contain the rationale for conducting the M4076 monotherapy. For discussion of the scientific rationale for study design, see Section 4.3, and for justification of dose, see Section 4.2.

2.1.1 M4076 Monotherapy

The rationale for Part 1 of this study (M4076 monotherapy), which includes participants with advanced solid tumors for which no approved/established effective treatment options exist, is that ATM inhibitors have shown antitumor effects in subsets of cancer models in vitro and in vivo. Specifically, M4076 decreases cell viability in vitro in a subset of 16/93 cancer cell lines tested (GI50 < 5uM) and in vivo caused tumor growth inhibition in multiple patient derived tumor PDX models derived from gastric, ovarian, triple negative breast cancer and pancreatic cancers.

The antitumor effects are believed to occur by the concept of synthetic lethality: two genes are synthetically lethal if mutation of either gene alone is compatible with cell viability whilst a mutation (or targeting) of both genes leads to cell death. It has been demonstrated that cancers with mutations in Fanconi anemia genes are sensitive to ATM inhibitors since the ATM and Fanconi anemia repair pathways are important for faithful repair of double-stranded DNA breaks and intra-strand DNA cross-links via the homologous recombination process (Kennedy 2007; Cai 2020). In addition, simultaneous inactivation of ATM and the tumor suppressor phosphatase and tensin homolog (PTEN) has been reported to be synthetically lethal (McCabe 2015; Cai 2020). The PTEN inactivation increased the level of reactive oxygen species-induced DNA damage, which likely requires ATM for repair. Consequently, chemical inhibition of ATM in PTEN-deficient cells resulted in cell cycle arrest, chromosomal aberrations, and apoptosis. Molecular characterization of the sensitive tumor models in vitro and in vivo and investigation of their underlying genetic dispositions and potential synthetic lethality targets are under evaluation.

2.2 Background

Inhibiting the DNA Damage Response (DDR) has become an attractive therapeutic concept in cancer therapy, since resistance to genotoxic therapies has been associated with increased DDR signaling, and many cancers have defects in certain components of the DDR rendering them highly dependent on the remaining DDR pathways for survival.

To ensure the faithful transmission of their genetic information to the progeny, mammalian cells have evolved an elaborate molecular machinery for detecting and repairing DNA lesions. A multitude of DNA repair mechanisms are described in human cells (Curtin 2012). Physical or chemical agents that generate breaks in DNA are among the most widely used classes of cancer therapeutics today. Radiotherapy, for example, induces multiple breaks in cellular DNA including DSBs. When left unrepaired, DSBs can lead to induction of cell cycle arrest and ultimately cell death. To repair DSBs, organisms have developed a complex response that includes recognition of the damaged DNA, cellular signaling including control of the cell cycle, and ultimately repair of the DNA lesion. Two major pathways mediate the repair of DSBs in mammalian cells termed homologous recombination (HR) and nonhomologous end-joining (NHEJ). The ATM acts as an upstream signaling kinase, which regulates several aspects of DNA repair including HR, NHEJ, and the cell cycle. The HR repair acts with high fidelity, relies on the intact sister chromatid as a template, and is active in the S and G2 phase of the cell cycle, while NHEJ is error-prone and active throughout all phases of the cell cycle.

M4076 (substance code MSC2585823A), a small molecule, is a highly potent and selective ATM kinase inhibitor. In line with its proposed mechanism of action, inhibition of ATM kinase activity by M4076 enhanced the therapeutic effect of DNA DSB-inducing treatment modalities including radiotherapy, chemotherapy and targeted agents like ATR inhibitors, topoisomerase inhibitors and poly ADP ribose polymerase inhibitors in vitro and in vivo. This potentiation can be attributed to inhibition of ATM-dependent DSB repair as well as inhibition of ATM-controlled cell cycle checkpoints.

Based on recent findings, ATM inhibition is expected to benefit patients harboring DDR mutations, for example, mutations in Fanconi anemia genes (Kennedy 2007; Cai 2020). Cancer-specific alterations in the DDR machinery represent the basis of synthetically lethal interactions with inhibitors of DNA damage response. Simultaneous inactivation of ATM and PTEN has been reported to be synthetically lethal (McCabe 2015_McCabe_N,_Hanna; Cai 2020). The PTEN inactivation increased the level of reactive oxygen species-induced DNA damage, which may require ATM activation for repair. Testing of M4076 in cancer cell lines and patient-derived xenograft models of human cancer (gastric, triple negative breast cancer, ovarian, pancreas) demonstrated single agent antitumor activity.

For details refer to the current M4076 IB.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of M4076 may be found in the M4076 IB.

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

2.3.1 Risk Assessment

Preclinical safety evaluation of M4076 indicates that treatment with this compound may be associated with increased heart rate, cytopenia and risks such as lymphocytopenia and infections, and drug-drug interactions when concomitantly administered with strong inhibitors or inducers of cytochrome P450 (CYP)3A4 or P-glycoprotein (P-gp), and genotoxicity (see Table 5). Concomitant administration with sensitive clinical substrates of UGT1A1 or P-gp, with potentially narrow therapeutic index or known safety risks are prohibited, specifically irinotecan, digoxin, and oral direct thrombin inhibitors. Therefore, regular laboratory monitoring for hematological parameters and ECG assessments are built into the current protocol. In addition, all the standard safety assessments including serum biochemistry, coagulations and urine analyses are performed on a regular basis (See Schedule of Activities in Section 1.3). Further, strict use of contraception is required, and male participants informed that fertility might be impaired long-term.

Table 5 Identified and Potential Risks of the Study Interventions and Procedures

Potential Risks	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention M4076		
Identified Risk (non important)		
Rash	Refer to Section 6.1 of the M4076 IB.	Grade 2 rash (without systemic symptoms) - Interrupt treatment and treat with topical and/or systemic steroids. Grade 2 and Grade 3 rash (without systemic symptoms) - manage with treatment interruption and supportive medications, including topical or oral steroids. Rash with associated systemic symptoms (e.g., fever) - stop treatment immediately and do not rechallenge with any dose of M4076. All cases of rash should be discussed with the medical monitor.
Important Potential Risk		
Hypersensitivity	Refer to Section 6.1 of the M4076 IB.	Participants who experience rash and systemic symptoms (e.g., fever, vomiting, diarrhea), or other signs of hypersensitivity should have M4076 discontinued immediately, and are not to be rechallenged with any dose of M4076.
Potential Risks		
Cytopenia, lymphopenia +/- infections	Refer to Section 6.1 of the M4076 IB.	Exclusion of participants with insufficient bone marrow function. Regular monitoring of laboratory evaluations for hematology and vital signs. Continuous monitoring of AEs with clinical management as indicated, including study intervention interruption, dose modification or discontinuation.
Increased heart rate	Refer to Section 6.1 of the M4076 IB.	Exclusion of subjects with significant cardiac conduction abnormalities. Regular monitoring of ECG and vital signs. Continuous monitoring of adverse events with clinical management as indicated, including study intervention interruption, dose modification or discontinuation.
Birth defects and abortions	In vitro and in vivo genotoxicity investigations showed M4076 to cause genotoxicity. Refer to Section 4.3.3 of M4076 IB.	Strict contraception for participants and their partners as inclusion criteria, during treatment, and thereafter 6 months for females and 3 months for males, including refraining from sperm donations.
Risks associated with drug-drug interactions	No formal drug-drug interaction studies have been conducted with M4076 in humans. Refer to Section 4.2.9 of M4076 IB.	Concomitant administration with strong inhibitors or inducers of CYP3A4 or P-glycoprotein agents is prohibited. Concomitant administration with sensitive clinical substrates of UGT1A1 or P-gp, with potentially narrow therapeutic index or known safety risks are prohibited, specifically irinotecan, digoxin, and oral

		direct thrombin inhibitors. Clinical substrates of CYP3A4 with narrow therapeutic index are prohibited. Clinical sensitive substrates and moderate inhibitors of CYP3A4 should be avoided and if permitted, should be used with caution.
Study Procedures		
Assessment	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Blood Sampling	Blood sampling is required for participants as detailed in the Schedule of Activities and is considered essential for the study's scientific objectives. Blood sampling carries a risk of AEs including pain, bruising, bleeding, redness and swelling of the site/vein, and infection.	Minimization of blood sampling was thoughtfully considered during protocol development weighing risk to participants versus achievement of the study's scientific objectives.
Tumor biopsies	Fresh tumor biopsies are required for subsets of participants as detailed in the Schedule of Activities and inclusion criteria and are considered essential for the study's scientific objectives. Biopsies carry a risk of AEs including bleeding and infection.	Investigators are to use clinical judgement and not proceed with biopsy if high risk of adverse events. Protocol allows omission of biopsies if contraindicated for medical reasons (see Section 8.6).

AE = adverse event; CYP = cytochrome P; ECG = electrocardiogram; IB = investigator's brochure.

2.3.2 Benefit Assessment

Preclinical pharmacology data show that M4076, a highly potent and selective inhibitor of ATM, exhibits anticancer activity as a monotherapy in a subset of cancer models.

2.3.3 Overall Benefit: Risk Conclusion

Based on the preclinical evaluation for toxicity, measures are taken to minimize risk to participants in this study. Given the preclinical evaluation for potential efficacy and toxicity (see Section 2.1), the conduct of this first-in-human study in patients with advanced solid tumors for which no standard of care exists is justified. Clinical safety and tolerability data will be reviewed on ongoing basis and further risk minimization measures if required will be implemented. As per new clinical data from this study rash was considered as an identified risk and hypersensitivity as important potential risk (For details refer to Section 6.1 of the IB).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of M4076 may be found in Section 4.3 and the IB.

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

3 Objectives and Estimands

Table 6 summarizes the objectives and estimands of the study. The statistical aspects of the endpoints are outlined in Section 9.

Table 6 Objectives and Estimands: M4076 Monotherapy Dose Escalation (Part 1A) and Preliminary Food Effect Assessment (Part 1B)

Objectives	Estimands attributes
Primary	
To determine dose-toxicity relationship and MTD (if reached) of M4076 monotherapy in patients with advanced solid tumors.	**Endpoints**: • Occurrence of Dose Limiting Toxicities (DLTs). • Occurrence of adverse events (AEs) and treatment-related AEs. • Occurrence of clinically significant changes in vital signs, laboratory parameters, and 12-lead electrocardiogram (ECG) findings. **Strategy for handling intercurrent events:** For DLTs: • Discontinuation of treatment (> 20% planned treatment missed during DLT period) to prevent a DLT: composite strategy (to be considered a DLT). • Discontinuation treatment administrations not due to DLT or preventing a DLT (> 20% of planned treatment missed during DLT period): participant not considered in DLT analysis. For other endpoints: All available data from participants in safety analysis set will be used. **Population:** Patients with advanced solid tumors, who are intolerant or have no effective standard therapies available to them. **Population level summary:** • DLT probability as estimated using BLRM and credibility interval (only applicable for DLTs). • Standard summary statistics.
Secondary	
To determine the recommended dose for expansion (RDE) of M4076 monotherapy in participants with advanced solid tumors.	• In addition to safety and tolerability, changes from baseline for the following Pd biomarkers may be considered for determining the RDE: ATM pathway readouts such as, but not limited to, p-ATM, γ-H2AX and p-CHK2 in blood and tumor. • In addition, pharmacokinetic (PK) data will be used to support determination of the RDE.
To characterize the PK profile of M4076 monotherapy in participants with advanced solid tumors.	• PK parameters of M4076 in plasma after single dose and multiple dose. • Urine PK parameters (e.g., renal clearance) will be characterized in Part 1B data permitted.

Objectives	Estimands attributes
To evaluate preliminary clinical activity parameters of M4076 monotherapy in participants with advanced solid tumors.	**Endpoints** • Objective response (OR) according to RECIST 1.1 assessed by Investigator. • Duration of response (DoR) according to RECIST 1.1 assessed by Investigator. • Progression Free Survival (PFS) according to RECIST 1.1 assessed by Investigator.
To assess the effect of food on the PK of M4076 administered as a single dose under fed/fasting conditions in a cohort of participants with advanced solid tumors at the RDE from Part 1A.	**Endpoints** Fed/fasted ratio of M4076 plasma PK parameters: $AUC_{0-tlast}$, $AUC_{0-\infty}$ and, C_{max} when administered as a single dose with or without food.
To assess changes in pharmacodynamic markers of M4076 activity in tumor and blood during M4076 monotherapy.	**Endpoints** Absolute and relative changes over time from baseline of ATM pathway readouts, such as, but not limited to p-ATM, p-CHK2 and γ-H2AX.
CCI	

AE = adverse event; ATM = ataxia-telangiectasia mutated; AUC = area under the concentration-time curve; BLRM = Bayesian 2-parameter Logistic Regression Model; DLT = dose limiting toxicity; DoR = duration of response; ECG = electrocardiogram; γ-H2AX = gamma histone family member X; MTD = maximum tolerated dose; OR = objective response; CCI ; p-ATM = phosphorylated ataxia-telangiectasia mutated; p-CHK2 = checkpoint kinase 2 protein; PFS = progression free survival; RECIST = Response Evaluation Criteria in Solid Tumors; RDE = recommended doe for expansion.

4 Study Design

4.1 Overall Design

This is an open-label, multicenter, Phase 1, clinical study of M4076 (see Table 7).

Part 1A is a M4076 monotherapy dose escalation designed to determine the safety, tolerability, PK, Pd and early signs of efficacy in participants with solid tumors. Once an RDE is declared in Part 1A, a preliminary food effect cohort, Part 1B, may follow and will be conducted at the RDE or a lower dose than RDE determined from Part 1A. Part 1B is a randomized, 2-sequence, 2-period, cross-over design.

Table 7 Summary of Overall Study Design

Study Part	Population	Design	Study Intervention
Part 1A	All patients with advanced solid tumors	Dose escalation enrolling patients in sequential cohorts at increasing dose levels.	M4076 monotherapy
Part 1B	All patients with advanced solid tumors	Once an RDE is determined in Part 1A, a preliminary food effect assessment will be included (2 × 2 randomized crossover).	M4076 monotherapy

RDE = recommended dose for expansion.

Individual participants will follow study procedures and assessments as shown in the Schedule of Assessment in Section 1.3. Section 1.2 presents the Study Schema for the study. For Part 1A, potential variations in study intervention schedules and schedule of activities due to alternative dosing schedules are found in Appendix 7.

