





## Clinical Study Protocol

### Title Page

<b>Clinical Study Protocol Title:</b>	First-in-Human Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M1069 in Participants with Metastatic or Locally Advanced Unresectable Solid Tumors
<b>Study Number:</b>	MS201929_0032
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<b>Merck Registered Compound Name in Japan:</b>	Not applicable
<b>Study Phase:</b>	Phase 1
<b>Short Title:</b>	First in Human Study of M1069 in Advanced Solid Tumors
<b>Coordinating Investigator:</b>	PPD    

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<b>Key Words:</b>	Adenosine antagonist, A2A/A2B receptors

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## Protocol Amendment Summary of Changes

### Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	24 September 2021
2.0	Global Amendment	11 November 2021

Note: No participants were enrolled on version 1.0.

### Protocol Version 2.0 (11 November 2021)

### Overall Rationale for the Amendment

To incorporate revisions based on feedback from a regulatory agency. Additionally, changes made to Sponsor's global protocol template implemented.

Section # and Name	Description of Change	Brief Rationale
Section 2.3.1 (Risk Assessment)	In Table 3, revise CNS AE to Excitatory AE.	Correction to align with Investigator's Brochure.
Section 5.1 (Inclusion Criteria), Criteria #6	Use only 1 method to establish renal eligibility.	Simplification.
Section 5.3.1 (Meals and Dietary Restrictions)	Clarify sequence for potential SMC recommendation to change to fed condition at higher doses.	Clarification.
Section 6.6.3 (Definition of Dose-limiting Toxicity) 6.6.4 (Dose Modification ...) 7.1 (Discontinuation of Study Intervention) 8.2.4 (Ophthalmologic Assessments)	CCI [REDACTED]	Clarification.
Section 8.3.1 (Time Period and Frequency of Collecting ....) 8.3.4. (Regulatory Reporting Requirements for Serious Adverse Events)	Clarification of Investigator reporting SAEs to Merck according to the required timeframe.	Change to Sponsor's global standard protocol.
Section 8.3.8 (Adverse Events of Special Interest)	Remove reference to central reader.	Correction

Section # and Name	Description of Change	Brief Rationale
Section 9.3 (Populations for Analysis)	Add a compliance criterion to DLT population.	Correction to standard description.
<a href="#">Appendix 4</a> , (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting)	Clarification of Investigator reporting SAEs to Merck according to the required timeframe.	Change to Sponsor's global standard protocol.
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

AE = Adverse event, DLT = Dose limiting toxicity, SAE = Serious adverse event, SMC = Safety Monitoring Committee.

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# 1 Protocol Summary

## 1.1 Synopsis

**Protocol Title:** First-in-Human Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M1069 in Participants with Metastatic or Locally Advanced Unresectable Solid Tumors

**Short Title:** First in Human Study of M1069 in Advanced Solid Tumors

### Rationale:

A<sub>2A</sub> and A<sub>2B</sub> adenosine receptors have been shown to mediate immunosuppressive and tumor-promoting signals in the tumor microenvironment. CCI

CCI

Based on results from nonclinical safety pharmacology and toxicology investigations, the safety profile of M1069 is considered adequate for patients with advanced/metastatic solid tumors at the projected dose levels. Clinical experience with dual adenosine A<sub>2A</sub>/A<sub>2B</sub> antagonism published in the literature suggests an acceptable safety profile as a monotherapy and no potentiating toxicities in combination with other immunotherapies.

### Objectives and Endpoints:

Objectives	Endpoints
Primary	
To determine dose toxicity relationship and MTD (if reached) of M1069 as a monotherapy in participants with solid tumors.	<ul style="list-style-type: none"><li>• Occurrence of DLTs.</li><li>• Occurrence of AEs and treatment-related adverse events.</li></ul>
To determine the RDE of M1069 for further exploratory clinical development.	In addition to safety, tolerability, PK, Pd (CCI in ex-vivo stimulated blood), post-treatment changes in TME in available paired tumor biopsies data are considered.
Secondary	
To characterize the PK profile of M1069.	PK parameters of M1069 after single dose administration and at steady state using non-compartmental analysis.
To evaluate indicators of clinical activity of M1069 in terms of objective response using RECIST v1.1.	Objective response using RECIST v1.1, as assessed by Investigator.

Objectives	Endpoints
To evaluate indicators of clinical activity of M1069 in terms of DoR using RECIST v1.1.	Duration of response according to RECIST v1.1 as assessed by Investigator, defined as time from first documentation of objective response to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or start of treatment.
To evaluate indicators of clinical activity of M1069 in terms of PFS using RECIST v1.1.	Progression-free survival as defined from date of first study intervention to PD according to RECIST v1.1 as assessed by Investigator or death. Events are considered only if occurring within 2 scheduled tumor assessments after last evaluable assessment or start of treatment.
To assess the effect of M1069 on QT interval.	Change from baseline QTc ( $\Delta$ QTc) over time.

AE = Adverse event, DLT = Dose-limiting toxicity, DoR = Duration of response, MTD = Maximum tolerated dose, CCI = Cardiac Conduction Interval, PD = Progressive disease, Pd = Pharmacodynamic, PFS = Progression-free survival, PK = Pharmacokinetic, QTc = QT interval corrected, RDE = Recommended dose for expansion, RECIST = Response Evaluation Criteria in Solid Tumors, TME = Tumor microenvironment.

### Overall Design:

This is a Phase I First in Human (FIH) dose escalation of M1069, noncontrolled, open label, multicenter clinical study designed to determine the safety, tolerability, PK, Pd and early signs of efficacy in participants with advanced solid malignancies. A Bayesian study design will be applied, using a Bayesian 2-parameter logistic regression model (BLRM).

The study will include up to 28 days Screening period, a study intervention period consisting of consecutive 21-day cycles with twice daily oral administration of M1069, a DLT observation period of 21 days, End of Study Intervention Visit and a Safety Follow-up period of  $30 \pm 7$  days after the last M1069 intake. Participants who tolerate treatment without significant clinically relevant toxicities may continue to receive their assigned dose until progressive disease. Participants who discontinue study intervention for any reason will complete the End of Study Intervention Visit.

**Disclosure Statement:** This is a single group treatment study with 1 arm that is not blinded.

**Number of Arms:** 1

**Blinding:** Open label.

**Number of Participants:** The total sample size will depend on the number of cohorts to be evaluated. The planned cohort size is 3 participants. Data observed during the dose escalation (e.g., number of DLTs) have an impact on the number of cohorts. The sample size for the RDE and MTD dose levels needs to be at least 6. It is anticipated that 21 to 30 participants (5 projected dose levels with 3 to 9 participants each) may be needed.

**Study Intervention Groups and Duration:** The treatment period will begin at the first dose of M1069 with Cycle 1 Day 1 (C1D1) and consists of consecutive 21-days cycles with twice daily

oral administration (BID) until disease progression, unacceptable toxicity, withdrawal of consent, or any criterion for withdrawal from study intervention.

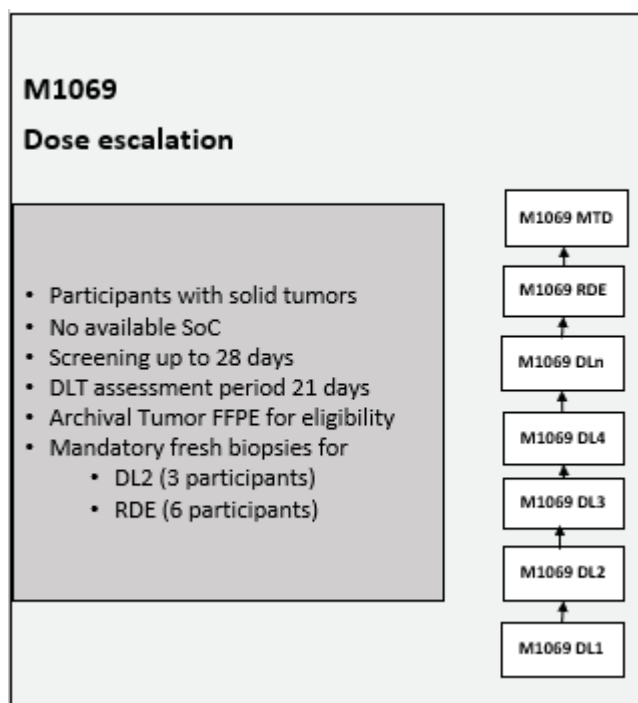
For dose cohorts, the SMC will provide recommendations on the dose level and regimen for the next cohort.

The term “cohort” with regards to dose escalation in this protocol is referring to a group of participants that are enrolled at the same dose level and evaluated by an SMC before the dosing decision for the next cohort is made. There may be more than one cohort on the same dose level, if the SMC decides that a further cohort on the same dose level is needed.

**Involvement of Special Committee(s): Yes, Safety Monitory Committee**

## 1.2 Schema

**Figure 1 Schema**



DL = Dose level, DLT= Dose-limiting toxicity, FFPE = Formalin-fixed paraffin-embedded, MTD= Maximum tolerated dose, RDE = Recommended dose for expansion.

For additional information on the study design, including adaptability of escalation scheme, see Section 4.1.

## 1.3 Schedule of Activities

Schedules of activities are presented in Table 1 and Table 2.