Duration of Study:

For each participant in Part 1A, the study will include a Screening period lasting up to 28 days. Participants will be treated until disease progression, death, or End of Study. It is estimated that participants will be on the study for an approximate duration of 105 days/15 weeks. There will also be an End of Study Intervention Visit (within 7 days after last dose), and a Safety Follow-up period of 30 days (±7 days) after the last study intervention intake.

For each participant in Part 1B, the study will include a screening period lasting up to 21 days, a preliminary food effect assessment of 7 days followed by study intervention with M4076 monotherapy until disease progression or end of study. From Day 5 onward, participants will continue to be treated as for Part 1A with same visits.

Screening:

Screening will be performed within 28 days prior to Day 1 of M4076 administration. If there are no clinically significant findings during Screening and the individual meets all the protocol-defined inclusion and none of the exclusion criteria, the individual will be considered eligible for participation in the study. Screening for the next cohort may be performed before the SMC has taken the decision on the next dose. The eligible participants screened for the next cohort will, however, only be treated after the decision for the next cohort has been taken by the SMC.

Individuals who fail to start study intervention, for instance due to unmet protocol-specified criteria or consent withdrawal, will be considered Screening Failures.

Study Intervention Period:

All participants will receive study intervention until disease progression (according to Response Evaluation Criteria in Solid Tumors Version 1.1, see Appendix 9), death, AE leading to discontinuation of study intervention(s), or withdrawal of consent, whichever occurs first.

Follow-up:

All participants are to be followed up after end of study intervention, including an End of Study Intervention Visit assessment (within 7 days of last dose). A Safety Follow-up Visit will occur 30 (±7) days after the last dose of M4076 for all participants who discontinued the study intervention permanently.

See Section 4.3 for End of Study definition.

Assumptions and projections about the likely duration of the study intervention and efficacy phases are provided in Section 9.

4.1.1 Part 1A – M4076 Monotherapy Dose Escalation

Part 1A of the study will define the MTD and/or RDE of M4076 monotherapy in participants with advanced solid tumors for which no standard therapy is available.

The first dose escalation cohort of 3 participants will receive M4076 monotherapy at the starting dose of 100 mg administered orally once daily under fasting conditions (see Section 6.1 for fasting window information). For further dose escalation cohorts, an SMC will meet and review all available safety, PK and Pd data to provide recommendations on the DL for the next cohort. A Bayesian dose-toxicity model (Appendix 12) will assist the SMC in dose recommendations. For details of statistical considerations, see Section 9.

Potential DLs are: 100 mg (starting dose), 200 mg, 300 mg, 400 mg, 600 mg. A DL of 50 mg will be explored in case the starting dose of 100 mg is not tolerated. Depending on the observed toxicity profile and available PK and Pd, the SMC may decide on doses different to, or higher or lower from what is prespecified. The SMC may also recommend changing the dosing regimen to e.g. thrice weekly (daily dosing on Days 1, 3, and 5 of each week), twice weekly (daily dosing on Days 1 and 4 of each week), and/or schedules with holidays from study intervention (e.g., 3 days on/4 days off, 7 days on/14 days off, 14 days on/7 days off). More details on the SMC and dose escalation can be found in Section 6.6.1. The SMC operational details will be provided in an SMC Charter, which will be established prior to the start of recruitment. The details will include, but not limited to SMC membership, meeting frequencies, minimum requirements for data review, and responsibilities.

Dose escalation will proceed according to SMC recommendation until MTD and/or a safe RDE is determined and/or the SMC recommends ending dose escalation. The MTD and RDE are defined by the SMC. Target DLT probability for the MTD determination is 30%. In determining the RDE, the SMC will also consider PK, Pd and information on the safety and tolerability of the study intervention beyond the DLT period.

At least 6 participants are required to be treated at the MTD and/or RDE.

RDE cannot exceed MTD. If suggested RDE is below MTD, dose escalation will continue until MTD is reached (if applicable) or SMC decides ending dose escalation.

At the discretion of the SMC, if the toxicity and tolerability profile of M4076 remains ambiguous at any DL, including the MTD or if additional PK/Pd data are felt necessary at any DL below the MTD, additional participants may be studied at that DL to better define the toxicity, tolerability, PK, and Pd. The study procedures for these additional participant(s)/cohort(s) will be the same as that specified for other study participants/cohorts.

This study part will also investigate the pharmacodynamics of M4076 as a secondary objective. Paired tumor biopsies (optional) and serial blood samples (mandatory) will be collected to evaluate markers of ATM inhibition.

If necessary, the Schedule of Activities will be adjusted, e.g. to ensure that PK and Pd samples are collected at the appropriate time points.

Once the MTD and/or RDE is determined in Part 1A, the RDE from Part 1A will be used for the food effect cohort in Part 1B.

Intraparticipant Dose Escalation: No intraparticipant dose escalation is allowed. However, upon declaration of safety and tolerability of the MTD or RDE by the SMC, participants who are still receiving ongoing study intervention at doses lower than the RDE may be switched to the RDE if participants have not experienced any treatment-emergent related AEs greater than Grade 1.

4.1.2 Part 1B – Preliminary Food Effect Assessment

Part 1B may begin enrolling once the MTD or RDE is defined in Part 1A and will follow a randomized, 2-sequence, 2-period, cross-over design with a target sample size of 12 participants. Participants will be randomized by the Interactive (phone and web) Response System (IXRS) to 1 of 2 sequences. Allocation assignment will be done on a 1:1 basis: (1) fasted followed by fed, or (2) fed followed by fasted.

Participants will visit the clinic from Day -7 to Day -4 during which they will receive a single M4076 dose with PK samples collected as outlined in Table 2. Participants will receive another dose on Day 1 to ensure an approximate one-week washout period between administrations. Once the PK of M4076 is characterized, the minimum washout period may be changed to 5 half-lives at the discretion of the Sponsor, if warranted. The fed meal condition is planned to be a standard low-fat meal (see Appendix 8). PK samples will be collected for both fed and fasted study interventions. Triplicate ECG samples will be collected only for participants dosed in the fasted state (see Section 6.1 for details regarding the fasting window). Additionally, if the half-life of M4076 is substantially longer than originally predicted, the PK sampling timepoints after the first dose on Day -7 may be adjusted, as described in the Schedule of Activities (Section 1.3.2).

The SMC will continue to monitor the safety of M4076 and may recommend continuing at the same dose, change the dose (not higher than MTD defined in Part 1A), or stop Part 1B.

Unacceptable toxicity for Part 1B will be AEs that fulfill the DLT criteria (as defined in Section 6.6) regardless of when they occur during treatment. Adverse events will be collected and reported in similar manner to Part 1A of the study. The SMC decisions in Part 1B will also be supported by a Bayesian Model. Refer to Section 9.4.4 for details.

The Pd of M4076 will also be investigated in Part 1B. Paired tumor biopsies and serial peripheral blood mononuclear cells samples will be collected to evaluate markers of ATM activation and inhibition, as well as of DNA damage. The collection of paired tumor biopsies is mandatory, unless contraindicated for medical reasons. If insufficient paired tumor biopsies are obtained, additional participants consenting to provide paired tumor biopsies may be added at the discretion of the Sponsor.

If necessary, the Schedule of Activities will be adjusted, e.g., to ensure that PK and Pd samples are collected at the appropriate time points.

After completion of the Part 1B assessments, participants will continue to be treated under the same schedule as participants in the dose escalation cohorts of Part 1A starting from Day 5.

Based on the results of Part 1B assessments, fasting restrictions may be modified for remaining and additional study participants in some or all study parts at the discretion of the SMC.

4.2 Justification for Dose

The starting dose of M4076 for this first-in-human study was determined based on the International Council for Harmonisation (ICH) Guideline S9 'Nonclinical Evaluation for Anticancer Pharmaceuticals' (2009) the FDA guidance (Food and Drug administration: Guidance for Industry: Estimating the Maximum Safe Starting Dose in initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 2005) and took into consideration the severely toxic dose (STD) and highest non-STD as well as the predicted human exposure and the PK/pharmacodynamic modeling of the predicted pharmacological active dose range in humans.

Completed Good Laboratory Practice 4-week repeat-dose toxicity studies in rats and dogs support the calculation of the starting dose. Applying the common approach of a 10-fold safety margin to the STD10 (> 100 mg/kg/day) in rats (most sensitive species) it corresponds to a human equivalent dose of 96 mg per day (Guidance ICH S9 2010); assuming 60 kg body weight and body surface area correction, which has been rounded to 100 mg.

At the 100 mg M4076 dose, unbound AUC multiples (observed toxicokinetic exposure/ predicted human exposure ratio) of approximately 3.0 and 1.5 relative to the toxic dose in 10% of the animals in rat and highest non-severely toxic dose (non-STD) in dog, respectively, are expected based on the predicted human PK. Unbound C_{max} multiples of approximately 6.0 and 5.5 relative to the toxic dose in 10% of the animals in rat and highest non-severely toxic dose in dog, respectively, are estimated based on the predicted human PK. The findings of primary interest in the repeat dose toxicity studies in establishing the starting dose were increased heart rate and lymphatic and hematological toxicity. Based on the nature of these findings and their ability to be monitored clinically, the proposed exposure margins were considered acceptable in the interest of minimizing the exposure of participants to potentially ineffective therapy.

Based on preclinical in vivo studies in settings relevant to pharmacologically evaluate the specific effect of an ATM inhibitor, M4076 is expected to be pharmacologically active at the starting dose of 100 mg.

Part 1B (the preliminary food effect assessment) will be conducted with two single doses of M4076 of the same amount. The dose of M4076 to be administered is planned to be the RDE, although a lower dose may be used at the discretion of the SMC. Based on nonclinical data and predicted high degree of absorption that is expected to be dose-linear up to 600 mg, a clinically relevant food effect is not anticipated. Based on nonclinical repeat dose toxicity and pharmacokinetic studies of M4076, increased exposure as a result of coadministration with food for a single dose is not expected to substantially alter the risk.

See Section 6.6 for information on dose selection and modifications.

4.3 Scientific Rationale for Study Design

The Phase 1, dose-escalation study is designed to establish a safe and tolerable dose of M4076 monotherapy (Part 1A) and to investigate PK, Pd, and early signs of efficacy in participants with advanced solid tumors for which no standard therapy is available.

Rationale for the cross over design for the preliminary food effect assessment (Part 1B): The 2-sequence cross over design, as compared to an alternative parallel design, minimizes the number of study participants required to identify the effect of food on the PK of M4076 since each participant serves as their own control. The selected washout period will sufficiently remove M4076 from the systemic circulation to eliminate the risk of carryover effects which can be deleterious to the study's outcome and interpretation.

Participant involvement in development of the study design was not sought.

4.4 End of Study Definition

End of Study for an Individual Participant: A participant has completed the study if he/she has completed all study parts, including End of Study Intervention Visit and Safety Follow-up Visit (see Section 1.3) or one of the following criteria applies:

- Withdrawal of consent to study
- Lost to Follow-up
- Died

All participants who do not fulfil one of the prior three criteria should be followed until the last participant has completed the Safety Follow-up Visit or transferred to study intervention access outside of this study.

End of Study Overall: The end of the study is defined as the date of completion of study intervention by all participants and all required study activities/visits (including the Safety Follow-up Visit).

Post Study Intervention for an Individual Participant: After the objectives of the study are achieved participants receiving ongoing study intervention may be offered the investigational drug outside of this study under observation of local regulations.

The Sponsor may terminate the study at any time once access to study intervention for participants still benefiting is provisioned via a rollover study, expanded access, marketed product or another mechanism of access, as appropriate.

5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative (where allowed by local laws and regulations) has provided written informed consent, as indicated in Appendix 2.

5.1 Inclusion Criteria

The following criteria apply for Part 1A and 1B of this study.

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

Age

1. Are ≥ 18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics (including organ function)

2. Patients with advanced solid tumors, for whom no standard of care therapy exists or for whom is not considered sufficiently effective, or who cannot tolerate standard of care.
3. Eastern Cooperative Oncology Group Performance status 0 or 1.
4. Adequate hematological function defined by absolute neutrophil count, ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, and hemoglobin ≥ 9 g/dL, and without growth factor treatment or blood transfusion within 2 weeks before the study intervention start.
5. Adequate hepatic function defined by total bilirubin level ≤ 1.5 × upper limit of normal (ULN), aspartate aminotransferase level ≤ 3 × ULN, and an alanine aminotransferase (ALT) level ≤ 3 × ULN. For patients with liver metastases, aspartate aminotransferase ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and total bilirubin ≤ 3.0× ULN is acceptable. For patients with Gilbert's disease, total bilirubin ≤ 2.0 mg/dL or direct bilirubin ≤ 1 × ULN is acceptable.

6. Adequate renal function defined by an estimated glomerular filtration rate > 60 mL/min according to the Cockcroft-Gault equation: (Glomerular filtration rate = {((140–age) x weight)/(72xSCr)} x 0.85 (if female).
7. Participants in Part 1B (the preliminary food effect assessment) must agree to provide paired tumor biopsies if not contraindicated for medical reasons.

Sex

8. Are male and/or female
9. Contraceptive use by males or females will be consistent with local regulations on contraception methods for those participating in clinical studies.

Male participants:

Agree to the following during the study intervention period and for at least 3 months after the last dose of study intervention:

- Refrain from donating sperm.

  PLUS, either:

- Abstain from any activity that allows for exposure to ejaculate.

  OR

- Use a male condom:

  When having sexual intercourse with a woman of childbearing potential (WOCBP) and advise her to use a highly-effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 3 since a condom may break or leak.

  When engaging in any activity that allows for exposure to ejaculate to another person.

- Male participants must use a male condom with pregnant female partners during the study.

Female participants:

Are not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Not a WOCBP

  OR

- If a WOCBP, use a highly effective contraceptive method (i.e., with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods:
  - Before the first dose of the study intervention(s), if using hormonal contraception:
    - Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses

  OR

- Has used a depot contraceptive or extended cycle oral contraceptive for at least 28 days and has a documented negative pregnancy test using a highly sensitive assay.

- During the intervention period
- After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 6 months after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period

The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention

- Have a negative urine pregnancy test, as required by local regulations, within 24 hours before the first dose of study intervention
- Women should not breastfeed during the study and for at least 1 month after the study period, (i.e., after the last dose of study intervention is administered).

Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

Informed Consent

10. Capable of giving signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Clinically significant (i.e., active) uncontrolled intercurrent illness including, but not limited to:

- Active infection (i.e., requiring systemic antibiotics or antifungals)
- Uncontrolled arterial hypertension (i.e., systolic blood pressure > 150 mmHg, diastolic blood pressure > 100 mmHg)
- Symptomatic congestive heart failure (≥ New York Heart Association Classification Class II), unstable angina, myocardial infarction or a coronary revascularization procedure within 180 days of study entry
- Calculated average QT interval corrected using Fridericia's formula (QTcF) of > 450 msec for males and > 470 msec for females.
- A history of additional risk factors for Torsades de Pointes (e.g., clinically relevant hypokalemia, family history of Long QT Syndrome)

- The use of concomitant medications that prolong the QT/QTc interval
- Severe cardiac arrhythmia requiring medication
- Cerebral vascular accident/stroke
- Clinically significant liver disease consistent with Child Pugh Class B or C; and/or
- Any psychiatric illness/social situations that would limit compliance with study requirements.

2. Presence of brain metastases unless clinically stable (without evidence of progression by imaging for at least four weeks prior to the first dose of study intervention and any neurologic symptoms have returned to baseline), no evidence of new brain metastases, and on a stable or decreasing dose or without steroids for at least 14 days prior to study intervention. Participants with carcinomatous meningitis are excluded regardless of clinical stability. Central nervous system imaging at Screening is not mandatory.
3. Has a known additional malignancy that is progressing and/or requires active treatment. In addition, participants are excluded who were diagnosed with another malignancy within 3 years of starting study intervention. Exceptions include fully resected basal cell carcinoma of the skin or squamous cell carcinoma of the skin, in situ cervical cancer, fully resected ductal carcinoma in situ, and Stage IA noninvasive grade I endometrioid endometrial cancer, that has undergone curative therapy. Participants with other localized malignancies treated with curative intent need to be discussed with the Medical Monitor. Participant must not have any known history of myelodysplastic syndrome or acute myeloid leukemia.
4. Has known ataxia telangiectasia
5. Participants with tumors harboring previously identified ATM mutations
6. Individuals with known human immunodeficiency virus and/or active viral hepatitis (B and/or C), and individuals on viral hepatitis B therapy are excluded. However, individual with Hepatitis C treated with curative therapy are not considered actively infected.
7. Has a history or current evidence of any condition, therapy, and/or laboratory abnormality that might confound the results of the trial, interfere with the participant's participation for the full duration of the trial, and/or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

Gastrointestinal Conditions

8. Serious gastrointestinal bleeding within 3 months, refractory nausea and vomiting, uncontrolled diarrhea, known malabsorption, significant small bowel resection or gastric bypass surgery, use of feeding tubes, other chronic gastrointestinal disease (including exocrine pancreatic insufficiency requiring pancreatic enzyme replacement therapy) and/or other situation that may preclude adequate absorption of oral medications

Prior/Concomitant Therapy

9. Participants who may have received any of the following anticancer therapy(ies), or concomitant medications within the following windows per the first day of study intervention administration:

- Hematopoietic growth factors (including erythropoietin, darbepoetin, granulocyte-colony stimulating factor, granulocyte macrophage-colony stimulating factor, and platelet stimulators [e.g. eltrombopag, romiplostim, or IL-11]) and blood transfusions within 2 weeks.
- Anticancer treatment within 28 days or 5 half-lives, whichever is shorter, except for nitrosoureas or mitomycin C (within 6 weeks).
- Participants receiving prior treatment with an ATM inhibitor.
- Prior curative-intent radiotherapy within 4 weeks. Prior palliative radiotherapy to metastatic lesion(s) is permitted provided it was completed $\geq$2 weeks prior to study enrollment and toxicities have recovered to Grade $\leq$ 1.
- Major surgery within 4 weeks and not recovered for side effects Grade $\leq$ 1, according to investigator's judgment.
- Any other type of anticancer therapy, not listed above, within 4 weeks.
- Clinical substrates of CYP3A4 with narrow therapeutic index. Stop at least 1 week before study intervention until safety follow-up visit.
- Strong inhibitors or inducers of CYP3A4 or P-gp that cannot be discontinued as outlined in Section 6.5.3. Examples of strong inhibitors of CYP3A4 and P-gp inhibitors or strong inducers of CYP3A are provided in Table 9.
- Additional excluded concomitant medications include irinotecan, oral direct thrombin inhibitors, and digoxin. Stop at least 1 week before study intervention until safety follow-up visit.
- Concomitant treatment with proton pump inhibitors is prohibited. The administration of H_2-receptor antagonists will be permitted as long as they are not administered for 12 hours before or 2 hours after the dosing of M4076. Antacids cannot be administered 2 hours before or 2 hours after the dosing of M4076.

10. Participants not recovered from AEs (i.e., Grade $\leq$ 1) of prior anticancer therapies. Exception: Grade 2 AEs not constituting a safety risk, based on the Investigator's judgement, must be consulted with the Sponsor prior to enrolment.

Prior/Concurrent Clinical Study Experience

11. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy and/or used an investigational device within 4 weeks of the first M4076 administration of study intervention or longer if described elsewhere.
12. Hypersensitivity to the active substance or to any of the excipients of M4076.

Other Exclusions

13. Pregnant or breastfeeding.
14. Part 1B only (food effect cohort): participants unable to consume a low-fat meal as specified in Appendix 8.

5.3 Lifestyle Considerations

No specific lifestyle or dietary restrictions are required throughout the study. Tobacco use status, e.g., former, current or never, will be collected at screening and recorded in the eCRF.

Refer to Appendix 8 for timing of meals in Parts 1A and 1B.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once after the reason for screening failure has been addressed. Rescreened participants will be reconsented and assigned a new participant number and will undergo Screening procedures as planned by the protocol. Any previous screening tests can be used for rescreening, provided they are within the new screening window.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol. Study intervention is used instead of "study drug, Investigational Medicinal Product, or study treatment".

6.1 Study Intervention Administration

Participants are planned to continue with study intervention (see Table 8) until documented disease progression, discontinuation due to adverse events, death or withdrawal from the study, whichever occurs earlier.

Fasting Window Definition

For Part 1A - The fasting window is defined as: 2 hours pre-dose to 1-hour post-dose in general, and 2 hours pre-dose to 4 hours post-dose on days where PK-time matched triplicate ECG will be collected. This fasting strategy facilitates more frequent daily dosing regimens and alleviates potential discomfort for advanced cancer patients during the dose escalation phase.

For Part 1B - The fasting window is defined as: 10 hours pre-dose to 4 hours post-dose.

Table 8 Study Intervention Details

Intervention Name	M4076
Type	Drug
Dose Formulation	Film-coated tablets
Unit Dose Strengths	50 mg
Dose Amount	M4076 will be administered orally, as planned, once daily per the dose escalation schema (Figure 2) and as determined by the SMC based on safety, tolerability, and preliminary PK and, if appropriate, Pd data. MTD/RDE to be determined. See Sections 4.1.1 and 6.6 for more information.

Frequency	Once daily; schedules may be adapted
Route of Administration	Oral
Use	Experimental
IMP/NIMP	IMP
Sourcing	Provided centrally by the Sponsor.
Packaging and Labeling	Study Intervention will be provided in participant kits containing M4076 tablets in blisters. Each kit will be labeled per country requirement.

IMP = investigational medicinal product; MTD = maximum tolerated dose; NIMP = non investigational medicinal product; Pd = pharmacodynamics; PK = pharmacokinetic; RDE = recommended dose for evaluation; SMC = safety monitoring committee.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

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

- Upon receipt of the study intervention(s), the Investigator or designee will confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Pharmacy Manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, medication numbers, expiry dates, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) will not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.

- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

The IXRS will be used to assign unique participant numbers, allocate participants to study intervention group at the randomization visit, and study intervention to participants at each study intervention visit.

Before the study is initiated, the directions for the IXRS will be provided to each site. The site will contact the IXRS prior to starting study intervention administration for each participant.

For Part 1B, after confirmation of participant's eligibility prior to study intervention administration, participants will be centrally allocated to either (1) fasted followed by fed, or (2) fed followed by fasted in a 1:1 ratio using an IXRS and per a computer-generated randomization list.

6.3.2 Blinding

This is an open-label study. Participants and Investigators will be aware of study intervention assignments.

Reduction of bias is mitigated by the randomized design in Part 1B (preliminary food effect assessment), which will use an IXRS to assist in randomization to fed/fasting schedules. The IXRS will also be used for study intervention assignment.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets during the site visits and documented in the source documents and CRF. Any deviation(s) from the prescribed dosage regimen are recorded in the CRF.

A record of the number of tablets dispensed to and taken by each participant will be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.5.1 Rescue Medicine

There is no specific treatment or medicine available to counteract the inhibition of ATM intended by M4076. For any unwanted events during study intervention with M4076, the oncological standards in supportive care should be applied.

6.5.2 Permitted Medicines

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

Outside the DLT observation period in Part 1A of the study, prophylactic or therapeutic use of hematopoietic growth factors is permitted to prevent toxicities requiring study intervention interruption or discontinuation. During the DLT observation period, prophylactic use is prohibited. Therapeutic use, if deemed necessary by the Investigator, is allowed and may constitute a DLT (see Section 6.6.2 for details of DLT criteria).

The administration of H_2-receptor antagonists is permitted as long as they are not administered for 12 hours before or 2 hours after the dosing of M4076. Antacids cannot be administered 2 hours before or 2 hours after the dosing of M4076.

The continuation of hormone therapy is allowed throughout the study if the participant has been on stable treatment for the last 3 months prior to enrollment and the Investigator recommends the need to continue this during the study.

6.5.3 Prohibited Medicines

Prohibited medications during the screening period are as defined in the prior/concomitant therapy exclusion criteria in Section 5.2.

Concomitant administration of M4076 with irinotecan, oral direct thrombin inhibitors, digoxin, and proton pump inhibitors is prohibited.

Concomitant administration of M4076 with clinical substrates of CYP3A4 with narrow therapeutic index is prohibited.

Examples of strong inhibitors of CYP3A4 and P-gp inhibitors or strong inducers of CYP3A4 are provided in Table 9. In order to be enrolled, participants must stop before study intervention administration:

- Strong inhibitors of CYP3A4 or P-gp, stop at least 1 week before study intervention administration.
- Strong inducers of CYP3A4, stop at least 2 weeks before study intervention administration.
- Clinical substrates of CYP3A4 with narrow therapeutic index, stop at least 1 week before study intervention until safety follow-up visit.

Table 9 Clinical Examples of Strong CYP3A and P-gp Inhibitors and CYP3A Inducers and sensitive CYP3A4 substrates with narrow therapeutic index

Transporter	Strong Inhibitor	
P-gp	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil.	
Enzyme	**Strong Inhibitors**	**Strong Inducers**
CYP3A	boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole.	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort (*Hypericum perforatum*).
Enzyme	Clinical substrates of CYP3A4 with narrow therapeutic index	-
CYP3A	Astemizole, Cyclosporine, Everolimus, Pimozide, sirolimus, tacrolimus	-

Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers #Table3-2

CYP3A = cytochrome P450; P-gp = P-glycoprotein.

Note: Most P-gp inhibitors also inhibit CYP3A.

If the administration of a nonpermitted concomitant drug becomes necessary during the study intervention period, e.g., due to AEs, study intervention must be interrupted, and permanent discontinuation should be discussed with medical monitor.

6.5.4 Other Interventions

Radiation therapy is not allowed on this study except for palliative treatment of lesions that are present at baseline and cause symptoms that cannot be adequately controlled by other means e.g. analgesics. If radiation therapy is required, the study intervention should be withheld for at least 4 half-lives before the administration of radiation and may be resumed once toxicities are Grade ≤ 1 (refer to the M4076 IB for more details). In addition, the Investigator should ensure that tumor assessments are recently obtained and reported as per RECIST 1.1 (Appendix 9), before initiation of radiation therapy.

6.6 Dose Selection and Modification

The recommendation in Part 1A to proceed to the next DL (including what DL), or to decrease the dose in the next cohort or to expand the current DL to include additional participants will be made by the SMC based on safety, tolerability, and preliminary PK and, if appropriate, Pd data. The SMC receives outputs of a Bayesian dose-toxicity model with estimated DLT probabilities for potential next DLs to support the decision making of the SMC. The Bayesian model (Appendix 12) will be based on prior information, observed number of evaluable participants and number of participants with DLT. Further details on the Bayesian model are provided in Section 9.4.2. Further details on the SMC are provided in Section 6.6.1.

Participants are eligible for the Bayesian dose-toxicity model for DLT probability, if they fulfill the criteria of the DLT analysis set, defined in Section 9.3.

Detailed justification of the starting dose for M4076 is provided in Section 4.2. Details of the dose escalation schema in Section 1.2.

6.6.1 Safety Monitoring Committee

During the dose-escalation part (Part 1A) of the study, the SMC will evaluate the safety (including DLTs), tolerability, and available PK, to include at least predefined PK of the previous cohort, and available Pd data. The SMC will decide on dose escalation, de-escalation, additional enrolment on same DL, MTD, or suspension of enrolment. In cases where enrollment of the last participant in a dosing cohort is significantly delayed, the SMC may decide (based on available data) upon enrolment and dose for the next dosing cohort before all participants in a cohort have completed the DLT period. For this participant, the SMC will consider all available data and any subsequent emerging data at a subsequent meeting. An ad-hoc meeting will be convened if this participant experiences a DLT.

The SMC can recommend modifying the schedule of administration. SMC will review PK to determine if adjustment of schedule (to predefined alternative schedules as defined in Appendix 7) is appropriate during the dose escalation based on the collected data. The usual cohort size is 3 participants, but the SMC can decide to change the size of cohorts. Based on the observed toxicity profile and available PK and Pd, DL(s) that are different to, or higher or lower than the prespecified doses may be tested. The SMC may also recommend changing the dosing regimen.

During the Part 1B of the study, the SMC will monitor the safety and may recommend by consensus on continuation, expansion, and modifications of the study. The SMC may modify the frequency of meetings as deemed appropriate during the study.

The specific working procedures will be described in an SMC Charter, which will be established before first informed consent signed.

6.6.2 Dose-limiting Toxicities – Definition and Criteria

A DLT is defined as any of the following AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 assessed by the Investigator and/or the Sponsor at any dose, judged not to be related to the underlying disease or any previous or concomitant medication or concurrent condition, occurring during the DLT observation period, which for Part 1A starts on the first day of study intervention (Day 1) and has a duration of 21 days.

Study accrual will be halted, pending discussions with the SMC or the study Sponsor, if there is an occurrence of a Grade 5 toxicity by the NCI-CTCAE Version 5.0 attributable to the treatment regimen or if more than 1 DLT is seen in DL 1 in Part 1A.

The treatment of toxicities with transfusions or growth factors (e.g., granulocyte-colony stimulating factor, erythropoetin) is not permitted during the DLT period and if it occurs will be considered a DLT.

AEs judged as DLT will include:

- Any Grade ≥ 3 **non-hematologic** AE with **exception** of:
  - Single laboratory values out of normal range that have no clinical correlate and resolve to Grade ≤ 1 or to baseline within 7 days with adequate medical management or asymptomatic Grade 3 lipase or amylase elevation (> 5 ULN) not associated with clinical manifestation of pancreatitis.
  - Infusion-related reaction resolving within 6 hours from the end of infusion and controlled with medical management (for iv compounds only)
  - Diarrhea persisting < 72 hours after initiation of medical management
  - Nausea and vomiting of ≤ 72 h duration with adequate and optimal therapy
  - Transient (≤ 72 h) fatigue, local reactions, flu-like symptoms, fever, headache, hypertension that resolves to Grade ≤ 1 with adequate treatment
  - Grade 3 non-recurrent skin toxicity that resolves to Grade ≤ 1 in less than 7 days after initiation of medical management
  - 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
  - Any death clearly due to the underlying disease or extraneous causes

- Grade ≥ 3 neutropenia with clinical signs/symptoms, such as fever > 38.5 °C (e.g., for febrile neutropenia, an ANC < 1000/mm^3 with single temp of 38.3 °C [101 °F] or a sustained temperature of ≥38 °C [100.4 °F] for more than one hour)
- Grade ≥ 3 thrombocytopenia with medically concerning bleeding
- Any Grade ≥ 4 hematologic AE, except:
    - Isolated Grade 4 lymphopenia without clinical correlate
    - Any Grade 4 neutropenia of < 7 days' duration not associated with any clinical symptoms
- All events of ALT ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT > 3 × ULN and international normalized ratio (INR) > 1.5, if INR measured, may indicate potential severe liver injury (possible Hy's Law), will require prompt permanent discontinuation from the study, and will be reported as an SAE (excluding studies of hepatic impairment or cirrhosis):
    - Without initial findings of cholestasis (elevated serum ALP).
    - In the absence of other reasons than drug toxicity to explain the laboratory constellation (e.g., viral hepatitis A, B, C or co-medication).
    - In the absence of other reasons than drug toxicity to explain the laboratory constellation.
- Any AE leading to the inability to deliver at least 80% of the planned total dose for the DLT period, except in situations other than toxicity, e.g. participant noncompliance or logistical issues with study intervention delivery.
- Death not clearly attributed to underlying disease or alternative cause.
- Additionally, the SMC may identify as a DLT:
    - A TEAE (inside or outside of the DLT period) that in the opinion of the SMC is of potential clinical significance such that further dose escalation would expose participants to unacceptable risk

The SMC must confirm any DLT.

If any change is made to the grade or causality of an AE during the study that may alter its DLT status, the Sponsor must be informed immediately as this may affect dose escalation decisions.

Additionally, participants excluded from the DLT analysis set may be replaced; the decision will be made by the SMC.

6.6.2.1 Dose Interruptions and Modifications

Participants who experience an AE meeting DLT criteria during the DLT assessment period need to interrupt M4076 (Table 10). No dose modifications of M4076 should be made during the DLT assessment period for the dose escalation part of the study (Part 1A).

Participants who experience rash and systemic symptoms (e.g., fever, vomiting, diarrhea), or other signs of hypersensitivity should have M4076 discontinued immediately and are not to be rechallenged with any dose of M4076. Grade 2 and Grade 3 rash (without systemic symptoms) should be managed with treatment interruption and supportive medications, including topical or oral steroids.

Dose modifications outside the DLT period are allowed. Participants who experience a Grade 4 drug-related toxicity should discontinue treatment promptly. For a Grade 3 drug-related toxicity, M4076 treatment should be interrupted and may resume at a reduced dose provided the toxicity has resolved to Baseline value or Grade $\leq$ 1 within 2 weeks. At the first instance of a Grade 3 toxicity, study intervention will be held, and allowed to resume with a 25% dose reduction once said toxicity recovers to Grade $\leq$ 1. Should a study participant develop a recurrent Grade 3 drug-related toxicity, study intervention will once again be held, and allowed to resume with a 50% dose reduction once said toxicity recovers to Grade $\leq$ 1. Subsequent recurrences of Grade 3 toxicity will prompt discontinuation of study treatment, i.e., no more than 2 dose reductions will be permitted. Based on emerging data (i.e. toxicity, PK, Pd) and tablet strength availability, different dose reductions may be recommended as agreed between Sponsor and investigator, such as alternative dose reduction steps or different dosing regimen. Recommended dose reductions for each potential DL are provided in Table 10.

Once the dose of M4076 has been reduced in an individual participant, it must not be escalated back to the original dose level. If more than 2 dose reductions of > 50% dose decrease are indicated, the participant will be permanently discontinued from study intervention. Consultation between Investigator and Sponsor about dose reduction is encouraged.

Table 10 M4076 Recommended Dose Modifications for Grade 3 Hematologic and Nonhematologic ADRs

Potential DLs – Starting doses	Grade 3 Hematologic and Nonhematologic ADRs		
	1st occurrence DR of 25%	2nd occurrence DR of 50%	3rd occurence
100 mg	50*	Discontinued	NA
200 mg	150	100	Discontinued
300 mg	200	150	Discontinued
400 mg	300	200	Discontinued
600 mg	450	300	Discontinued

ADR = adverse drug reaction; DL = dose level; DR = dose reduction; NA = not applicable.
* reduction is 50% based on available tablet strengths.

For delays in study intervention exceeding 2 weeks, the intervention will be permanently discontinued, except for a situation where the participant has benefitted from study intervention with M4076 before the administration delay and is expected to continue to benefit from resumed study intervention after the interruption.

See Section 7 for information regarding discontinuation of study intervention and participant discontinuation/withdrawal.

6.7 Study Intervention after the End of the Study

Participants still benefitting from study treatment will be offered continued access to the treatment they received during the study after the end of the study, when appropriate, within defined limitations and as described below.

A roll-over study or Single Patient Post-study Access may be implemented. Under this mechanism, individual participants who completed the study may be provided with their assigned treatment outside of the clinical study under the responsibility of the treating physician. This treatment should comply with any legal and regulatory requirement as there are no appropriate alternative treatments available.

Data on safety events continue to be collected per a safety reporting agreement with the participants treating physician.

The Sponsor will not provide any additional care to participants after they leave the study because such care would not differ from what is normally expected for patients with advanced solid tumors.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

The participant must be withdrawn from study intervention in the event of any of the following:

- At his/her request (withdrawal of consent of study intervention).
- Development of unacceptable toxicity.
- Occurrence of progressive disease according to RECIST 1.1 (Appendix 9). Study intervention may continue past the determination of progressive disease if deemed indicated by the Investigator and discussed with the Sponsor.
- Initiation of any other anticancer therapy, except for palliative radiation therapy (see Section 6.5.4).
- Occurrence of an exclusion criterion that is clinically relevant and affects the participant's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor.
- Occurrence of pregnancy.
- Use of a nonpermitted concomitant drug (including any other drug with known anticancer activity unless specified otherwise).
- Noncompliance that is deemed by the Investigator or the Sponsor to compromise participant safety or study integrity.

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for an End of Study Intervention Visit. The Schedule of Activities indicates data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Pregnancy:

For information regarding pregnancy, see Section 8.3.5.

The Schedule of Assessments specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time, at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral compliance, or administrative reasons.
- At the time of discontinuing from the study, if possible, a discontinuation visit will be conducted, as listed in the Schedule of Activities. The Schedule of Activities specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.

- If the participant withdraws consent for future involvement in the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- A participant has the right at any time to request destruction of any biological samples taken. The Investigator will document this in the site study records.

Additional participants may be enrolled for each participant who withdraws from the study after signing consent and successfully meeting entry criteria but did not receive study intervention. Additionally, participants excluded from the DLT analysis set may be replaced.

The Investigator will be responsible for the safety of the study participants and make every attempt to collect data. See Section 7.3 for further details.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts will be documented in the participant's medical record.
- If the participant continues to be unreachable, he/she will be deemed as "lost to follow-up".

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the Schedule of Activities.
- No protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to

record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.

- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

8.1 Efficacy Assessments and Procedures

Radiographic images and physical findings (physical assessments) will be used by the Investigators for the local determination of disease progression and participant treatment decisions. Refer to the RECIST 1.1 publication for additional information (Eisenhauer 2009).

Whenever available, the longest diameter measurement of each target lesion and short axis for nodes derived from historical computerized tomography (CT)/magnetic resonance imaging (MRI) scans over a period of up to 100 days prior to enrollment should be collected in order to assess tumor growth dynamics prior to study enrollment. For comparability, target lesions in both historical and on-treatment scans should match, if possible. Participants will have a chest and abdominal imaging scan (e.g., computed tomography, magnetic resonance imaging) as appropriate and, if clinically indicated, imaging scans of other body areas (e.g., bone, pelvis). Participants should have a repeat imaging scan as described in the Schedule of Activities in Section 1.3. All imaging scans to assess disease progression should be performed using similar imaging platforms and imaging techniques, including the use or absence of contrast, and should be of consistent anatomic locations with prior imaging scans, whenever possible. At End of Study Intervention visit, the tumor assessment should only be performed if no disease progression was previously documented.

Imaging scans will be locally read for all parts of the study. The applicable overall response category for each visit that includes disease assessment, based on evaluation of imaging scan, will be recorded in the CRF. Determination of participant study disposition (i.e., discontinuation or extension of therapy) will be based on disease progression as interpreted from the local evaluation of the imaging scan.

For assessment time points and procedures for primary, secondary, and tertiary/exploratory efficacy endpoints, see Schedule of Activities (Section 1.3).

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, adverse events (AEs), physical examination findings, vital signs, electrocardiograms, Eastern Cooperative Oncology Group performance status (see Appendix 10), and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Height at screening and weight will be measured and recorded as per timepoints noted in the Schedule of Assessments.
- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a semi-recumbent position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

8.2.3 Electrocardiograms

8.2.3.1 Standard Single 12-lead Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the Schedule of Activities using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.

8.2.3.2 Digital Triplicate Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the Schedule of Activities using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.

At each time point at which triplicate ECG are required outside of Holter collection, 3 individual ECG tracings will be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates will be completed in less than 4 minutes and will occur in a resting state without prior procedure such as blood draw.

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 6 at the time points listed in the Schedule of Activities. All samples will be clearly identified. See Table 20.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by local laboratory.
- The Sponsor will receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study will be forwarded to the Sponsor.
- The Investigator will review each laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports will be filed with the source documents.

Additional serum or highly sensitive urine pregnancy tests may be conducted, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study.

8.3 Adverse Events and Serious Adverse Events

The definitions of an Adverse Event (AE) and a Serious Adverse Event (SAE) are in Appendix 4.

The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious or that caused the participant to discontinue the study intervention or study, as specified in Section 8.3.3.

Requests for follow-up will usually be made via the Study Monitor, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All SAEs will be collected from the signing of the ICF until the safety follow-up visit at the time points specified in the Schedule of Activities (Section 1.3). Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.

All AEs will be collected from the signing of the ICF until the safety follow-up visit at the time points specified in the Schedule of Activities.

AEs/SAEs that begin before the start of study intervention but after obtaining ICF will be recorded on the Medical History/Current Medical Conditions CRF, not on the AE CRF.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.

Investigators are not obligated to actively solicit AEs or SAEs after the end of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and adverse events of special interest (AESIs) (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Reasonable attempts to obtain this information will be made and documented. It is also the Investigator's responsibility to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is in Appendix 4.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Individual Case Safety Reports will be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

An Investigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g., Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will review and then file it along with the Investigator Brochure in the Investigator's Site File and will notify the IRB/IEC, if appropriate according to local requirements.

In this global clinical multicenter study, the Sponsor is in the best position to determine an unanticipated problem (as defined in US Regulations 21 CFR 312.66). The Sponsor will immediately notify all Investigators of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IRB's approval/favorable opinion to continue the study. An unanticipated problem is a serious adverse event that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report, specified in Section 2.3

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 28 days after the last study intervention administration. Inadvertent pregnancies will be followed-up as per local/country (health authorities) guidelines.
- If a pregnancy is reported, the Investigator will inform the Sponsor within 24 hours of learning of the pregnancy and will follow the procedures specified below for collection of pregnancy information.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner, who becomes pregnant while the participant is in this study. This applies only to participants who receive study intervention.
- After obtaining signed consent from the pregnant female partner directly, the Investigator will record the pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while she is in the study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of the pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.3.6 Adverse Events of Special Interest

For this study, AESIs include only the following:

- Cytopenia (lymphopenia, leukopenia/neutropenia, thrombocytopenia, anemia), Grade ≥ 3 or with complications, e.g., neutropenia with fever or infection or thrombocytopenia with medically concerning bleeding.

An AESI (serious or nonserious reaction) is one of scientific and medical concern specific to the study intervention, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such events of interest may require further investigation or in-depth evaluations to better characterize and understand the association between the AE and M4076. Based on nonclinical data, the following AEs will be considered AESI (Table 11).

Table 11 Adverse Events of Special Interest

AE	Management
Cytopenias (lymphopenia, leuko/neutropenia, thrombocytopenia, anemia), Grade ≥ 3 or with complications, e.g. neutropenia with fever or infection or thrombocytopenia with medically concerning bleeding.	Repeat blood test within 72 hours of receiving the abnormal lab result. Continuous monitoring of AEs with clinical management as indicated, including study intervention interruption, dose modification or discontinuation (see Table 10).

AE = Adverse event.

The Investigator must complete the AESI Report Form and communicate with the Sponsor within 24 hours of occurrence of AESI. Serious AESI (based on SAE reporting criteria) should always be reported as SAE as outlined in Section 8.3.4.

8.4 Treatment of Overdose

For this study, any dose of M4076 greater than the specified dose for each study cohort will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose, other than symptomatic treatment of AEs as deemed necessary.

Even if not associated with an AE or an SAE, any overdose is recorded in the CRF and reported to global patient safety in an expedited manner. Overdoses are reported on an SAE and Overdose Report Form, following the procedure in Appendix 4, the section on Reporting SAEs.