**Table 1**      **Schedule of Activities**

Assessments and Procedures	Screening	D -1	Intervention Period (21-Day Cycles)								EOSI	Safety FU	Notes
			Cycle 1, 2			Cycles 3, 4, 5		Cycles $\geq 6$ Even cycles		Cycles $\geq 7$ Odd cycles			
Day	-28 to -1	-1	1	8	15	1	15	1	15	8	EOSI +7 Days	Last Dose + 30 Days	
Visit window (days)	Up to 28 days before Day 1			( $\pm 1$ )	( $\pm 1$ )	( $\pm 1$ )	( $\pm 1$ )	( $\pm 1$ )	( $\pm 1$ )	( $\pm 1$ )		( $\pm 7$ )	EOSI within 7 days of decision to discontinue but before start of subsequent anticancer treatment.
Informed consent	X												
Inclusion and exclusion criteria	X		X										In- and exclusion criteria will be reviewed during Screening and must still be met prior to initial dosing on C1D1.
Demography	X												
Physical examination	X		X	X <sup>a</sup>	X <sup>a</sup>	X	X <sup>a</sup>	X	X <sup>a</sup>	X <sup>a</sup>	X	X	Details in Section 8.2.1. X <sup>a</sup> Brief physical examination including peripheral motor and sensory nervous system.

Assessments and Procedures	Screening	D -1	Intervention Period (21-Day Cycles)								EOSI	Safety FU	Notes
			Cycle 1, 2			Cycles 3, 4, 5		Cycles ≥ 6 Even cycles		Cycles ≥ 7 Odd cycles			
Day	-28 to -1	-1	1	8	15	1	15	1	15	8	EOSI +7 Days	Last Dose + 30 Days	
Visit window (days)	Up to 28 days before Day 1			(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)		(± 7)	EOSI within 7 days of decision to discontinue but before start of subsequent anticancer treatment.
CCI													
Medical and disease history (includes substance usage)	X												Substances: drugs, alcohol, tobacco, and caffeine (see Section 5.3).
Prior anticancer therapies	X												
Pregnancy Test (WOCBP only)	X		X			X		X		X	X	X	Serum only at Screening and urine or serum for all other cycles. Details in <a href="#">Appendix 6</a> .

Assessments and Procedures	Screening	D -1	Intervention Period (21-Day Cycles)								EOSI	Safety FU	Notes
			Cycle 1, 2			Cycles 3, 4, 5		Cycles ≥ 6 Even cycles		Cycles ≥ 7 Odd cycles			
Day	-28 to -1	-1	1	8	15	1	15	1	15	8	EOSI +7 Days	Last Dose + 30 Days	
Visit window (days)	Up to 28 days before Day 1			(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)		(± 7)	EOSI within 7 days of decision to discontinue but before start of subsequent anticancer treatment.
HBV, HCV, HIV testing (if applicable)	X												HIV according to country policy. Details in <a href="#">Appendix 6</a> .
Clinical laboratory tests	X		X	X	X	X	X	X	X	X	X	X	72 h-window allowed prior to C1D1, refers to biochemistry, hematology and coagulation. Details in <a href="#">Appendix 6</a> .
ECOG PS	X		X	X	X	X	X	X	X	X	X	X	72h-window allowed prior to C1D1.
Urine analysis	X		X <sup>†</sup>			X <sup>†</sup>				X <sup>†</sup>			X <sup>†</sup> Only in odd Cycles Every 6 weeks (± 7 days) Details in <a href="#">Appendix 6</a> .
Vital signs	X		X	X <sup>†</sup>	X <sup>†</sup>	X <sup>#</sup>	X	X <sup>@</sup>	X	X	X	X	Includes height (collect at Screening only) and weight. See Table 2 for detailed timepoint on the following cycle days: X <sup>†</sup> Only in Cycle 1 X <sup>#</sup> Only in Cycle 4 X <sup>@</sup> Only C6D1 and C8D1

Assessments and Procedures	Screening	D -1	Intervention Period (21-Day Cycles)								EOSI	Safety FU	Notes
			Cycle 1, 2			Cycles 3, 4, 5		Cycles ≥ 6 Even cycles		Cycles ≥ 7 Odd cycles			
Day	-28 to -1	-1	1	8	15	1	15	1	15	8	EOSI +7 Days	Last Dose + 30 Days	
Visit window (days)	Up to 28 days before Day 1			(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)		(± 7)	EOSI within 7 days of decision to discontinue but before start of subsequent anticancer treatment.
Chest X-ray	X												To exclude infections, to be done before CT for RECIST assessment, if applicable.
CT (chest, abdomen) or MRI	X					X <sup>†</sup>				X <sup>†</sup>			X <sup>†</sup> Only in odd Cycles At Screening and for response assessment via RECIST v1.1; tumors will be assessed every 6 weeks (± 7 days) until progression. With contrast only if renal activity allows.
Holter ECG (Holter recorder)		X	X <sup>#</sup>	X <sup>#</sup>									X <sup>#</sup> Only in Cycle 1 Detailed timepoints in Table 2.

Assessments and Procedures	Screening	D -1	Intervention Period (21-Day Cycles)								EOSI	Safety FU	Notes
			Cycle 1, 2			Cycles 3, 4, 5		Cycles ≥ 6 Even cycles		Cycles ≥ 7 Odd cycles			
Day	-28 to -1	-1	1	8	15	1	15	1	15	8	EOSI +7 Days	Last Dose + 30 Days	
Visit window (days)	Up to 28 days before Day 1			(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)		(± 7)	EOSI within 7 days of decision to discontinue but before start of subsequent anticancer treatment.
Triplicate digital ECG (Holter recorder)			X <sup>a</sup>	X <sup>#a</sup>	X <sup>#</sup>	X <sup>†</sup>							X <sup>#</sup> Only in Cycle 1. X <sup>†</sup> Only in Cycle 4. X <sup>a</sup> Included in the Holter ECG. To be taken before any blood sampling; Detailed timepoints in Table 2.
12-lead ECG Safety (Holter recorder)	X		X	X <sup>#</sup>	X <sup>#</sup>	X <sup>†</sup>		X <sup>†</sup>			X	X	X <sup>#</sup> Only in Cycle 1 X <sup>†</sup> Only in even Cycles To be taken before any blood sampling; safety ECGs to be locally read. and extracted from Holter recorder; Detailed timepoints in Table 2
PK			X	X <sup>†</sup>	X <sup>†</sup>	X <sup>#</sup>		X <sup>@</sup>					X <sup>†</sup> Only in Cycle 1. X <sup>#</sup> Only in Cycle 4. X <sup>@</sup> Only C6D1 and C8D1. Detailed timepoints in Table 2.

Assessments and Procedures	Screening	D -1	Intervention Period (21-Day Cycles)								EOSI	Safety FU	Notes
			Cycle 1, 2			Cycles 3, 4, 5		Cycles ≥ 6 Even cycles		Cycles ≥ 7 Odd cycles			
Day	-28 to -1	-1	1	8	15	1	15	1	15	8	EOSI +7 Days	Last Dose + 30 Days	
Visit window (days)	Up to 28 days before Day 1			(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)		(± 7)	EOSI within 7 days of decision to discontinue but before start of subsequent anticancer treatment.

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Assessments and Procedures	Screening	D -1	Intervention Period (21-Day Cycles)								EOSI	Safety FU	Notes
			Cycle 1, 2			Cycles 3, 4, 5		Cycles ≥ 6 Even cycles		Cycles ≥ 7 Odd cycles			
Day	-28 to -1	-1	1	8	15	1	15	1	15	8	EOSI +7 Days	Last Dose + 30 Days	
Visit window (days)	Up to 28 days before Day 1			(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)		(± 7)	EOSI within 7 days of decision to discontinue but before start of subsequent anticancer treatment
CCI													
Drug dispense			X	X	X	X	X	X	X	X			

Assessments and Procedures	Screening	D -1	Intervention Period (21-Day Cycles)									EOSI	Safety FU	Notes
			Cycle 1, 2			Cycles 3, 4, 5		Cycles ≥ 6 Even cycles		Cycles ≥ 7 Odd cycles				
Day	-28 to -1	-1	1	8	15	1	15	1	15	8	EOSI +7 Days	Last Dose + 30 Days		
Visit window (days)	Up to 28 days before Day 1			(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)		(± 7)	EOSI within 7 days of decision to discontinue but before start of subsequent anticancer treatment.	
M1069 administration			←===== twice daily oral administration (BID) =====→										SMC may recommend alternative regimens.	
AE & SAE review	←=====→												From the time of signing ICF to Safety Follow-up Visit.	
Concomitant medication and procedure review	←=====→												From the time of signing ICF to Safety Follow-up Visit.	

AE = Adverse event, BID = Twice daily, C = Cycle, CREB = cAMP response element-binding protein, CT = Computed tomography, D = (Study) Day; DL = Dose Level; ECG = Electrocardiogram, ECOG = Eastern Cooperative of Oncology Group, EOSI = End of Study Intervention, FU = Follow-up, HBV = Hepatitis B virus, HCV = Hepatitis C virus, HIV = Human immunodeficiency virus, ICF = Informed Consent Form, MRI = Magnetic resonance imaging, CCI, Pd = Pharmacodynamic, PK = Pharmacokinetic, CCI, RDE = Recommended dose for expansion, RECIST = Response Evaluation Criteria in Solid Tumors, SAE = Serious adverse event, SMC = Safety Monitoring Committee, WOCBP = Women of childbearing potential.

See for Table 2 timepoints within visit days for ECG, PK, **CC** and **CCI** assessments. At visits where assessment timepoints coincide with each other: (ECG, PK, **CCI** the following is the order of assessments:

1. Put the participant at supine position at least 15 min before the PK blood sampling timepoint to allow a 10 min supine rest and a 5 min window for ECG data collection.
2. Perform vital signs assessments first.
3. ECG assessments slightly before the specific collection timepoint; ECGs have to be taken before any blood sampling.
4. PK assessments at scheduled collection timepoint.
5. **CCI** assessment as last assessment.