8.5 Pharmacokinetics

Sampling times for the determination of M4076 can be found in Table 3 for Part 1A and Table 4 for Part 1B. The PK sampling schedule may be modified upon agreement of the clinical pharmacologist, investigators, and SMC to optimize the definition of the pharmacokinetic profiles but will not increase the number of PK draws.

The following PK parameters will be calculated, when appropriate (see Table 12). A non-compartmental analysis (NCA) will be performed to estimate these PK parameters for M4076.

Table 12 Assessment of Blood Pharmacokinetic Parameters

Symbol	Definition
$AUC_{0\text{-}tlast}$	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0\text{-}tlast}$/Dose	The Dose normalized AUC from time zero to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Normalized using the actual dose, using the formula $AUC_{0\text{-}tlast}$ /Dose.

Symbol	Definition
AUC_{τ}	The AUC over the dosing interval from $T_1 = 0$ h to $T_2 = {}_{\tau}$h. Calculated using the mixed log-linear trapezoidal rule (linear up, log down). For single dose, AUC_{τ} is calculated as a partial area with the defined time range. In multiple dose profiles AUC_{τ} is calculated at steady state from one pre-dose time point to the dosing interval time. In cases where the actual observation time is not equal to the scheduled observation time AUC_{τ} will be calculated based on the estimated concentration at ${}_{\tau}$hours, and not the concentration at the actual observation time.
AUC_{τ}/Dose	The dose normalized AUC over the interval from $T_1 = 0$ h to $T_2 = {}_{\tau}$ h. Normalized using actual dose, using the formula AUC_{τ}/Dose.
AUC_{0-72}	The AUC from time zero (= dosing time) to 72 hours post-dose. Calculated using the mixed log-linear trapezoidal rule (linear up, log down). In cases where the actual observation time is not equal to the scheduled observation time (72 hours), AUC_{0-72} will be calculated based on the estimated concentration at 72 hours, and not the concentration at the actual observation time.
AUC_{0-72}/Dose	The dose normalized AUC from time zero (= dosing time) to 72 hours post-dose. Normalized using actual dose, using the formula AUC_{0-72}/Dose.
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λ_z determination. $AUC_{0-\infty} = AUC_{0-tlast} + C_{last\ pred}/\lambda_z$
$AUC_{0-\infty}$/Dose	The dose normalized AUC from time zero extrapolated to infinity. Normalized using actual dose, using the formula $AUC_{0-\infty}$/Dose.
CL/F	The apparent total body clearance of study intervention following extravascular administration. $CL/F = Dose_{p.o.}/AUC_{0-\infty}$.
C_{max}	Maximum observed concentration
C_{max}/Dose	The dose normalized maximum concentration. Normalized using the actual dose, and the formula C_{max}/Dose.
C_{trough}	The concentration observed immediately before next dosing
LI	The linearity index after repeated administration calculated as LI = (AUC_{τ} after multiple dose) / ($AUC_{0-\infty}$ after single dose)
$R_{acc(AUC\tau)}$	The accumulation ratio after repeated administration calculated as $R_{acc(AUC\tau)}$ = (AUC_{τ} after multiple dose) / (AUC_{τ} after single dose)
$R_{acc(Cmax)}$	The accumulation factor to assess the increase in maximum concentration until steady state is reached. $R_{acc(Cmax)}$ = (C_{max} after multiple dose)/ (C_{max} after single dose)
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$
t_{last}	The last sampling time at which the concentration is at or above the lower limit of quantification
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)
V_z/F	The apparent volume of distribution during the terminal phase following extravascular administration. $V_z/F = Dose/(AUC_{0-\infty}*\lambda_z)$ following single dose. $V_z/F = Dose/(AUC_{\tau}*\lambda_z)$ following multiple dose.

- Whole blood samples (of approximately 2 mL) and urine samples (Part 1B only) will be collected for measurement of plasma and urine concentrations of M4076. Collection times are specified in the Schedule of Activities (Table 3 for Part 1A and Table 4 for Part 1B). The actual date and time (24-hour clock) of each sample will be recorded to calculate actual time

elapsed since the prior dose administration. The sampling timing may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. In addition, actual date and time of start and end of the urine collection fraction and the volume of each urine collection fraction will be recorded in the CRF.

- The quantification of M4076 concentrations in plasma and urine will be performed using validated bioanalytical methods and will be reported in a separate bioanalytical report. Concentrations will be used to evaluate the PK of M4076.
- Remaining samples collected for the analysis of M4076 plasma and urine concentrations may be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, which will be reported outside of the clinical study report (CSR).
- The following pharmacokinetic parameters will be estimated from urine concentration of M4076 in Part 1B (Table 13), where possible:

Table 13 Assessment of Urine Pharmacokinetic Parameters

Symbol	Definition
Ae_{t1-t2}	Total amount excreted between times t1 (= start) and t2 (= end) of the current collection interval. Calculated by interval Ae_{t1-t2} = Conc * $Vu_{(t1-t2)}$ and cumulative.
fe_{t1-t2} %	Fraction of administered drug that is excreted unchanged in urine between times t1 (= start) and t2 (= end) of the current collection interval. Calculated by interval fe_{t1-t2} = Ae_{t1-t2}/Dose and cumulative.
CL_R	The renal clearance of study intervention. CL_R = Ae_{0-t}/AUC_{0-t}.

Additional parameters may be calculated if appropriate.

Methodology for the calculation of pharmacokinetic parameters will be detailed in the Integrated Analysis Plan (iAP).

- Details on processes for collection and handling of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

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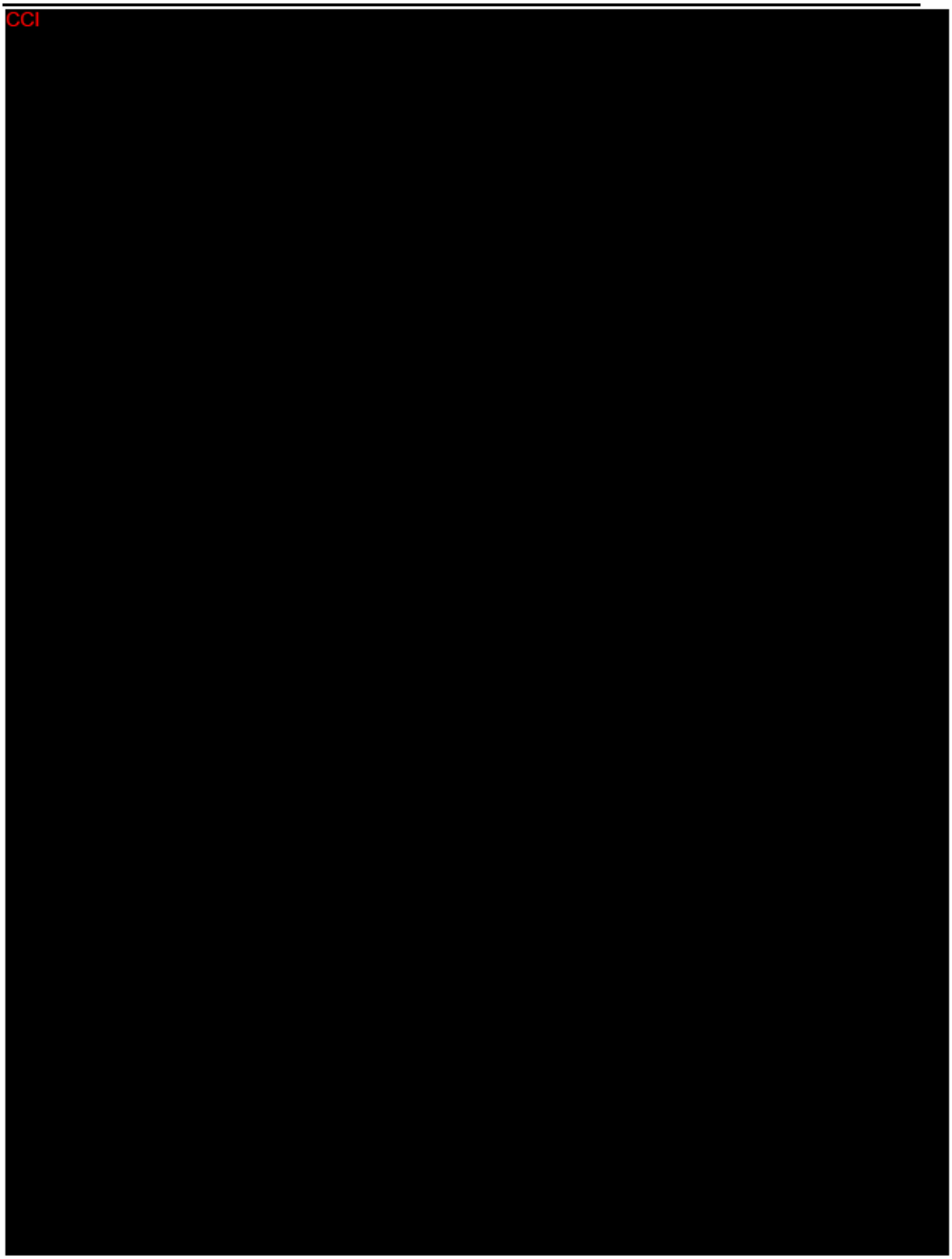

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8.9 Immunogenicity Assessments

Not applicable

8.10 Health Economics

Not applicable

9 Statistical Considerations

Analysis of all data, including safety and PK data will be performed by the Sponsor or its designee. The results of all study parts will be reported in the CSR. Details of the analysis of safety, efficacy, PK, Pd, and biomarker data will be presented in the iAP.

9.1 Statistical Hypotheses

No formal hypothesis testing will be performed. This is an exploratory study.

9.2 Sample Size Determination

Part 1A – Dose Escalation

A Bayesian 2-parameter Logistic Regression Model will assist the SMC in dose recommendations. The planned cohort size is approximately 3 participants. The total sample size will depend on the number of cohorts to be evaluated. Approximately 40 participants are planned to be assigned to study intervention, including 22 to 28 participants in Part 1A (planned 4 potential DLs of 100, 200, 400, and 600 mg), and 12 participants in Part 1B; the sample size for the MTD and/or RDE DL needs to be at least 6 participants.

Part 1B – Preliminary Food Effect Assessment Sample Size Justification

For a preliminary assessment of the effect of food on the systemic exposure of M4076, 12 participants will be randomized 1:1 in a randomized, 2-sequence, 2-period, cross-over design to receive a single dose M4076 under a fed condition in 1 of the following sequences 1) fasted followed by fed, or 2) fed followed by fasted. The dose of M4076 will be the RDE from Part 1A.

This sample size is expected to result in sufficient precision for the estimate of the ratio between PK parameters under fed and fasted conditions in order to guide further development. Assuming that the within-subject coefficient of variation (CV) for $AUC_{0\text{-}24h}$ and C_{max} is between 10% and 30%, the 2-sided 90% confidence interval (CI) for the geometric mean ratio (GMR) will be contained in the boundaries presented in Table 14, with 80% probability.

For example, if the within-subject CV is 20%, and a GMR of 50% is observed, then the 90% CI for the GMR will be contained in [35.6%; 70.2%] with 80% probability. With a CV of 30% and an observed GMR of 100%, the corresponding boundaries are [60.5%; 165%].

Table 14 80% Coverage Interval for the 90% Confidence Intervals for Estimated Fed/Fasted Ratio, n = 6 per Sequence (12 in total)

CV	GMR	80% Coverage Interval n = 6 per Sequence	
	Fed versus Fasted	Lower Bound	Upper Bound
10%	0.50	42.1%	59.3%
20%	0.50	35.6%	70.2%
30%	0.50	30.2%	82.7%
10%	1.00	84.3%	119%
20%	1.00	71.2%	140%
30%	1.00	60.5%	165%
10%	2.00	169%	237%
20%	2.00	142%	281%
30%	2.00	121%	331%

CV = coefficient of variation; GMR= Geometric mean ratio.

These calculations were performed using the module MTC1 1 of the software nQuery Advisor® 7.0 for natural logarithm transformed data, and back-transformed to the original scale.

9.3 Populations for Analyses

The analysis populations are specified below (Table 15). The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock. However, for the DLT analysis set, the decision on evaluability will be made by the SMC.

Table 15 Populations for Analyses

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent.
Full Analysis Set (FAS) / Safety Analysis Set (SAF)	All SCR participants, who received at least one dose of any study intervention. Analyses will consider participants as treated.
DLT	All FAS/SAF participants who meet at least one of the following criteria: • Experienced at least one DLT during the DLT period, regardless of the administered number of doses of study intervention/completion of the DLT period. • Received at least 80% of the planned cumulative dose during the DLT period of each study intervention and completed the DLT period. • Additionally, participants who did not receive 80% of the planned total dose of study intervention, but at least 80% dosing of a different dose cohort and finished the DLT period are eligible for the DLT analysis set to be analyzed in the highest dose cohort for which they received 80% of dosing. The final decision on evaluability for dose escalation analysis will be made by the SMC (e.g. considering relevant deviations from dosing schedule).
PK (PKAS)	All participants who receive at least one dose of study intervention and provide at least one measurable post-dose concentration. A measurement below lower limit of quantification (BLQ) is considered a valid measurement. Participants will be analyzed according to the actual treatment they received. All PK analyses will be based on the PK Analysis Population.
Pd	All participants, who receive at least one dose of study intervention, have no clinically important protocol deviations or important events affecting Pd, and provide at least one measurable Pd endpoint postdose. Participants will be analyzed per the actual study intervention they received. All Pd analyses will be based on this analysis population.

DLT = dose limiting toxicity; Pd = pharmacodynamics; PK = pharmacokinetics; PKAS = pharmacokinetic analysis set.

9.4 Statistical Analyses

All analyses will be prepared by DL and will be described in detail in the iAP. Except for the analysis of DLTs, all analyses will be performed on the Safety Analysis population.

The following statistics will be used to summarize the study data (e.g. baseline characteristics) unless otherwise specified:

- **Continuous variables:** number of non-missing observations, mean, standard deviation, median, 25% Percentile to 75% Percentile (Q1 to Q3), minimum, and maximum, 95% CIs for the mean, as appropriate.

- **Categorical variables:** frequencies and percentages.

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

Baseline is defined as last non-missing value prior to first administration of study intervention

On-treatment values are defined as those measured during the study intervention period.

Besides the details outlined below, more details will be specified in the iAP finalized before database lock.

9.4.1 Efficacy Analyses

All efficacy analyses will be performed on the Full Analysis Set population unless otherwise specified (Table 16).

Table 16 Part 1A Efficacy Analyses

Endpoint	Statistical Analysis Methods
Part 1A	
Primary	No primary efficacy endpoint is specified.
Secondary	
Objective response according to RECIST 1.1 assessed by Investigator	ORR will be determined as the proportion of participants with a confirmed objective response of PR or CR. Confirmation of the response according to RECIST 1.1 will be required no sooner than 4 weeks after the initial documentation of CR or PR. The number and proportion of overall response (defined as CR + PR) will be tabulated. The 95% CI for the ORR will be calculated using the Clopper-Pearson method.
DoR according to RECIST 1.1 assessed by Investigator	DoR is defined as the time (months) from first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause, whichever occurs first. Duration of response data will be censored on the date of the last non-missing tumor assessment for participants who do not have an event (PD or death) or for participants for which the event is reported after two or more missed subsequent scheduled tumor assessments. Participants who do not have a baseline tumor assessment or who do not have any post baseline tumor assessments will be censored at the date of the start of study intervention. Kaplan-Meier estimates (product-limit estimates) will be presented for the analysis of DoR together with a summary of associated statistics (median DoR and response rate estimates at 3, 6, 12 months and every 6 months thereafter if applicable) including the corresponding 2-sided 95% CIs.

PFS according to RECIST 1.1 assessed by Investigator	PFS is defined as the time (in months) from date of first administration of study intervention to the date of the first documentation of PD or death due to any cause, whichever occurs first. The censoring rules for PFS are as described above for DoR. Kaplan-Meier estimates (product-limit estimates) will be presented for the analysis of PFS together with a summary of associated statistics (median PFS time and PFS rate estimates at 3, 6, 12 months and every 6 months thereafter if applicable) including the corresponding 2-sided 95% CIs.
Tertiary/Exploratory	Will be specified in the Integrated Analysis Plan, finalized before database lock.

CI = confidence interval; CR = complete response; DoR = duration of response; ORR = objective response rate; PD = disease progression; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

9.4.2 Safety Analyses

The DLT analysis will be performed on the DLT Analysis population. All other safety analyses will be performed on the Safety Analysis population. See Table 17.

Table 17 Safety Analyses

Endpoint	Statistical Analysis Methods
	Part 1A
Primary	
DLT	AEs classified as DLTs as assessed by SMC will be evaluated. Bayesian dose toxicity analysis. At primary analysis for Part 1A, the number and proportion of participants experiencing DLTs will be reported by dose level, based on observations during the first study intervention evaluation (21 days). Posterior probabilities (2.5%, 25%, 50%, 75%, and 97.5% quantiles) for DLT rates at selected doses will be estimated from the Bayesian dose toxicity model. Sensitivity analysis using frequentist modeling (without prior). Regarding intercurrent events: These are considered in the definition of DLTs and DLT analysis set.
Secondary	
AE	AEs will be coded according to the latest available version of MedDRA. Severity of AEs will be graded using the NCI-CTCAE (Version 5.0). Missing classifications concerning study intervention relationships will be considered related to the study intervention. TEAEs are defined as AEs emerging or worsening after start of study intervention until 30 days after the end of study intervention period. Following TEAEs will be presented in summaries by incidence and type according to MedDRA System Organ Classes and Preferred Terms: • TEAEs. • SAEs. • TEAEs related to study interventions. • NCI-CTCAE Grade 3 or higher TEAEs. • NCI-CTCAE Grade 3 or higher related TEAEs. • TEAEs leading to interruptions, dose modifications of study interventions. • TEAEs leading to permanent discontinuation of study interventions. • TEAEs leading to death.

Death	Counts and percentages.
Changes in laboratory measurements	Summary statistics and boxplots. Laboratory results will also be classified by Grade according to NCI-CTCAE. Worst on-treatment grades as well as shifts to worst on treatment grades will be summarized. Measurements without NCI-CTCAE grading will be summarized by above, within and below normal limits.
Vital signs and ECOG performance status	Baseline and on-treatment values will be summarized. Summary statistics: Increase/decrease in vital signs (body temperature, heart rate, blood pressure and respiratory rate), ECOG performance status and body weight will be categorized and summarized descriptively in shift tables from baseline to minimum and maximum on-treatment values.
ECGs	Clinically significant, abnormal findings from 12-lead ECGs during the treatment phase will be presented descriptively. Change from baseline to worst on-treatment value will be summarized descriptively for the QTcF interval in accordance to ICH E14 criteria.
CCI [redacted]	[redacted]

AE = adverse event; DLT = dose limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ICH = International Council for Harmonisation; MedDRA = Medical Dictionary for Regulatory Activities; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QTcF = QT interval corrected using Fridericia's formula; SAE = serious adverse event; SMC = safety monitoring committee; TEAE = treatment emergent adverse event.

9.4.2.1 Part 1A: Dose Escalation

Analyses to decide on dose escalation will be performed on the DLT set and will be based on available safety and preliminary PK data. To support the decision on dose escalation, the SMC will receive results of a Bayesian dose-toxicity model, including the recommendation of next DL. This Bayesian dose-toxicity model (Neuenschwander 2008) is further specified in Appendix 12. For each SMC meeting, the model will be updated with the number of DLTs and evaluable participants per DL.

Potential DLs are: 100 mg (starting dose), 200 mg, 400 mg, 600 mg. However, the SMC may decide to have different, or additional DLs or skip DLs (total daily dose increases must not exceed 100% of the highest total daily DL currently considered safe). Based on the observed toxicity profile and available PK and Pd, DL(s) that are different to, or higher or lower than the prespecified DLs may be tested.

The dose suggested by the model for the next cohort will be based on minimizing the Bayesian Risk.

The SMC may choose a different dose than suggested by the Bayesian escalation approach. Also, the SMC may decide to change the dosing regimen. In such a case the dose-toxicity model will be extended, or a separate model will be set up using the information from previous cohorts to define a new prior information for the new schedule.

The MTD will be defined by the SMC. The target DLT probability for the MTD is 30%.

Usually, decisions on dose escalation are taken once all participants of the most recent cohort have completed the DLT period or dropped out. In exceptional cases, however, the SMC may decide on the next cohort earlier, i.e., before the last participant of a cohort has finished the DLT

period (considering the model recommendation). Per definition of the DLT analysis set, participants who have not completed the DLT period are not included for update of the model, unless they experienced a DLT. However, data of such participants will be included at next SMC.

Details on analyses for SMC will be described in the SMC iAP.

Before first dosing, the assumed relationship between DL and toxicity is specified through the prior distribution. The prior distribution chosen for this study corresponds to the following (Table 18):

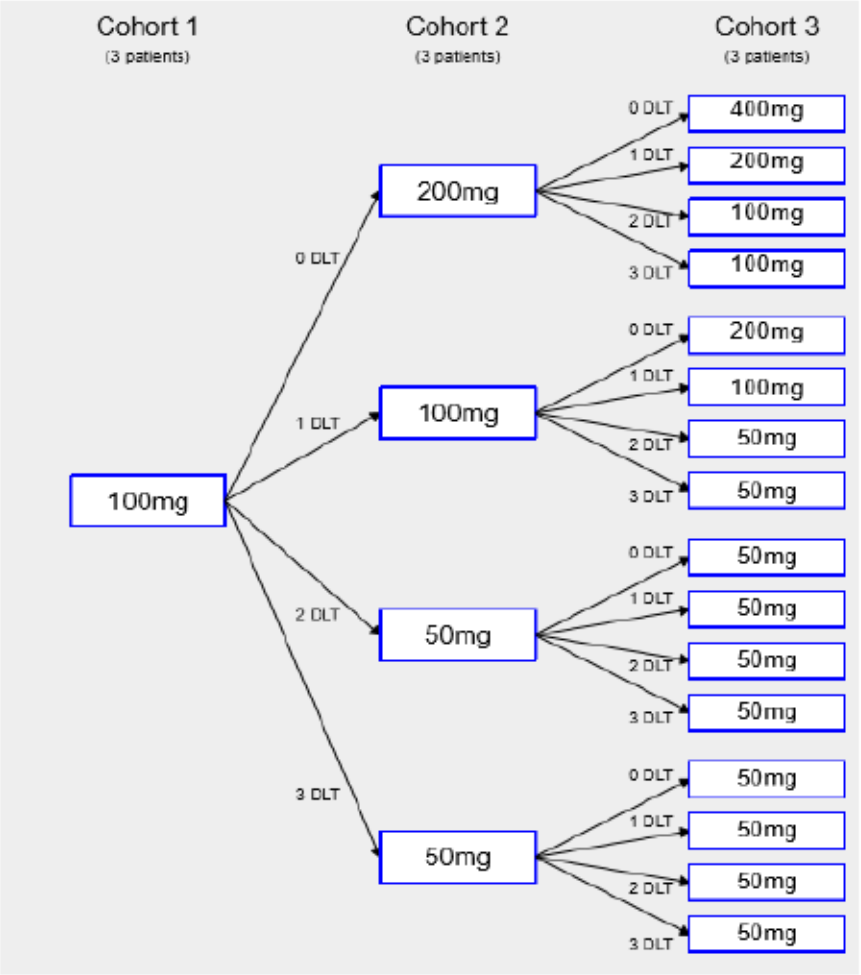
CCI [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DLT = Dose limiting toxicity.

In Figure 3 several examples of dose escalation recommendations by the model for the first 3 cohorts (each with 3 participants) depending on the number of experienced DLTs (from 0 to 3) are shown:

Figure 3 **Escalation Tree: Examples of Dose Recommendations Based on the Bayesian Model for the First 3 Cohorts**



The recommendations illustrated in the decision tree are not binding. The SMC may choose a different dose than suggested by the Bayesian escalation approach.

Details of the model, including the prior distribution are in Appendix 12.

9.4.2.2 Part 1B: Preliminary Food Effect Assessment

Part 1B may start once the RDE has been defined in Part 1A. M4076 will be administered at a dose and schedule that was determined as the RDE in Part 1A.

The SMC will continue to monitor the safety of M4076 during Part 1B. The SMC will be supported by the results of the Bayesian model used in Part 1A. During Part 1B, the model will support the SMC e.g. when a change in dose is considered by providing toxicity estimates for the doses. Unacceptable toxicity in the food effect cohort is defined as AEs that meet the DLT criteria (as defined in Section 6.6) regardless of when they occur during treatment.

9.4.3 Other Analyses

Details on the PK, CC and CCI biomarker analyses will be in the iAP that will be finalized before database lock. Integrated analyses across studies, such as the population PK analysis and PD analyses will be presented separately from the main CSR.

PK parameters will be calculated using standard non-compartmental methods and the actual administered dose. PK parameters will be calculated using the actual elapsed time postdose, with the exception of PK analysis for SMC review, which will be calculated using scheduled sampling times (see Table 19). Where the actual sampling time is missing the calculations may be performed using the scheduled sampling times.

Noncompartmental analysis will be performed using Phoenix® WinNonlin® (Certara, L.P., 1699, S Hanley Road, St Louis, MO, 63144, USA) Version 6.3 or higher.

The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary, NC, USA windows Version 9.4 or higher) may be used to produce tables listings and figures.

Table 19 Part 1 - Other Analyses

Other Analyses	Part 1A: Dose Escalation
C_{max}, C_{max}/Dose, t_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}tlast}$/Dose, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}\infty}$/Dose, $t_{1/2}$, AUCτ, AUC_{τ} /Dose, CL/F, V_z/F C_{trough}, $R_{acc}(AUC_{\tau})$, $R_{acc}(C_{max})$, LI, t_{last}	PK parameters of M4076 (in plasma) after single and multiple dose (monotherapy) will be calculated by noncompartmental analysis. Summary statistics of PK parameters and associated PK concentrations will be determined and reported. Analyses will be performed on the PKAS.
	Part 1B: Preliminary Food Effect Assessment
$AUC_{0\text{-}tlast}$, C_{max}, $AUC_{0\text{-}\infty}$	PK parameters of M4076 will be calculated after single dose using noncompartmental analysis. A mixed model with study intervention, period and sequence as fixed effects and a random effect for participant within sequence will be applied to log-transformed PK parameters C_{max} and AUCτ. Analyses will be based on the PKAS.
C_{max}/Dose, t_{max}, $AUC_{0\text{-}tlast}$/Dose, $AUC_{0\text{-}\infty}$/Dose, $t_{1/2}$, AUCτ, AUC_{τ} /Dose, $AUC_{0\text{-}72}$, $AUC_{0\text{-}72}$/Dose, CL/F, V_z/F $C_{trough,}$, $R_{acc}(AUC_{\tau})$, $R_{acc}(C_{max})$, LI, t_{last}, CL_R, $Ae_{(t1\text{-}t2)}$, $fe_{(t1\text{-}t2)}$	Additional M4076 PK parameters (plasma and urine) and summary statistics.
Concentration-QTc	Relationship of time matched PK concentration to change from baseline QTc will be explored by concentration-QT analysis. This analysis may include PK time-matched QTc data from other M4076 clinical studies. The details of this analysis will be described in a separate analysis plan, and the results reported separately from the CSR.

FAS = full analysis set; PK = pharmacokinetic; PKAS = pharmacokinetic analysis set; QTc = corrected QT interval; R_{acc} = accumulation ratio.

9.4.4 Sequence of Analyses

SMC for Part 1A: The SMC will review available data during study conduct. The cut-off for dose escalation assessments by the SMC will usually be triggered by the completion of the DLT period (or dropout) of the last participant in the respective dose escalation cohort of usually 3 participants. When enrolment of last participant in a dosing cohort is delayed, the SMC may decide (based on available data) upon enrolment and dose for the next dosing cohort before all participants in a cohort have completed 21 days. The Bayesian model will then be updated with the available data, and the data from the participant not having completed the DLT period at time of SMC will be considered in the next SMC. In these cases, cut-off can be earlier (after DLT period of the first 2 subjects is finished or they experienced a DLT).

SMC for Part 1B: The cut-off of the SMC will be triggered when the 6th participant has been treated for 28 days (or has dropped out). The SMC will be supported by the results of the Bayesian model used in Part 1A.

Primary analysis for dose escalation

The cut-off for an exploratory analysis of the safety, available PK, available Pd and preliminary antitumor activity data from Part 1A will be triggered when all participants have reached either the first on-treatment tumor assessment, or experienced death or premature withdrawal for any reason, whichever comes first.