**Table 2** Schedule of Electrocardiogram, Pharmacokinetic, and Biomarker Assessments during Dose Escalation

Cycle/Day Hour (±min)	Hour (±min) (relative to the first dose on the day)	Vital signs	Holter recorder for continuous ECG	Holter recorder for triplicate digital ECG	Holter recorder for safety ECG	PK	<b>CCI</b>	Notes
C1D -1			X Start Holter recording					
C1D1*	Predose (within 2h)	X			X -15 min	X		<p>On C1D-1: set-up Holter recorder and encourage normal activity, record continuous Holter ECGs until C1D1 8h post-dose.</p> <p>On C1D1 and C1D8: Start recording Holter ECGs at least 1 hour before the first dose. Triplicate digital ECGs will be extracted from Holter ECGs at predose (-45, -30, -15min), 1h, 2h, 4h, 6h and 8h.</p>
	0.5h (±5 min)					X		
	1h (±5 min)	X			X	X		
	1.5h (±5 min)					X		
	2h (±10 min)	X			X	X		
	4h (±15 min)	X			X	X		
	6h (±15 min)	X			X	X		
	8h (±15 min)	X	X		X	X		

Cycle/Day Hour (±min)	Hour (±min) (relative to the first dose on the day)	Vital signs	Holter recorder for continuous ECG	Holter recorder for triplicate digital ECG	Holter recorder for safety ECG	PK	Notes
			Stop Holter recording				
C1D8*#	Predose (within 2h)	X	Start Holter recording		X -15 min	X	At indicated timepoints during C1D1 and C1D8 Holter recorder needs to be used for print out of safety ECGs. The safety ECG has to be read immediately and locally; for AE management see Section 7.1  X* For C1D1 and C1D8, SMC may recommend adjustment of the sample collection timepoints with support of human PK data after the first cohort (e.g. 24h post-dose, time point close to t <sub>max</sub> etc.).  X& These timepoints may be adjusted with support of human data after the first cohort.
	0.5h (±5 min)					X	
	1h (±5 min)	X			X	X	
	1.5h (±5 min)					X	
	2h (±10 min)	X			X	X	
	4h (±15 min)	X			X	X	
	6h (±15 min)	X			X	X	
	8h (±15 min)	X	X  Stop Holter recording		X	X	
C1D15&	Predose (within 2h)	X		X	X	X	
C2D1&	Predose (within 2h)	X		X	X	X	
	2h (±10 min)	X		X	X	X	
C4D1&	Predose (within 2h)	X		X	X	X	
≥ C6D1, every 2 cycles	Predose (within 2h)	X			X	X@	X@ Only C6D1 and C8D1.

C = Cycle, D =(Study) Day, ECG = Electrocardiogram; eCRF = electronic Case Report Form;  
Pd = Pharmacodynamic; PGx = Pharmacogenetic, Pk = Pharmacokinetic.

## 2 Introduction

M1069 is a novel, orally administered, highly selective antagonist of the A<sub>2A</sub> and A<sub>2B</sub> adenosine receptors that is being developed for the treatment of participants with advanced solid tumors.

By binding adenosine receptors A<sub>2A</sub> and A<sub>2B</sub> expressed on immune cells, adenosine promotes immunosuppression by inhibiting activation, proliferation, and cytotoxic activity of effector T cells (Cekic 2016). Although initially the A<sub>2A</sub> adenosine receptor was considered to be the most central adenosine signaling pathway in cancer development, more recent research has revealed the significance of A<sub>2B</sub> receptor signaling which was shown to induce immune suppression, tumor proliferation, tumor angiogenesis, tumor cell invasion and metastasis (Gao 2019). A<sub>2B</sub> activation is known to suppress IFN-enhanced expression of major histocompatibility complex Class II (MHC-II) transactivator required for CD4<sup>+</sup> T cell anti-tumor responses (Fang 2013). It has been suggested that high A<sub>2B</sub> receptor expression levels are generally associated with worse prognosis or poor survival (Mittal 2016). Moreover, multiple studies have shown the importance of several signaling pathways related to A<sub>2B</sub> receptor activation and the subsequent release of various cytokines and growth factors, which eventually led to cancer cell proliferation.

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Detailed information on the chemistry, pharmacology, efficacy, and safety of M1069 is in the Investigator's Brochure.

### 2.1 Study Rationale

The administration of M1069 to participants with advanced/metastatic solid tumors, for which no tolerated or approved/established effective treatment option exists, is justified by the following:

- A<sub>2A</sub> and A<sub>2B</sub> adenosine receptors have been shown to mediate immunosuppressive and tumor-promoting signals in the tumor microenvironment (TME).

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- CCI [REDACTED]
- Based on results from nonclinical safety pharmacology and toxicology investigations, the safety profile of M1069 is considered adequate for patients with advanced/metastatic solid tumors at the projected dose levels. Clinical experience with dual adenosine A<sub>2A</sub>/A<sub>2B</sub> antagonism published in the literature suggests an acceptable safety profile as monotherapy and no potentiating toxicities in combination with other immunotherapies.
- Early signs of clinical activity in advanced solid tumors including colorectal cancer has been reported (Cecchini 2021) from a Phase Ib dose expansion study with etrumadenant, the A<sub>2A</sub>/A<sub>2B</sub> antagonist from Arcus Biosciences, evaluating it in combination with chemotherapy.

## 2.2 Background

An increase in energy consumption or hypoxia in metabolically stressful conditions, including cancer, result in dramatic increases in extracellular concentrations of immunosuppressive adenosine (Cronstein 1994; Ohta 2016). Most evidence linking adenosine signaling to immunosuppression has been related to A<sub>2A</sub>. The A<sub>2A</sub> adenosine receptor has been recognized as the key receptor for adenosine driven suppression of anti-tumor CD4<sup>+</sup> and CD8<sup>+</sup> T cell, NK cell, and myeloid cell functions directly or through recruitment of other immunoregulatory cells, including regulatory T cells (Tregs) (Cekic 2014). However, the A<sub>2A</sub> receptor shares signaling with the lower affinity A<sub>2B</sub> adenosine receptor through Gs GPCR subunit activation of adenylate cyclase (Fredholm 2001). In this regard, the A<sub>2B</sub> receptor can compensate for inhibition of A<sub>2A</sub> in an adenosine rich tumor microenvironment (TME). Moreover, blocking A<sub>2B</sub> is expected to suppress adenosine-mediated tumor promotion by blocking of Gq subunit of GPCRs, leading to reduced tumor neovascularization through decreased production of VEGF by myeloid cells and tumor cells (Ryzhov 2008; Ryzhov 2014; Sorrentino 2015). In addition, blocking A<sub>2B</sub> is likely to support vascular permeability that may promote infiltration of leukocytes into tumors (Yang 2006; Eckle 2008). Furthermore, inhibition of A<sub>2B</sub> is presumed to prevent accumulation of immune suppressive precursors of dendritic cells (Novitskiy 2008) and polarization of pro-tumorigenic M2 macrophage cells (Csoka 2012). Taken together, inhibition of A<sub>2B</sub> receptors, in addition to inhibition of A<sub>2A</sub> receptors, is expected to provide more robust protection from adenosine driven tumor promotion.

Multiple compounds targeting adenosine signaling in the TME, either by inhibiting production of adenosine (anti-CD39 or anti-CD73) or downstream to A<sub>2A</sub> and/or A<sub>2B</sub> receptors, are in development for multiple tumor types. CCI [REDACTED]

[REDACTED]

In summary, the Sponsor has developed a potent dual A<sub>2A</sub>/A<sub>2B</sub> adenosine receptor antagonist, M1069, that is expected to counteract adenosine-mediated pro-tumorigenic mechanisms and to enhance therapeutic efficacy for other anticancer agents, including checkpoint inhibitors for solid tumors.

## **2.3 Benefit/Risk Assessment**

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of M1069 may be found in the Investigator's Brochure for M1069.

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

### **2.3.1 Risk Assessment**

Based on preclinical data and/or data from other compounds targeting A<sub>2A</sub> and A<sub>2B</sub> adenosine receptors, the following potential risks (Table 3) are being considered.

Table 3 Potential risks of M1069

Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b>Study Intervention(s)</b>		
Gastrointestinal adverse events	<p>For the dual A<sub>2A</sub>/A<sub>2B</sub> receptor antagonist AB928 mild to moderate abdominal pain (20%) and nausea (17%) have been identified as the most common adverse events in a first-in-human trial in healthy volunteers. (Seitz 2019).</p> <p>For M1069, gastrointestinal effects, mainly vomiting, salivation and red buccal mucosa, conjunctiva and gums were observed in repeat-dose toxicity studies in dogs.</p>	<p>Monitoring for adverse events during the trial and appropriate management as medically indicated.</p> <p>The SMC might change their recommendation of Study Intervention administration from an empty stomach condition to fed condition as deemed appropriate by the committee (see Section 5.3.1 and Section 6.6.2).</p>
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Excitatory adverse events	<p>Agitation, anxiety and insomnia have been observed with certain adenosine inhibitors, such as Ciforadenant (Voss 2020), and istradefylline (USPI). Convulsions, dizziness, headache and tremor have also been observed with theophylline (EU SmPC).</p>	<p>Monitoring for adverse events during the trial and appropriate management as medically indicated.</p>

Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In rats, M1069 produced an excitatory effect with increased CNS activity and respiration at single doses of all dose levels tested (30, 100 and 300 mg/kg). In dogs, mild to moderate increases in physical activity were observed at all dose levels tested (single doses of 30, 60, or 100 mg/kg).	
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Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CCI [REDACTED]	[REDACTED]	[REDACTED]
<b>Study Procedures</b>		
Tumor biopsies	Tumor biopsies are required for study participants as detailed in the Schedule of Activities. These are considered essential for the study's scientific objectives. Biopsies carry a risk of adverse events including bleeding and infection.	Monitoring for any risks associated with tumor biopsy collection and appropriate management as medically indicated.

ECG = Electrocardiogram, EOSI = End of Study Intervention, CCI [REDACTED] SMC = Safety Monitoring Committee, SmPC = Summary of Product Characteristics (European Union), USPI = Prescribing Information (United States).

### 2.3.2 Benefit Assessment

Based on preclinical experiments and available data for other compounds, therapeutic inhibition of adenosine signaling can potentially contribute to an anti-tumor immune response and inhibit growth of tumor cells. Therefore, treatment with M1069 may offer patients with advanced solid tumors which have failed approved therapies the chance of a treatment option by inhibiting a new signaling pathway that has not been targeted by their previous therapies.

### 2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with M1069 as monotherapy are justified by the anticipated benefits that may be afforded to participants with advanced solid tumors.

## 3 Objectives and Estimands

This study is conducted in participants with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them. Objectives, endpoints and other key estimand attributes are presented in Table 4.

**Table 4 Objectives, Endpoints and Other Estimand Attributes**

Objectives	Estimand Attributes
<b>Primary</b>	
To determine dose toxicity relationship and maximum tolerated dose (MTD, if reached) of M1069 as a monotherapy in participants with solid tumors.	<p><b>Endpoints:</b></p> <ul style="list-style-type: none"> <li>• Occurrence of DLTs.</li> <li>• Occurrence of AEs and treatment-related adverse events.</li> </ul> <p><b>Strategy for handling intercurrent events:</b></p> <p>For DLTs:</p> <ul style="list-style-type: none"> <li>• Discontinuation/interruption/delay of treatment (&gt; 20% planned treatment missed during DLT period) to prevent a DLT: composite strategy (to be considered a DLT).</li> </ul> <p>For other endpoints:</p> <p>The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment policy strategy):</p> <ul style="list-style-type: none"> <li>• Treatment discontinuation</li> <li>• Start of subsequent anticancer therapy.</li> </ul> <p><b>Population:</b></p> <p>Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them.</p> <p><b>Population level summary:</b></p> <ul style="list-style-type: none"> <li>• DLT probabilities and associated credibility intervals as estimated using the BLRM model (for DLTs only)</li> <li>• Standard summary statistics.</li> </ul>
To determine the RDE of M1069 for further exploratory clinical development.	<p><b>Endpoints:</b></p> <p>In addition to safety, tolerability, PK, Pd (CCI in ex-vivo stimulated blood), post-treatment changes in TME in available paired tumor biopsies data are considered.</p> <p><b>Strategy for handling intercurrent events:</b></p> <p>The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment policy strategy):</p> <ul style="list-style-type: none"> <li>• Discontinuation of treatment</li> <li>• Start of subsequent anticancer therapy.</li> </ul> <p><b>Population:</b> Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them.</p> <p><b>Population level summary:</b></p> <p>Standard summary statistics.</p>
<b>Secondary</b>	
To characterize the PK profile of M1069.	<p><b>Endpoints:</b> PK parameters (see Section 8.5) of M1069 after single dose administration and at steady state using non-compartmental analysis.</p>

Objectives	Estimand Attributes
To evaluate indicators of clinical activity of M1069 in terms of objective response using RECIST v1.1.	<p><b>Endpoint:</b> Objective response using RECIST v1.1, as assessed by Investigator.</p> <p><b>Strategy for handling intercurrent events:</b></p> <ul style="list-style-type: none"> <li>Discontinuation of treatment (treatment policy strategy; i.e. ignoring intercurrent event)</li> <li>Start of subsequent anticancer therapy (treatment policy strategy; i.e. ignoring intercurrent event)</li> <li>Progression according to RECIST v1.1 (while not progressed strategy).</li> </ul> <p><b>Population:</b> Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them.</p> <p><b>Population level summary:</b> Rate.</p>
To evaluate indicators of clinical activity of M1069 in terms of DoR using RECIST v1.1.	<p><b>Endpoint:</b> Duration of response according to RECIST v1.1 as assessed by Investigator, defined as time from first documentation of objective response to PD or death, occurring within 2 scheduled tumor assessments after last evaluable assessment or start of treatment.</p> <p><b>Strategy for handling intercurrent events:</b></p> <ul style="list-style-type: none"> <li>Death within 2 scheduled tumor assessments after last evaluable assessment or first study intervention will be considered as event (composite strategy).</li> </ul> <p>The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment policy strategy):</p> <ul style="list-style-type: none"> <li>Discontinuation of treatment</li> <li>Start of subsequent anticancer therapy.</li> </ul> <p><b>Population:</b> Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them.</p> <p><b>Population level summary:</b> Median DoR.</p>

Objectives	Estimand Attributes
To evaluate indicators of clinical activity of M1069 in terms of PFS using RECIST v1.1.	<p><b>Endpoint:</b> Progression-free survival as defined from date of first study intervention to PD according to RECIST v1.1 as assessed by Investigator or death. Events are considered only if occurring within 2 scheduled tumor assessments after last evaluable assessment or start of treatment.</p> <p><b>Strategy for handling intercurrent events:</b></p> <ul style="list-style-type: none"> <li>Death within 2 scheduled tumor assessments after last evaluable assessment or first study intervention will be considered as event (composite strategy).</li> </ul> <p>The endpoint will be analyzed regardless of whether or not the following intercurrent events had occurred (treatment policy strategy):</p> <ul style="list-style-type: none"> <li>Discontinuation of treatment</li> <li>Start of subsequent anticancer therapy.</li> </ul> <p><b>Population:</b> Patients with metastatic or locally advanced unresectable solid tumors, who are intolerant or have no effective standard therapies available to them.</p> <p><b>Population level summary:</b> Hazard ratio.</p>
To assess the effect of M1069 on QT interval	<p><b>Endpoints:</b> Change from baseline QTc (<math>\Delta</math>QTc) over time.</p>

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AE = Adverse event, BLRM = Bayesian 2-parameter logistic regression model, C = Cycle, CCI = (Study) Day, DLT = Dose-limiting toxicity, DoR = Duration of response, MTD = Maximum tolerated dose, CCI, PD = Progressive disease, Pd = Pharmacodynamic, PFS = Progression-free survival, PK = Pharmacokinetic, QT interval, corrected, RDE = Recommended dose for expansion, RECIST = Response Evaluation Criteria in Solid Tumors.

## **4 Study Design**

### **4.1 Overall Design**

This is a Phase I FIH dose escalation of M1069, noncontrolled, open label, multicenter clinical study designed to determine the safety, tolerability, PK, Pd and early signs of efficacy in participants with advanced solid malignancies. A Bayesian study design will be applied, using a Bayesian 2-parameter logistic regression model (BLRM).

The study for a participant will include up to 28 days Screening period, a study intervention period consisting of consecutive 21-day cycles with twice daily oral administration of M1069, a DLT observation period of 21 days, End of Study Intervention Visit (within 7 days from decision to stop M1069 intake), and a Safety Follow-up period of  $30 \pm 7$  days after the last M1069 intake. Participants who tolerate treatment without significant clinically relevant toxicities may continue to receive their assigned dose until progressive disease (PD) (Section 7.1.1). Participants who discontinue study intervention for any reason will complete the End of Study Intervention Visit.

#### **Screening**

Screening will be performed within 28 days prior to Day 1 of M1069 administration. If the participant meets all the protocol-defined inclusion and none of the exclusion criteria, the participant will be considered eligible for participation in the study. Screening for the next cohort should usually start before the SMC has taken the decision on the next dose. The eligible participants screened for the next cohort will, however, only be treated pending decision by the SMC.

Participants who fail to meet the protocol-specified criteria or who withdraw their consent prior to start of treatment will be considered Screening Failures.

#### **Treatment Period**

The treatment period will begin at the first dose of M1069 with Cycle 1 Day 1 (C1D1) and consists of consecutive 21-day cycles with twice daily oral administration (BID) of M1069 or QD regimen determined by the SMC (see Section 6.6.2) until disease progression, unacceptable toxicity, withdrawal of consent, or any criterion for withdrawal from study intervention (Section 7.1).

#### **Safety Follow-up**

Safety Follow-up visit will occur 30 days ( $\pm 7$  days) after last dose of study drug.

#### **Sample Size**

The total sample size will depend on the number of cohorts to be evaluated. The planned cohort size is 3 participants. Data observed during the dose escalation (e.g., number of DLTs) have an impact on the number of cohorts. The sample size for the RDE and MTD dose levels needs to

be at least 6 participants. It is anticipated that 21 to 30 participants (5 projected dose levels with 3 to 9 participants each) may be needed.

### Dose Escalation

The first dose escalation cohort will receive M1069 as a monotherapy at the starting dose of 150 mg BID. For further dose cohorts, the SMC will meet and review all available safety, PK and Pd data to provide recommendations on the dose level and regimen for the next cohort. Decision making of the SMC will be supported by results of a Bayesian 2-parameter logistic regression model.

The term “cohort” with regards to dose escalation in this protocol is referring to a group of participants that are enrolled at the same dose level and evaluated by an SMC before the dosing decision for the next cohort is made. There may be more than one cohort on the same dose level, if the SMC decides that a further cohort on the same dose level is needed.

More details on the SMC and dose escalation can be found in Section 6.6.2. The following predefined doses of M1069 are foreseen: 150, 300, 450, 600, and 700 mg BID. If deemed necessary based on obtained pharmacological data, higher dose levels than 700 mg BID with an increase by 15% may be recommended by the SMC. Participants will receive study intervention twice daily with a food restriction for 2 hours before and 1 hour after dose administration.

Depending on the observed PK or toxicity profile the SMC may recommend QD regimen, different dose levels (higher or lower) or dosing conditions (fasted or fed; see Section 5.3.1). At each dose level, the first participant enrolled will be observed for DLTs for at least 3 days before further individuals are enrolled. However, the SMC may decide to shorten or prolong this interval based on available results.

In principle, dose escalation in monotherapy will proceed according to SMC recommendation until MTD and/or until a safe RDE is determined and/or the SMC recommends ending dose escalation. Target DLT probability for the MTD suggested by the Bayesian model is 30%.

A potential RDE dose level will be selected based on the data of at least 3 participants. At this dose level, 2 additional confirmatory cohorts with 3 participants each may be enrolled (2nd cohort pending SMC decision). For these additional cohorts, mandatory paired pre- and on-treatment biopsies will be collected.

The final RDE will be based on all available safety, tolerability, PK, CCI



The RDE cannot exceed the MTD. If the suggested RDE is below the MTD, dose escalation may continue until the MTD is reached (if applicable) or SMC recommends ending dose escalation.

Additional dose escalation cohorts assessing M1069 in combination with other anticancer agents may be added by protocol amendment.

### Dose Expansion

Additional expansion cohorts assessing M1069 alone or in combination with other anticancer agents, potentially in diseases-specific settings, may be added by protocol amendment.

## 4.2 Scientific Rationale for Study Design

Small molecule inhibitors specific to A<sub>2A</sub> as well as dual inhibitors of A<sub>2A</sub> and A<sub>2B</sub> have been investigated in humans previously and have demonstrated an acceptable safety profile and early signs of clinical activity in Phase I studies in patients with solid tumors. CCI

As safety, tolerability and also anticancer activity of M1069 have never been investigated in humans, the target population for initial investigation is restricted to adult participants who have histologically or cytologically proven locally advanced or metastatic solid malignancies and who are refractory to or have progressed under standard treatment and have no other treatment options known to confer clinical benefit.

Escalating doses of M1069 are considered an acceptable approach to establish safety, PK, Pd and early signs of anti-tumor activity without putting participants at high risk of experiencing undue toxicity. Supervision by an SMC is necessary in order to frequently review safety and reassess benefit and risk.

A Bayesian logistic regression model will be used in order to support SMC recommendations. Application of such a model for dose escalation will enable implementation of alternative dose levels not defined a priori in order to ensure participant safety and optimized definition of RDE and MTD as compared to a classical 3 + 3 dose escalation approach.

### 4.2.1 Participant Input into Design

None.

## 4.3 Justification for Dose

The proposed clinical study is a Phase I dose escalation trial aiming to explore the safety and tolerability of M1069 in participants with advanced cancer and limited therapeutic options. Therefore, ICH S9 has been considered for the determination of the FIH starting dose, (i.e., a dose that is expected to have pharmacologic effects and is reasonably safe to use). The selected starting dose of M1069 for first in human trials is 150 mg BID, and followed by dose escalation to 300, 450, 600, and 700 mg BID. Participants should keep at least 10 hours in between the 2 daily doses. Participants will receive study intervention twice daily with a food restriction for 2 hours before and 1 hour after dose administration (for fed conditions see Section 5.3.1). If

deemed necessary based on emerging pharmacological data, higher dose levels than 700 mg BID might be explored in 15% increments. The rationale is listed as below.

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At 150 mg BID, the projected CCI inhibition (a proximal pharmacodynamic biomarker for M1069) in human at  $C_{min,ss}$  is 89%, based on a mechanistic model developed and verified using published Phase I clinical study data from etrumadenant (AB928), a compound from Arcus Biosciences with the same mechanism of action (Seitz 2019). Doses with > 90% CCI inhibition at  $C_{min,ss}$  were shown to be well tolerated in clinical studies with AB928: no  $\geq$  Grade 3 AEs in healthy volunteers and no > Grade 3 AB928 related AEs in cancer patients (Powderly 2019). This further supports the selected M1069 starting dose, which is expected to be well tolerated in the FIH study.

At the proposed human exposure expected at a starting dose of 150 mg BID, the projected tumor growth inhibition (TGI) is 77%, based on a Simeoni TGI model (Simeoni 2004) developed using

in vivo tumor growth data from adenosine rich (CD73<sub>high</sub>) mouse 4T1 breast tumor model that is refractory to checkpoint inhibitors. These analyses indicate that the proposed starting dose is expected to achieve exposures in humans associated with tumor growth inhibitory pharmacologic effects.

Based on brain exposure studies in rats, the brain penetration of M1069 (kp,uu=0.166) at the proposed human starting dose of 150 mg BID is expected to be limited.

#### **4.4 End of Study Definition**

A participant has completed the study if he/she has completed all study parts, including EOSI and the Safety follow-up Visit.

The end of the study is defined as the date of the last participant has completed the last Safety follow-up Visit.

The Sponsor may terminate the study at any time once access to study intervention for participants still benefitting is provided 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 should be taken into consideration 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 has provided written informed consent, as indicated in [Appendix 2](#).

#### **5.1 Inclusion Criteria**

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

##### **Age**

1. Are  $\geq 18$  years of age at the time of signing the informed consent.

##### **Type of Participant and Disease Characteristics**

2. Participants who have histologically or cytologically proven locally advanced or metastatic solid malignancies and who are refractory to or have progressed under standard treatment or for whom standard treatment is not expected to deliver clinical benefit.

3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1 at Screening.
4. Adequate hematological function as defined below:
  - a. Absolute neutrophil count  $\geq 1,500/\text{mm}^3$  or  $\geq 1.5 \times 10^9/\text{L}$  (Note: hematopoietic growth factors are not permitted in the 2 weeks before first dose).
  - b. Platelet count  $\geq 100,000/\text{mm}^3$  or  $\geq 100 \times 10^9/\text{L}$  (no transfusion in the past 2 weeks before first dose).
  - c. Hemoglobin  $\geq 9 \text{ g/dL}$  (no transfusion in the past 2 weeks before first dose).
5. Adequate hepatic function defined: by a total bilirubin level  $\leq 1.5 \times$  upper limit of normal (ULN), an aspartate aminotransferase (AST) level  $\leq 2.5 \times$  ULN, and an alanine aminotransferase (ALT) level  $\leq 2.5 \times$  ULN.
  - a. Subjects with documented Gilbert disease are allowed if total bilirubin  $> 1.5 \times$  ULN but  $< 3 \times$  ULN.
  - b. Subjects with tumor involvement in their liver: AST  $< 3.0 \times$  ULN, ALT  $< 3 \times$  ULN, with normal bilirubin  $\leq 1.5 \times$  ULN and INR  $< 1.5 \times$  ULN.
6. Adequate renal function defined by an estimated creatinine clearance  $\geq 60 \text{ mL/min} \times$  ULN according to the Cockcroft-Gault formula.
7. Ability to swallow oral dose forms (e.g. capsules).
8. Fresh tumor **biopsies mandatory for participants at DL2** and 6 participants upon potential determination of **RDE**. Providing consent to fresh tumor biopsies taken during the Screening period and an on-treatment biopsy is mandatory.

**For all other dose levels:**

- Formalin-fixed paraffin-embedded block containing tumor tissue or a minimum of 15 (preferably 25) unstained tumor slides suitable for immunohistochemistry-based staining of protein expression from recently obtained tumor biopsies (non-irradiated area) ideally at or after progression on the most recent line of anticancer treatment required.
  - Recommended paired fresh and on-treatment biopsies, as feasible.
  - Patients for which tumor tissue is not available and a new biopsy is not acceptable/feasible or medically inadvisable, may be deemed eligible for study after consultation with “Sponsor Medic”.
9. Life expectancy of at least 12 weeks according to Investigator judgement.
  10. Measurable disease according to RECISTv1.1.

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## Sex

14. Are male or female.

Contraceptive use 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 100 days after the last dose of study intervention:

- Refrain from donating fresh unwashed semen.

PLUS, either:

- Abstain from intercourse with a WOCBP

OR

- Use a male condom:
  - When having sexual intercourse with a WOCBP, who is not currently pregnant, and instruct 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.

### Female participant:

- Is not breastfeeding
- Is not pregnant (i.e., has a negative pregnancy test) as required by local regulations, within 24 hours before the first dose of study intervention.
- Is not a WOCBP

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.

1. 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 least 28 days and has a documented negative pregnancy test using a highly sensitive assay.
2. During the study intervention period:
  - Since in vitro data shows M1069 could affect metabolizing enzymes and transporters of hormonal contraceptives, WOCBP who are currently using hormonal contraception that contains estrogen and/or progestins should also use double barrier contraception.
3. After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 180 days 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.

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**

15. 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. Persisting toxicity related to prior therapy Grade > 1 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, however, alopecia, sensory neuropathy hypothyroidism and diabetes mellitus Grade ≤ 2, despite treatment, are allowed.
2. Prior organ transplantation including allogeneic stem cell transplantation.
3. Participants with known brain metastases, except those meeting the following criteria:
  - a. Brain metastases that have been treated locally and are clinically stable for at least 4 weeks prior to the start of treatment.
  - b. No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable).

4. Participants must be either off steroids or on a stable or decreasing dose of < 10 mg daily prednisone (or equivalent).
5. Current significant cardiac conduction abnormalities, including corrected QT interval (QTcF, corrected with Fridericia formula) prolongation of > 470 ms or impaired cardiovascular function, ventricular tachycardia (including Torsades de Pointes), or a history of paroxysmal atrial fibrillation, serious cardiac arrhythmia and family history of sudden death or long QT syndrome.
6. A history of vascular, cardiovascular or cerebrovascular disease as follows: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class  $\geq$  II), pulmonary thrombosis/embolism (< 3 months prior to enrollment), uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment, renal artery stenosis.
7. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent including but not limited to inflammatory bowel diseases, autoimmune hepatitis, interstitial lung disease of immunologic origin, systemic lupus erythematosus, etc, with the following exceptions:
  - a. Participants with diabetes type I, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
8. Significant acute or chronic fungal, bacterial and/or viral infections requiring systemic therapy including COVID-19
9. Known hypersensitivity to the trial treatment or to one or more of the excipients.

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### Prior/Concomitant Therapy

12. Prior treatment with another agent targeting the adenosine signaling pathway (inhibitors of CD39, CD73 and/or A<sub>2A</sub> or A<sub>2B</sub> receptors).
  13. Concurrent treatment with a nonpermitted drug/intervention and prohibited concomitant medication as listed in Section 6.5.3.
- Strong inhibitors or inducers of CYP3A4, strong P-gp inhibitors, sensitive CYP3A4 substrates with narrow therapeutic index, drugs associated with Torsade de Pointes should be

discontinued 7 days prior to treatment and avoided during treatment (see Section 6.5.3 for a list. The link to the website to be consulted, in case of doubt, is provided in Section 6.5.3).

- Medications or herbal supplements known to be strong CYP3A4 inhibitors/inducers should be discontinued 7 days prior to treatment and avoided during treatment (see Section 6.5.3 for a list). The link to the website to be consulted, in case of doubt, is provided in Section 6.5.3).
- Anticancer treatment (e.g., cytoreductive therapy, radiotherapy, immune therapy, cytokine therapy, monoclonal antibody, targeted small molecule therapy) or any investigational drug within 4 weeks or 5 half-lives, whichever is shorter prior to start of study treatment, with the following exceptions:
  - i. Palliative bone-directed radiotherapy is permitted (concurrently or within pretreatment period, see further details under prohibited medicines, Section 6.5.3).
  - ii. Hormonal therapies acting on the hypothalamic pituitary gonadal axis are permitted (i.e., luteinizing hormone releasing hormone agonist/antagonists). No other hormonal anticancer therapy is permitted.
- Major surgery (as deemed by the Investigator) for any reason, except diagnostic biopsy, within 4 weeks of the study treatment.
- Participants receiving immunosuppressive agents (such as steroids), for any reason, should be tapered off these drugs before start of study treatment, with the following exceptions:
  - i. Participants with adrenal insufficiency may continue corticosteroids at physiologic replacement dose, equivalent to < 10 mg prednisone daily.
  - ii. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation).
  - iii. Previous or ongoing administration of systemic steroids for the prophylaxis or treatment of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the dose after 14 days will be equivalent to  $\leq$  10 mg prednisone daily.

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

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

## **5.3 Lifestyle Considerations**

The following lifestyle considerations apply for participants in this study.

### **5.3.1 Meals and Dietary Restrictions**

M1069 will be administered with 240 mL (8 fluid ounces) of ambient temperature water on an empty stomach. All participants will abstain from all food for at least 2 hours before oral

administration of M1069 and for 1 hour after administration of M1069. Water can be consumed ad libitum.

Dosing with food has been shown to improve GI tolerability of orally administered drugs, and bosutinib and ceritinib have been approved to be administered under fed condition even with positive food effects (Cho 2017). CCI

If GI adverse events are frequently reported in a dose escalation cohort, SMC retains the right to start the next cohort at the same dose level under fed with low-fat meal condition. Pending review of PK and safety data from the empty stomach and fed cohorts at the same dose level, the SMC may also suggest continuing future cohorts at higher dose levels under fed with low-fat meal condition. The meal should be consumed within approximately 30 minutes, and the drug should then be administered at 30 minutes after the start of the meal, with 240 mL (8 fluid ounces) of water.

Per the FDA guidance, a low-fat meal is defined as approximately including 400 to 500 calories of which 25% come from fat (i.e., 2.8 grams fat per 100 calories). A typical low-fat breakfast contains 8 ounces milk, one boiled egg, and one packet flavored instant oatmeal made with water (FDA 2019). A standard low-fat breakfast will be provided on the PK sampling days (C1D1 and C1D8). Considering the participants will self-administer M1069 at home most of the time, the low-fat meal can be extended as containing <600 calories and < 30% fat. For breakfast and dinner, it is encouraged for the participants to choose lower-fat and lean options of dairy, meat and poultry, such as skim milk, lean beef, and grilled chicken breast without the skin. Also, try to limit the amount of ingredients high in fat consumed, such as cheese, butter, margarine, cream, sausage and oils. There are no food restrictions on lunch.

Refer to Operations Manual to obtain the written guidance and food diary.

Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice from 7 days before the start of study intervention until after the final dose.

### 5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid

For visits on C1D1 and C1D8, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until after collection of the final PK and/or Pd sample.

### 5.3.3 Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., watching television or reading).

## 5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants will be assigned a new participant number.

## 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.

### 6.1 Study Intervention(s) Administration

<b>ARM Name</b>	
<b>Intervention Name</b>	M1069
<b>Type</b>	Drug
<b>Dose Formulation</b>	M1069 filled CCI . Capsule color is white for the doses 10 mg and 75 mg and orange for the 25 mg dose.
<b>Unit Dose Strength(s)</b>	10 mg, 25 mg or 75 mg per capsule
<b>Dose Amount</b>	multiple dose levels (dose escalation)
<b>Frequency</b>	twice daily (alternative: once daily if recommended by SMC)
<b>Route of Administration</b>	Oral
<b>Use</b>	Experimental
<b>Investigational Medicinal Product (IMP) and Non- Investigational Medicinal Product (NIMP)</b>	IMP
<b>Sourcing</b>	Sponsor
<b>Packaging and Labeling</b>	Study Intervention will be provided in a bottle. Each bottle will be labeled per country requirements.

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 Operations 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, bottle 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 Operations Manual.
- M1069 capsules should be stored in a refrigerator at or below 5°C (2°C to 8°C) until use. After opening, an in-use stability of 14 days is assigned, with storage at or below 25°C.

## **6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding**

### **6.3.1 Study Intervention Assignment**

Not applicable. A single study intervention will be administered in the study

### **6.3.2 Emergency Blinding**

Blinding is not applicable as the study intervention administration is open label and none of the assessments is blinded.

## 6.4 Study Intervention Compliance

On visit days, participants will receive study intervention at the investigation site. 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 eCRF. 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.

On non-visit days, participants will self-administer study intervention at home. Participants will be instructed by the Investigator/designee regarding off-site self-administration of M1069 and asked to record self-administration in a dosing diary. When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by reviewing the dosing diary and counting returned capsules during the site visits and documented in the source documents and eCRF. Any deviation(s) from the prescribed dosage regimen are recorded in the eCRF.

A record of the number of capsules 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 eCRF.

The Investigator will ensure that the information entered into the eCRF regarding drug administration is accurate for each participant. Any reason for noncompliance should be documented. In the situation where participants discontinue study intervention for more than 5 days per cycle, or if  $\geq 6$  consecutive planned doses of M1069 are missed for reasons other than toxicity, re-introduction can be agreed upon after consultation with the Sponsor and the review of safety and efficacy (Sections 7.1).

## 6.5 Concomitant Therapy

Record in the eCRF 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

Not applicable.

### 6.5.2 Permitted Medicines

The only permitted medications are the following:

1. Hematopoietic growth factors or blood transfusions can be used if medically indicated according to standard of care only after the DLT period of 21 days. In case administration of growth factors during the DLT period is deemed necessary by the

Investigator to prevent serious conditions, administration will be regarded as “dose limiting” if considered to be related to study intervention. In such case a DLT needs to be documented.

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

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.

### 6.5.3 Prohibited Medicines

Prohibited medicines at study entry are indicated in the exclusion criteria (see Section 5.2).

During administration of study intervention and before the EOSI Visit, any other investigational drug, chemotherapy, extensive radiotherapy (involving  $\geq 30\%$  of bone marrow) or any other anticancer therapy (cytotoxic agents, biologics or other targeted therapy) are prohibited.

The following treatments must not be administered during the study:

- Immunotherapy including interferons, immunosuppressive drugs (eg, chemotherapy or systemic corticosteroids or other experimental pharmaceutical products).
  - Exception: Endocrine replacement therapy at low dose prednisone ( $\leq 10$  mg daily) or equivalent, short term treatment of allergic reactions. Short term administration of systemic steroid (e.g., for treatment or prophylaxis of infusion-related reactions (IRRs) or prevention of hypersensitivity to concomitant medication including contrast media) or other immunosuppressant such as infliximab or mycophenolate (i.e., for allergic reactions) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are allowed. For participants with glioblastoma, steroid use is allowed.
- Any live vaccine therapies for the prevention of infectious disease within 28 days prior to study entry and during study. Administration of mRNA vaccines and inactivated vaccines is allowed (e.g., inactivated influenza vaccines); COVID-19 vaccinations or booster should be performed at least 72 hours before and not before 72 hours after the DLT period.
- Blood transfusions and growth factors are not allowed during the 21-day DLT observation period except to avoid damage to the participant. In case a blood transfusion or use of growth factors during the DLT observation period is necessary, participants are considered to have had a DLT if the underlying reason is assessed as related to the study intervention.
- Radiotherapy, with the exception of palliative short course, limited field (i.e.,  $\leq 10$  fractions and  $\leq 30\%$  bone marrow involvement or per institutional standard) radiotherapy, which may be administered during the study.

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days before the first administration of the study intervention and may not be administered during the time of study intervention administration. See Table 7 regarding drug-drug interactions.

CCI [REDACTED] Thus, drugs mainly metabolized by CYP3A4 with a narrow therapeutic index (NTI) should also be avoided during the time of study intervention administration.

CCI [REDACTED] Medications or herbal supplements known to be strong P-gp inhibitors must stop at least 7 days before the first administration of the study intervention and may not be administered during the study intervention administration.

If the administration of a nonpermitted concomitant drug becomes necessary during the study, the Medical Monitor must be contacted to discuss whether the study intervention must be discontinued.

Please see Table 7 for the list of strong inhibitors of CYP3A4, P-gp, strong inducer of CYP3A4, sensitive CYP3A4 substrate with NTI, drugs with Torsade de Pointes risk, UGT1A1 or UGT1A9 substrate with NTI.

For further reference, refer to the Food and Drug Administration Drug Development and Drug Interactions website and the University of Washington Drug Interactions Solutions website <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>, and <https://didb.druginteractionsolutions.org/>.

**Table 7 List of Prohibited Drugs and Drugs To Be Used with Caution**

Categories	Examples	Action
Strong P-gp inhibitor	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, and verapamil.	Prohibited.
Strong CYP3A4 inhibitor	boceprevir, ceritinib, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, josamycin, ketoconazole, LCL161, lonafarnib, lopinavir and ritonavir, mibefradil, mifepristone, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ribociclib, ritonavir, saquinavir and ritonavir, telaprevir, telithromycin, tipranavir and ritonavir, telithromycin, troleandomycin, tucatinib, VIEKIRA PAK, voriconazole.	
Strong CYP3A4 inducer	apalutamide, avasimibe, carbamazepine, enzalutamide, ivosidenib, lumacraftor, mitotane, phenobarbital, phenytoin, rifampin, rifapentine, St. John's wort ( <i>Hypericum perforatum</i> ).	
Sensitive CYP3A4	abemaciclib, acalabrutinib, bosutinib, cobimetinib, conivaptan, dasatinib, dronedarone, entrectinib, everolimus, lomitapide,	

Categories	Examples	Action
substrate with NTI	midostaurin, neratinib, sirolimus, tacrolimus, tolvaptan, venetoclax, zanubrutinib.	
Drugs associated with Torsade de Pointes	amiodarone, chlorpromazine, clarithromycin, disopyramide, dofetilide, erythromycin, haloperidol, methadone, procainamide, quinidine, sotalol.	
CYP3A4 and UGT1A1 substrate with NTI	Irinotecan.	
UGT1A9 substrate with NTI	Not applicable	Use with caution.
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## 6.5.4 Other Interventions

In vitro studies suggest M1069 is an inhibitor of UGT1A1 and UGT1A9, and clinical DDI risk may exist with their substrates at high M1069 concentrations. Thus, drugs as substrates of these enzymes with a narrow therapeutic index as judged by the Investigator (and after optional consultation with the Sponsor) should be used with caution or avoided if possible, during the time of study intervention administration.

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## 6.6 Dose Selection and Modification

Dose escalation, expansion or de-escalation will proceed according to the SMC recommendation. The SMC will provide recommendations on the next dose level based on safety, tolerability, and available preliminary PK and, if appropriate, Pd data. The SMC receives outputs of a Bayesian dose toxicity model with estimated DLT probabilities for potential next dose levels to support the SMC recommendation. The Bayesian model 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 [Appendix 8](#). The SMC may also recommend a change in regimen to the following prespecified regimens: administration of M1069 QD instead of BID.

Further details on the SMC are provided in Section 6.6.2.

### **6.6.1                      Retreatment Criteria**

Not applicable.

### **6.6.2                      Safety Monitoring Committee (SMC)**

During the dose escalation part of the study, the SMC will evaluate the safety (including DLTs), tolerability and available PK, and available Pd data. The SMC will decide on dose escalation, de-escalation, additional enrolment on same dose level, dosing regimen, MTD, suspension of enrolment.

In cases where enrolment of the last participant in a dosing cohort was delayed the SMC may decide (based on available data) upon enrolment on a 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 emerging data at a subsequent meeting. An ad-hoc meeting will be convened if this participant experiences a DLT.

The SMC recommends an RDE but the determination of the RDE is made by the Sponsor. For RDE criteria see Section 4.1.

The SMC can recommend modifying the schedule of administration. Based on the observed toxicity profile and available PK, dose level(s) that are different than, or higher or lower than the prespecified doses may be tested (see Section 9.4.2.1).

The SMC can decide to change the dosing regimen and administration condition to the following:

- Once daily
- Administration under fed conditions

The SMC may recommend to start a new cohort under fed with low-fat meal conditions depending on the nature of reported gastrointestinal and other adverse events (see Section 5.3.1 for details).

The usual cohort size is 3 participants, but the SMC can modify the size of cohorts. The specific working procedures will be described in an SMC charter, which will be established before first informed consent signed.

### **6.6.3                      Definition of Dose-limiting Toxicity**

A DLT is defined as any of the following AEs according to the NCI-CTCAE v5.0 assessed by the Investigator /or the Sponsor at any dose and judged not to be related to the underlying disease or any previous or concomitant medication or concurrent condition occurring during the DLT observation period (21 days starting on the day of first administration of study intervention on C1D1).

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 v 5.0 attributable to the treatment regimen or if more than 1 DLT is seen in dose level 1.

The treatment with transfusions or growth factors (e.g., granulocyte-colony stimulating factor [G-CSF], erythropoietin) is not permitted during the DLT period and if it occurs will be considered a DLT unless the reason for use is clearly attributable to the underlying disease or extraneous causes (also see Sections 6.5.2 and 6.5.3).

Participants who develop a DLT will permanently discontinue study intervention. Any DLT must be confirmed by the SMC. In exceptional cases, the SMC may decide on re-introduction of the study intervention after careful evaluation of clinical data of the individual participant.

AEs judged as DLT will include:

- Any Grade  $\geq 3$  **non-hematologic** AE with **exception** of:
  - Single laboratory value(s) abnormality that has no clinical correlate, and resolves to Grade  $\leq 1$  or to baseline within 7 days with adequate medical management or asymptomatic Grade  $\geq 3$  amylase or lipase elevation not associated with clinical symptoms of pancreatitis
  - Diarrhea persisting  $\leq 72$  hours after initiation of medical management
  - Nausea and vomiting of  $\leq 72$  hours duration with adequate and optimal therapy
  - Transient ( $\leq 72$  hours) Grade 3 fatigue, local reactions, flu-like symptoms, fever, headache, hypertension that resolves to Grade  $\leq 1$  with adequate treatment
  - Grade 3 non-recurrent skin toxicity that resolves to Grade  $\leq 1$  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  $\leq 2$  within 6 days
  - Any autoimmune thyroid-related toxicity that clinically resolves to  $\leq$  Grade 2 within 7 days of initiating therapy.
  - Any death clearly due to the underlying disease or extraneous causes
- Any Grade  $\geq 4$  hematologic AE, including:
  - Grade  $\geq 3$  neutropenia with clinical signs/symptoms, such as fever  $> 38.3$  degrees C (e.g., for febrile neutropenia, an ANC  $< 1000/\text{mm}^3$  with single temperature of 38.3 degrees C [101 degrees F] or a sustained temperature of  $\geq 38$  degrees C [100.4 degrees F] for more than one hour)

- Grade  $\geq 3$  thrombocytopenia with medically concerning bleeding

**Exceptions:**

- Isolated Grade 4 lymphopenia without clinical correlate
- Any Grade 4 neutropenia or thrombocytopenia of  $< 7$  days duration not associated with any clinical symptoms

Further DLTs include:

- Hy's law: Evidence of hepatocellular toxicity without clear alternative reason to explain the observed liver-related laboratory abnormalities, such as increase in AST or ALT of  $\geq 3 \times \text{ULN}$  elevation and elevation of serum total bilirubin  $\geq 2 \times \text{ULN}$ , without initial findings of cholestasis (elevated serum ALP) or other apparent clinical causality (e.g., viral hepatitis A, B, C or co-medication). For patients with hepatic metastases, AST or ALT  $> 8 \times \text{ULN}$  or AST or ALT  $> 5 \times \text{ULN}$  for  $\geq 14$  days.

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- Any interruption/delay of study drug  $\geq 5$  days to prevent a DLT

Additionally, the SMC may identify as a DLT:

- An AE (inside or outside of the DLT period), including CCI [REDACTED] that in the opinion of the SMC is of potential clinical significance such that further dose escalation would expose participants to unacceptable risk.

#### 6.6.4 Dose Modification Outside of the DLT Period

Participants who experience a Grade  $\geq 3$  nonhematological AEs (for exceptions see DLT criteria) or Grade 4 hematological AEs, after completion of the DLT assessment period, will need to interrupt study treatment. However, participants may continue on study treatment of M1069 at a reduced dose provided the reaction has resolved to baseline value or Grade  $\leq 1$  within 2 weeks and there is no progressive disease. The dose of M1069 will be reduced by at least one dose level. If indicated, a further dose reduction is possible. Re-escalation of M1069 dose escalation

to the original level should not be considered for an individual participant once dose modification has been applied for safety or tolerability reasons. For dose modification for general toxicity see Table 8 and for ophthalmological see Table 9.

**Table 8 Recommended Temporary Treatment Discontinuation for M1069 for General Toxicity (outside of DLT Period)**

<b>Organ involved</b>	<b>Specifics</b>	<b>Toxicity NCI-CTCAE 5.0 Grade</b>	<b>Management of Toxicity with permanent Discontinuation or Dose Interruption and Modification</b>
Renal	Creatinine increased	Grade 3	Hold M1069 until recovery to Grade $\leq$ 1 or baseline.  Upon recovery or returning to baseline, dosing may continue at same, or the previous lower dose level based on clinical judgment.
Hepatic	Increased AST /ALT	Grade 3	Isolated occurrence and not related to liver metastases; repeat test within 72 hours; if persistent or worsening, may hold off the M1069 until recovery to Grade $\leq$ 1 or baseline, based on Investigator's clinical judgement.
	Increased total bilirubin	Grade 3	Isolated occurrence and not related to liver metastases; repeat test within 72 hours; if persistent or worsening, may hold off the M1069 until recovery to Grade $\leq$ 1 or baseline, based on Investigator's clinical judgement.
Other nonhematological toxicities	i.e., diarrhea, vomiting; GI hemorrhage	Grade 3	Withhold M1069 administration until recovery to Grade $\leq$ 1, or to baseline.  Gastrointestinal symptoms such as nausea and vomiting can be treated as per local institutional guidelines.
	Other	Grade 3+	Hold M1069 based on Investigator's clinical judgement.

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; DLT = Dose-limiting toxicity; GI = Gastrointestinal, NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events.

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## **6.7 Study Intervention After the End of the Study**

The Sponsor will not provide 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

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for clinical response/tumor assessment. The SoA specifies data to be collected at the time of discontinuation of study intervention and follow-up and any further evaluations that need to be completed. Importantly, tumor assessments will be continued during the follow-up period until confirmed PD according to the SoA.

Participants must be withdrawn from study interventions if any of the following occurs:

- General important safety concerns:

A participant's study intervention should be discontinued if the Investigator believes that for safety reasons (e.g., AE) it is in the participant's best interest.

- Occurrence of DLT during the DLT observation period:

Participants experiencing DLTs as described in Section 6.6.3 will not receive further study intervention. When the resumption of treatment following the resolution of a DLT is deemed in the best interest for the participant, the Medical Monitor and the Sponsor Medical Responsible should be consulted to discuss.

- Cardiac changes (e.g., QTc):

If a clinically significant finding is identified (including changes from baseline in QT interval corrected using Fridericia's formula [QTcF] by >60 ms or above 500 ms after start of treatment), the Investigator or qualified designee upon consultation with the Sponsor's Medical Responsible will determine if the participant can continue in the study and if any change in participant management is needed. While increases in QT/QTc to > 500 ms or of > 60 ms over baseline are commonly used as thresholds for potential discontinuation, the exact criteria chosen for this study will depend on the risk-benefit level considered appropriate for the participant in question. This review of the ECG at the time of collection will be documented. Any new clinically relevant finding is reported as an AE. The final decision on the continuation of treatment upon the emergence of clinically significant AEs remains with the Investigator.

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- CCI [REDACTED]
- Pregnancy:  
See also Section 8.3.5
- Disease progression:  
Progressive Disease (PD) as defined by RECIST v1.1 while on treatment. Participants who experience PD may continue treatment with study interventions under conditions described in Section 7.1.1 if the Investigator believes the participant will experience clinical benefit from the treatment and there is no unacceptable toxicity resulting from the treatment. Such participants will be withdrawn from the treatment if any other criteria for withdrawal are met or if alternative treatment options are available and indicated.
- Clinical deterioration:  
If a patient experiences significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms or therapeutic failure requiring urgent alternative anticancer treatment (if available), discontinuation of the study intervention should be considered after discussion with the Medical Monitor.
- Missed doses:  
A participant's study intervention can be re-introduced after a safety-related interruption and temporary discontinuation if the participant's underlying disease is thought to benefit from re-introduction of the intervention at the discretion of the Investigator.
- Prohibited concomitant medication:  
If the administration of a prohibited concomitant medication becomes necessary during the study, study intervention will be discontinued. The Investigator may contact the Medical Monitor to discuss if the study intervention may be continued after application of a prohibited concomitant medication if patient is expected to benefit from a continuation of treatment.
- Other reasons:  
The participant will be withdrawn from the study intervention if any of the following occurs: discontinuation of or noncompliance with the study intervention or failure to attend scheduled assessments that are deemed necessary for the participants' safety or study integrity for more than 2 weeks in the absence of any medical reasons.

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

### **7.1.1 Treatment Beyond Initial Progression**

Participants will receive M1069 as study interventions as outlined in the SoA until confirmed disease progression. Study interventions may continue past the initial determination of disease progression according to RECIST v1.1 as long as the following criteria are met:

- No new symptoms or worsening of previous symptoms (including laboratory values) indicating disease progression
- Tolerance of study intervention
- Stable ECOG PS
- Study intervention beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

A radiographic assessment should be performed within 4 to 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with study intervention.

### **7.1.2 Treatment Beyond Confirmed Progression**

After confirmed PD, if the Investigator feels that the participant continues to achieve clinical benefit by continuing administration of study intervention, the participant should remain on the intervention and continue to receive monitoring according to the SoA. The decision to continue administration of study intervention beyond confirmed PD should be discussed with the Medical Monitor and documented in the study records.

Participants who continue beyond confirmed progression will be followed as per the protocol schedule. Study interventions should be discontinued permanently upon documentation of further, unequivocal, disease progression unless there are no alternative therapeutic options and the benefit-risk assessment is favorable in consultation between the Investigator and the Medical Monitor and Medical Responsible. Treatment will also be discontinued once any other criteria for withdrawal are met.

### **7.1.3 Continuation of Study Intervention After Local Treatment of Disease Progression**

If disease progression is due to brain metastasis, participants may continue study interventions after the local treatment of the brain lesions provided that the above criteria (Section 7.1.1) are met in addition to the following:

- Tumor assessment showing disease progression of brain lesion has been performed and was documented according to RECIST v1.1 prior to the procedure.

- Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to re-initiation of study interventions.
- There are no ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable).
- Participants must be either off steroids or on a stable or decreasing dose of  $\leq 10$  mg daily prednisone (or equivalent).
- Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

In addition, if disease progression is mainly due to a metastatic lesion which in the opinion of the Investigator may be surgically removed, participants may continue study interventions after the local treatment of such a lesion provided that:

- Tumor assessment showing disease progression has been performed and was documented according to RECIST v1.1 prior to the procedure.
- It has been at least 2 weeks and the participant has fully recovered from the surgery.
- Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

#### **7.1.4 Rechallenge**

Not applicable.

### **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 SoA. The SoA 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 must document this in the site study records.

### 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 must be taken if a participant fails to return to the clinic for a required study visit:

- The site must 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 must 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 should 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 SoA.

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 SoA, 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 SoA.

## 8.1 Efficacy Assessments and Procedures

Computed tomography (CT) or magnetic resonance imaging (MRI) scans will be performed and collected until confirmed PD is assessed by the Investigator according to RECIST v1.1 ([Eisenhauer 2009](#)) or until start of new anticancer therapy in case of continuation of study intervention beyond PD, according to the SoA (Section 1.3) and definition of local treatment of disease progression (Section 7.1.3).

All images should be available for collection and potential retrospective central analysis.

Radiographic images and physical findings (physical assessments) will be used by the Investigator for the local determination of PD and participant's treatment decisions.

For each participant, tumor response assessment will be performed by CT scan or MRI (if MRI is used, chest CT is mandatory) imaging of the chest/abdomen/pelvis (plus other regions as specifically required) and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual participant. All scans performed at Screening and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent visits. In general, lesions detected at Screening need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

For each participant, the Investigator will designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and/or metastatic tumor masses, physical examination findings, and the results of other assessments. All available images collected during the study period will be considered. The most appropriate measures to evaluate the tumor status of a participant should be used. The measure(s) to be chosen for sequential evaluation during the study must correspond to the measures used to document the progressive tumor status that qualifies the participant for enrolment. The tumor response assessment will be assessed and listed according to the SoA (Section 1.3).

Treatment decisions will be made by the Investigator based on the Investigator's assessment of disease status. Investigator's assessment of objective tumor response to treatment will be performed according to RECIST v1.1 (all measurements should be recorded in metric notation, as described in RECIST v1.1).

- At Baseline, tumor lesions will be categorized in target and non-target lesions as described in RECIST v1.1.
- Results for these evaluations will be recorded with as much specificity as possible so that pretreatment and post-treatment results will provide the best opportunity for evaluating tumor response.
- Any complete response (CR) or partial response (PR) should be confirmed, preferably at the next subsequent scheduled imaging interval, but no sooner than 6 weeks after the initial documentation of CR or PR.
- The Investigator may perform scans in addition to a scheduled study scan for medical reasons or if the Investigator suspects PD. Participants who withdraw from the investigational

treatment for clinical or symptomatic deterioration before objective documentation of PD or who discontinue from investigational treatment for reasons other than objective PD will be requested to continue appropriate imaging according to the study schedule until determination of confirmed PD or discontinuation from the study, whichever occurs earlier. Every effort should be made to confirm a clinical diagnosis of PD by imaging.

## **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, 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**

Physical examination will be performed at the time points specified in the Schedule of Activities in Section 1.3.

- A complete physical examination will include, at a minimum, assessments of the dermatological, pulmonary, cardiovascular, gastrointestinal, genitourinary, lymphatic, neurologic and musculoskeletal systems