Final Analysis for Part 1A and 1B

Follow-up analyses to report further efficacy, safety, and PK data if applicable for Part 1A and all analyses for Part 1B will be performed once the End of Study has been reached.

Additional Analyses

Further analyses may be performed, e.g. for publication purposes or decision-making purposes.

More details will be described in the iAP.

10 References

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11 Appendices

Appendix 1 Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ATM	ataxia-telangiectasia mutated
ATR	ataxia-telangiectasia and rad3-related
BLRM	Bayesian 2-parameter Logistic Regression Model
CI	confidence interval
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
DDR	DNA Damage Response
DL	dose level
DNA	deoxyribonucleic acid
DSB	double-strand break
ECG	electrocardiogram
FAS	full analysis set
γ-H2AX	gamma histone family member X
GCP	Good Clinical Practice
GMR	geometric mean ratio
HR	homologous recombination
iAP	integrated analysis plan
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IXRS	Interactive (phone and web) Response System
MTD	maximum tolerated dose

NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHEJ	nonhomologous end-joining
p-ATM	phosphorylated ataxia-telangiectasia mutated
PD	disease progression
Pd	pharmacodynamics
P-gp	P-glycoprotein
PK	pharmacokinetics
PKAS	pharmacokinetic analysis set
PTEN	phosphatase and tensin homolog
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RDE	recommended dose for expansion
SAE	serious adverse event
SAF	safety analysis set
SCR	screening analysis set
SMC	Safety Monitoring Committee
STD	severely toxic dose
ULN	upper limit of normal
WOCBP	woman of childbearing potential

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with enough, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (where allowed by local laws and regulations) and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants or their legally-authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent will also sign the ICF.
- If the ICF is updated during their participation in the study, participants will be re-consented to the most current, approved version.
- A copy of the ICF(s) will be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and will be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

Participants who are rescreened are required to reconsent.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.
- The participant will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by

appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

- The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

  The study will appear in the following clinical studies registry: ClinicalTrials.gov.

Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will be formed in this study. The SMC consists of Sponsor representatives (including, but not limited to the Medical Responsible, the Patient Safety Strategy Lead, the Biostatistician, and the PK expert) and Investigators. The Medical Monitor from the Contract Research Organization may be a SMC member. The SMC may modify the frequency of meetings as deemed appropriate during the study. Refer to Sections 4.1.1, 4.1.2, and 6.6.1, for more details.

The Clinical Research Organization, CCI will be responsible for the following activities:

- CCI central lab services
- Clinical data management study design and programming
- Clinical ancillary supplies services
- Clinical data management
- Clinical operations
- Feasibility
- Global regulatory services
- Global site services
- Medical writing
- Medical monitoring
- Operational strategy and planning
- Pharmacovigilance and Drug safety services
- Project financial analysts
- Project management
- Project vendor management
- Statistical analysis
- Statistical programming

- Fisher is responsible for drug supply and distribution responsibilities (e.g., use of regional distribution centers).
- The IXRS will be used to assign unique participant numbers, allocate participants to study intervention group at the randomization visit, and study intervention to participants at each study intervention visit.
- The Sponsor is responsible for supply and manufacture of M4076 and for study oversight.
- The study will be conducted at approximately 4 study sites in North America, including approximately 2 study sites in the US.
- Details of structures and associated procedures will be defined in a separate Project Management Plan.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The Investigator will submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC will review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
  - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
  - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as

participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.
- When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor (or designee) physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor (or designee) physician to assist with the medical emergency.

Clinical Study Insurance and Compensation to Participants

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

Clinical Study Report

- After study completion, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by agreement.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- 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 and will be submitted in accordance with local regulations.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Data Management Plan.

- The Investigator will maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.
- Study Monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator will keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file will identify each participant, contain the following demographic and medical information for the participant, and will be as complete as possible:
  - Participant's full name, date of birth, sex, height, and weight
  - Medical history and concomitant diseases
  - Prior and concomitant therapies (including changes during the study)
  - Study identifier (i.e., the Sponsor's study number) and participant's study number.
  - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
  - Any medical examinations and clinical findings predefined in the protocol
  - All AEs

  - Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.
- All source data will be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document will have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records will be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic CRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records will be available.
- The Study Monitors will use printouts of electronic files for source data verification. These printouts will be signed and dated by the Investigator and kept in the study file. Printing the files will not be necessary if the study monitor is permitted to access and review electronic participant files or other electronic study records at Investigator sites, provided that they are given their own unique access and is "Read Only".
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in Monitoring Plan.

Study and Site Start and Closure

- First Act of Recruitment
  - The study start date is the date when the clinical study will be open for recruitment.
  - The first act of recruitment is when the first site is opened and will be the study start date.
- Study Closure and Site Termination
  - The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
  - The Investigator may initiate site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended termination.
  - Reasons for the early closure of a study site by the Sponsor or Investigator may include:
    - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
    - Inadequate recruitment of participants by the Investigator
    - Discontinuation of further development of the Sponsor's compound
  - If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research

organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Contraception

Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

A WOCBP is **not**:

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

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

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

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods That Have Low User Dependency • Implantable progestogen-only hormone contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - Oral
  - Injectable
- Sexual abstinence: a highly effective method **only** if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence is evaluated in relation to the duration of the study.

Acceptable Methods

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide. Male condom and female condom cannot be used together (due to risk of failure with friction)
- Cervical cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)

Contraceptive use by men or women is consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

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

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

Acceptable methods are considered effective, but **not** highly effective (i.e., have a failure rate of ≥ 1% per year). Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are **not** acceptable methods of contraception.

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, and are judged to be more severe than expected for the participant's condition are considered clinically significant in the medical and scientific judgment of the Investigator (e.g., not related to progression of underlying disease, leading to study intervention discontinuation). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or an SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or an SAE if they fulfil the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied within the expectedness for participant's condition, as judged by the Investigator. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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) will not be reported as AEs/SAEs, unless the participant's general condition is more severe than expected for the his/her condition and/or unless the outcome is fatal within the AE reporting period, as defined in Section 8.3.1.

SAE Definition

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**

- **Is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization**
- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE will be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization must be documented and reported as SAEs.

- **Results in persistent disability/incapacity**

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is **not** intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

- **Other situations**
- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually considered as serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission of an infectious agent via a study intervention is also considered an SAE for reporting purposes, as specified below for reporting SAEs or DLTs.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- As needed, Sponsor may ask for copies of certain medical records (e.g., autopsy reports, supplemental lab reports, documents on medical history/concomitant medications, discharge letters), as supporting source documentation. All participant identifiers, except the participant number, will be redacted on these copies before submission to Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- If an AE constitutes a DLT this is documented accordingly.
- Specific guidance is in the CRF Completion and Monitoring Conventions.

Assessment of Intensity

Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (CTCAE), Version 5.0 (publication date: 27 Nov 2017), a descriptive terminology that can be used for AE reporting.

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

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using 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

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 specified below.

If death occurs, the primary cause of death or event leading to death will 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 (e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

Assessment of Causality

- The Investigator will assess the relationship between study intervention and each AE/SAE occurrence:
  - Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention. A reasonable alternative explanation will be available.
  - Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator will document in the medical notes that he/she has reviewed the AE/SAE and assessed causality.

- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.
- The Investigator may change his/her causality assessment after considering follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE, as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting by an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE in multicenter studies to the Sponsor or its designee will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE form, specified below, to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Sponsor's safety department.
- By exception, an SAE (or follow-up information) may be reported by telephone. The site will complete the electronic SAE data entry immediately thereafter.

SAE Reporting by a Paper Form

- SAE reporting on a paper report form is used as a back-up method for an EDC system failure. The form includes completion instructions for the Investigator, names, addresses,

and telephone and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available.

- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the form within 24 hours after becoming aware of the event.
- Additional documents (e.g. laboratory reports, autopsy report, hospital discharge letter) and relevant pages from the CRF may be required in addition (e.g. medical history, concomitant medication). The data provided will be consistent with the information in the CRF.

Recording and Reporting of DLTs

- Each event that meets the DLT criteria, as specified in Section 6.6.2, will be recorded in the CRF within 24 hours after awareness of the event.
- Serious DLTs will be reported in an expedited manner, using the SAE reporting process, as specified above.
- Notification of each DLT related event (non-serious and serious) will be reported to the Sponsor or its designee within 24 hours from the date of awareness.

Reporting of AESIs

- For a non-serious AESI, the site will complete the specific AESI report form and notify the Sponsor immediately (within 24 hours), using the same process for reporting SAEs, as specified above.
- For a serious AESI, the site will complete an SAE report form, using the SAE reporting process, specified above.

Reporting of Pregnancies

- Pregnancy will be reported whether related to the study intervention using the applicable paper form.
- The applicable form will be used to report if an abnormal outcome of the pregnancy occurs and the child/fetus sustains an event.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

Appendix 5 Liver Safety: Suggested Actions and Follow-up Assessments

If a study participant is noted to have alanine aminotransferase or aspartate aminotransferase elevated 3 times or greater above upper limit of normal (ULN; new or worsening of preexisting), the abnormality should be recorded as an adverse event, regardless if clinical symptoms are present or not. If a study participant is noted to have alanine aminotransferase or aspartate aminotransferase 3 times or greater above ULN and total bilirubin > 2 ULN for which an alternative etiology has not been identified, the event should be reported as a serious adverse event. The Investigator must contact the Sponsor Medical Responsible for discussion (see Section 7.1 for details).

Appendix 6 Clinical Laboratory Tests

Table 20 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count		Mean corpuscular volume (MCV)	White Blood Cell Count with absolute and/or percentage (%): • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Reticulocytes			
	Hemoglobin		Mean corpuscular hemoglobin (MCH)	
	Hematocrit			
Coagulation	INR, prothrombin time, partial thromboplastin time (aPTT)			
Biochemistry	Blood Urea Nitrogen or Urea	Potassium	Aspartate aminotransferase	Bilirubin (total and direct)
	Creatinine	Sodium	Alanine aminotransferase	Protein and albumin
	Glucose	Calcium	Alkaline phosphatase	
	Gamma glutamyltransferase (gGT)	Lipase	Amylase	
Details of liver chemistry stopping criteria and required actions are given in Section 6.6.1 and Appendix 5.				
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Serum and urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential). Serology (with no preclinical signs of hepatotoxicity, hepatitis B surface antigen, hepatitis C virus antibody) to rule out active infection will be performed at the Investigator's discretion. HIV screening is optional at the Investigator's discretion unless required locally. All study-required laboratory assessments will be performed by a central laboratory, except for safety laboratory assessments.			

Appendix 7 Potential Variations in Study Intervention Schedules and Schedules of Activities

Additional schedules may also be evaluated at the discretion of the Sponsor and SMC.

Summary of alternate schedules of M4076 and changes to the Schedule of Activities in Part 1A (Table 21):

Table 21 Summary of Alternate Schedules of M4076

Part 1A	
Twice weekly	
Clinic visits	No change
M4076 administration	M4076 dosing is twice daily on Days 1 and 4 of each week (e.g., Mon, Thu).
PK sampling	No change
Three times weekly	
Clinic visits	No change
M4076 administration	M4076 dosing is on Days 1, 3 and 5 of every week (e.g., Mon, Wed, Fri).
PK sampling	-DLT Period Days 1 and 12: predose at 0 hours, postdose at 0.5, 1, 2, 3, 4, 6, 8 hours. -DLT Period Days 2 and 13: 24 hour (±4 hour) postdose on D1 and D12 -3-week Periods Day 1 and subsequently every other 3-week Period: take two samples at start and end of visit, at least 1 hour apart.
4 days on/3 days off	
Clinic visits	No change
M4076 administration	M4076 dosing is on 4 consecutive days of a week (e.g., Mon, Tue, Wed, Thu)
PK sampling	-DLT Period Days 1 and 11: predose at 0 hours, postdose at 0.5, 1, 2, 3, 4, 6, 8 hours. -DLT Period Days 2 and 12: 24 hour (±4 hour) post dose on D1 and D11 (to be taken prior to next dosing). -3-week Periods Day 1 and subsequently every other 3-week Period: take two samples at start and end of visit, at least 1 hour apart.
7 days on/7 days off	
Clinic visits	No change
M4076 administration	M4076 dosing on Days 1-7 followed by a 7-day drug holiday.
PK sampling	For DLT period starting with on weeks: -DLT Period Days 1 and 21: predose at 0 hours, postdose at 0.5, 1, 2, 3, 4, 6, 8 hours. -DLT Period Days 2 and 22: 24 hour (±4 hour) post dose on D1 and D21 (to be take prior next dosing). -3-week Periods Day 1 and subsequently every other 3-week Period: take two samples at start and end of visit, at least 1 hour apart. It is advisable to have all DLT periods for this scheme to start with 7 dosing days. However, for patients who start with 7 days off, the following sampling strategy applies:

	-DLT Period Day 8, Day 15: predose at 0 hours, postdose at 0.5, 1, 2, 3, 4, 6, 8 hours. -DLT Period Day 9: 24 hour (±4 hour) post dose on D8 (to be taken prior to next dosing). -3-week Periods Day 8 and subsequently every other 3-week Period: take 2 samples at start and end of visit, at least 1 hour apart.
14 days on/14 days off	
Clinic visits	Days 1, 2, 14, and 15
M4076 administration	M4076 dosing on Days 1-14 followed by a 14-day drug holiday.
PK sampling	-DLT Period Days 1 and 14: predose at 0 hours, postdose at 0.5, 1, 2, 3, 4, 6, 8 hours. -DLT Period Days 2 and 15: 24 hour (±4 hour) post dose on D1 and D14 (to be taken prior next dosing). -3-week Periods Day 1 and subsequently every other 3-week Period: take two samples at start and end of visit, at least 1 hour apart. It is advisable to have all DLT periods for this scheme to start with 14 dosing days. However, for patients who start with 14 days off, the following sampling strategy applies: -DLT Period Days 15 and 21: predose at 0 hours, postdose at 0.5, 1, 2, 3, 4, 6, 8 hours. -DLT Period Day 16: 24 hour (±4 hour) post dose on D15 (to be taken prior next dosing). -3-week Periods Day 15 and subsequently every other 3-week Period: take two samples at start and end of visit, at least 1 hour apart.

D = Day; DLT = dose limiting toxicity; PK = pharmacokinetic.
Urine PK parameters will be assessed in Part 1B only

Appendix 8 Example of Low-fat Meal for Food Effect Cohort (Part 1B)

Per FDA's "Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry", the composition of a low-fat meal includes 400 to 500 calories of which 25% or 11 to 14 grams come from fat. An example of a low-fat breakfast listed by the agency consists of the following: eight ounces of milk (1% fat), one boiled egg, and one packet of flavored instant oatmeal made with water.

The meal should be consumed within approximately 30 minutes, and the M4076 dosage form should be administered at 30 minutes after the start of the meal for the fed state.

Appendix 9 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

The text below was obtained from Eisenhauer 2009 and Schwartz 2016.

Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the RECIST Committee (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
- 10 mm caliper measurement by clinical exam (when superficial)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

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 no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET 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 or MRI 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) since 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 noncystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other local regional therapy, 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.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis $<$ 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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.

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 examination.

No photographs, no skin lesion measurement by calipers and no measurements on chest X-ray will be done in this study.

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. As is described in Appendix II of the original source article cited above (Eisenhauer 2009), when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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 complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit; however, they must normalize for a participant to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-

specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in 1st-line studies in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (e.g., 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 event (AE) of treatment (e.g., 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 (SD) in order to differentiate between response (or SD) and progressive disease (PD).

RESPONSE CRITERIA

Evaluation of Target Lesions

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: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

PD: 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 1 or more new lesions is also considered progression).

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms (CRFs) or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement

should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

When the participant also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the participant has only non-measurable disease. This circumstance arises in some Phase 3 studies when it is not a criterion of study entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the

change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the participant should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (e.g., some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the participant's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the participant who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The participant's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, e.g., because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fludeoxyglucose positron emission tomography (FDG-PET) response assessments need additional studies, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best overall response (BOR) is the best response recorded from the start of the study intervention until the end of treatment taking into account any requirement for confirmation. On occasion, a response may not be documented until after the end of therapy, so protocols should be clear if post treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The participant's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either 1 the 'BOR'.

The BOR is determined once all the data for the participant is known. Best response determination in studies where confirmation of complete or PR IS NOT required: Best response in these studies is defined as the best response across all time points (for example, a participant who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When SD 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 SD is otherwise the best time point response, the participant's best response depends on the subsequent assessments. For example, a participant who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same participant lost to follow-up after the first SD assessment would be considered inevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PR = partial response; PD = progressive disease; SD = stable disease.
See text for more details.

Note:

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of 'zero' on the CRF.

In studies where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of response and progression. For example, in most studies, it is reasonable to consider a participant with time point responses of partial response-NE-partial response as a confirmed response.

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.

Conditions that define 'early progression, early death, and inevaluability' are study-specific and should be clearly described in each protocol (depending on treatment duration, and treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. The use of FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure the responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, i.e., in randomized studies (Phase 2 or 3) or studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of the study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 to 8 weeks) that is defined in the study protocol.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of participants achieving SD for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

Note: The duration of response and SD as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

Appendix 10 Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead


CCI

Appendix 12 Model for Bayesian Dose Escalation

The Bayesian model results are based on the number of DLTs and evaluable participants per dose level (DL). The SMC will receive results of a Bayesian two-parameter logistic regression model updated with the observed DLT data (Neuenschwander 2008), including a recommendation for the next dose. For a DL d_j, the relationship between dose and probability of toxicity P (DLT) is defined by:

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

with bivariate normally distributed parameters (α, β) using the following parameterization:

- Pre-selected DL d_j ε {50 mg, 100 mg, 200 mg, 400 mg, 600 mg}
- Reference dose d_{ref} = 800 mg

[redacted]

The following toxicity regions (Table 22) will be defined:

Table 22 Toxicity Intervals

Toxicity intervals	Probability of DLT	Loss term (weight in loss function)
Under-Dosing	[0.0, 0.20)	1
Target toxicity	[0.20, 0.35]	0
Excessive toxicity	(0.35, 0.60]	1
Unacceptable toxicity	(0.60, 1.00]	1.5

DLT = dose limiting toxicity.

The model-based recommendation for the next DL is the DL that minimizes the loss function. The loss function is defined as the sum of products of the probability to lie within each of the toxicity regions, and the associated loss term:

- 1 × P (Under-Dosing) + 0 × P (targeted toxicity) + 1 × P (excessive toxicity) + 1.5 × P (unacceptable toxicity).
- Increase of DLs is limited by 100% of the highest current total daily DL.

The model will be provided with the following pre-selected DLs: 50 mg, 100 mg, 200 mg, 400 mg, 600 mg. The set of doses can be changed any time by the SMC.

The target DLT probability for the MTD is 30%.

The SMC will be notified of a potential MTD once the estimate for DLT probability of a potential MTD reaches sufficient precision, i.e.:

- The upper bound of the one-sided 95% credible interval is not more than 40%,
- and the estimated DLT probability for the suggested MTD is in [17%-30%].

In case information arises from other studies that changes current knowledge on the dose toxicity relationship, the prior distribution will be updated prior to the first participant being treated in this study. This change will be documented in the SMC charter. If changes are needed due to a change in regimen, these will also be documented in the SMC charter prior to first SMC with participants with new regimen.

The Bayesian model used in Part 1A will be used continuously to also monitor the toxicity results in Part 1B with all participants. Unacceptable toxicity in the food effect cohort is defined as AEs that meet the DLT criteria (as defined in Section 6.6) regardless of when they occur during treatment.

Posterior distribution and the recommended next DL suggested by the model will be calculated using SAS Version 9.4 or higher, EAST Version 6.5 or higher, or R Version 3.5.1 or higher with library package bcrm (Sweeting 2013) or package CRMpack (Bové 2019).

Appendix 13 Protocol Amendment History

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

Protocol Version 3.0 (25-Oct-2021)

The overall rationale for this amendment is based on the need to update the adverse events of special interest (AESI) information in this protocol.

Section # and Name	Description of Change	Brief Rationale
Title page	Title page modifications in placement of version reporting and removal of other information.	To follow internal quality standards for clinical study protocols.
1.3.1 Table 1 Schedule of Activities: M4076 Monotherapy Dose Escalation (Daily Dosing), Part 1A. 1.3.2 Table 2: Schedule of Activities: Preliminary Food Effect Assessment, Part 1B.	For DLT Period Day 1, a window period of '- 1 day' was added to specific assessments. Additional text was added to the Medical history regarding the collection of information pertaining to tobacco use. Added requirement for extended follow-up of SAEs and AESIs. Prohibition of tissue samples of bone biopsies for [redacted] submission.	A Visit window was added for participant flexibility. To provide transparency and clarity that this information is being collected for potential use in PK assessment. For consistency with Section 8.3.6. Limited tumor cellularity in biopsies obtained from bone(s) is insufficient to perform [redacted] analysis.
1.3.3 Table 4 Part 1B Preliminary Food Effect Assessment: PK, ECG and [redacted] Assessments	Urine collection interval for PK was further specified.	Clarification.
2.1 Study Rationale 2.2 Background 2.3.2 Benefit Assessment	Removed mention of ataxia-telangiectasia and rad3-related (ATRi) combination.	No longer needed in this protocol.
2.3 Benefit/Risk Assessment	Added required text per Merck protocol standards.	To follow internal quality standards for clinical study protocols.
5 Study Population Appendix 2 Study Governance (Informed Consent Process)	Textual changes regarding legal or legally authorized representative.	To follow internal quality standards for clinical study protocols.
5.3 Lifestyle Considerations	Added that tobacco use status (former, current, never) will be collected at screening and recorded in the eCRF.	To evaluate potential impact of tobacco use on PK, efficacy, and safety.

Section # and Name	Description of Change	Brief Rationale
6.6.2.1 Table 10 M4076 Recommended Dose Modifications	'Grade 3 Hematologic and Nonhematologic ADRs' was added in the Table title and 'hematologic' was added in the Table header.	To include hematologic toxicities for clarity and consistency with the requirements already stated in this section.
Section 8.3 Adverse Events and Serious Adverse Events (AE/SAE detection method)	Added sentence referencing to Appendix 4 for information regarding recording, evaluating, and assessing causality of AEs and SAEs and procedures for completing and transmitting SAE reports.	To follow internal quality standards for clinical study protocols.
8.3.6 Adverse Events of Special Interest	Added definition of AESIs of cytopenia.	To allow closer monitoring of AEs consistent with the potential risk of cytopenia.
CCI [redacted]		
9.4.3 Other Analyses Table 19 Part 1 Other Analyses	Concentration-QTc analysis details are specified.	Clarification.
Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and reporting (adverse event/serious adverse event detection method)	Update of text regarding guidance to the Principal Investigator.	To follow internal quality standards for clinical study protocols and clarifications to the text for better understanding of guidance of adverse events/serious adverse events definition.
Throughout	Removal of Overall Survival and mention of Survival Follow-up.	To align with standard Phase 1 study design template, where no overall survival is included.
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

ADR = adverse drug reaction; AE = adverse event; AESI = adverse event of special interest; ATR = ataxia telangiectasia; DLT = dose limiting toxicity; ECG = electrocardiogram; eCRF = electronic case report form; PD = pharmacodynamic; PK = pharmacokinetic; QTc = Corrected QT Interval; SAE = serious adverse event.

Protocol Version 2.0 (07-Apr-2021)

Overall Rationale for the Amendment

The overall rationale for this amendment is based on the fact that the full toxicity profile of M4076 remains unknown in humans; therefore, measures regarding concomitant medications and dose modifications were adopted.

Section # and Name	Description of Change	Brief Rationale
1.3.1 Part 1A – M4076 Monotherapy Dose Escalation (Daily Dosing)	Added the Part 1A fasting window information	For clarity
1.3.2 Part 1B	Added the Part 1B fasting window information	For clarity
Table 1: Part 1A Schedule of Activities	Fasting window added to the "Study Intervention Administration" row.	For clarity
Table 2: Part 1B Schedule of Activities	Fasting window added in the "Low-fat Meal or Overnight Fasting" row. Vital signs assessments timing note added.	For clarity
Table 3: Part 1A M4076 Monotherapy Dose Escalation: Pharmacokinetic, ECG and Pharmacodynamics Biomarker Assessments	Added a footnote outlining fasting window.	For clarity
Table 4: Part 1B Preliminary Food Effect Assessment: Pharmacokinetic, ECG and Pharmacodynamics Biomarker Assessments	Added a footnote outlining ECG fasting window.	For clarity
4.1.1 Part 1A – M4076 Monotherapy Dose Escalation	Added reference to fasting window information in Section 6.1. Added note that, in determining the RDE, the SMC will additionally consider PK and Pd information. Removed the following sentence: *If MTD is not reached, the SMC may define the RDE based on the PK, Pd, and safety profile.*	For completeness and clarity
4.1.2 Part 1B- Preliminary Food Effect Assessment	Added reference to fasting window information in Section 6.1.	For clarity.
5.1 Inclusion Criteria	Updated Inclusion Criterion of CLcr from 30 mL/min to 60 mL/min by Cockcroft-Gault equation	Safety measure in this FIH study.
5.2 Exclusion Criteria	Added the following bullets: • A history of additional risk factors for Torsades de Pointes (e.g., clinically relevant hypokalemia, family history of Long QT Syndrome)	As additional safety measures.

Section # and Name	Description of Change	Brief Rationale
	• The use of concomitant medications that prolong the QT/QTc interval	
5.2 Exclusion Criteria; 6.5.2 Permitted Medicines; 6.5.3 Prohibited Medicines	As appropriate in respective sections, added information regarding exclusion of irinotecan, oral direct thrombin inhibitors, digoxin, and proton pump inhibitors with time window caveats for acceptable administration of H2-receptor antagonists and antacids	For clarity and to avoid potential effect of concomitant administration.
6.1 Study Intervention Administration	Added Parts 1A and 1B fasting window information	For clarity
6.6.2 Dose-limiting Toxicities – Definition and Criteria	Added that the possibility of Hy's Law parameters as listed will require prompt permanent discontinuation from the study.	As additional safety measure
6.6.2.1 Dose Interruptions and Modifications; Table 10	Modified as follows as it pertains to text and Table 10: • To require permanent discontinuation of M4076 for Grade 4 drug-related toxicity. Provide justification for any exceptions. • To provide guidelines for recurrent Grade 3 events. • To require permanent discontinuation for cases meeting Hy's law criteria. Alternatively provide justification for why this is not necessary.	As additional safety measures
7.1 Discontinuation of Study Intervention	Deleted text referring to Investigator determination of whether or not to discontinue study interventions for liver injury or cardiac changes	As there is insufficient information to support evidence-based decisions by the Investigators.
9.4.2.1 Part 1A: Dose Escalation	Added that the total daily dose increased must not exceed 100% of the highest total daily dose level considered safe.	For clarity
Appendix 6 Clinical Laboratory Tests; Table 19	In the Table row of "Other Screening Tests", clarified that except for safety laboratory assessments, all study-required laboratory assessments will be performed by a central laboratory.	For clarity
Throughout	Minor administrative, editorial, and document formatting revisions	Minor; therefore, have not been summarized

Appendix 14 Sponsor Signature Page

Study Title:	A First-in-human, Phase 1, Open-label Study of the ATM inhibitor M4076 in Participants with Advanced Solid Tumors
Regulatory Agency Identifying Numbers:	IND number PPD
Clinical Study Protocol Version:	27 October 2022/4.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD PPD
Function/Title:	Protocol / Medical Lead
Institution:	Merck Healthcare KGaA
Address:	Frankfurter Str. 250 | 64293 Darmstadt | Germany
Telephone number:	PPD
Fax number:	Not Applicable
E-mail address:	PPD

Appendix 15 Coordinating Investigator Signature Page

Study Title:	A First-in-human, Phase I, Open-label Study of the ATM inhibitor M4076 in Participants with Advanced Solid Tumors
Regulatory Agency Identifying Numbers:	IND number CCI
Clinical Study Protocol Version:	27 October 2022/4.0
Site Number:	201

I approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signat

October 28, 2022

Date of Signature

Name, academic degree:	PPD PPD
Function/Title:	PPD
Institution:	PPD
Address:	PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Appendix 16 Principal Investigator Signature Page

Study Title:	A First-in-human, Phase 1, Open-label Study of the ATM inhibitor M4076 in Participants with Advanced Solid Tumors
Regulatory Agency Identifying Numbers:	IND number 138694
Clinical Study Protocol Version:	27 October 2022/4.0
Site Number:	

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

I also 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 complying with the regulatory requirements. Therefore, I 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: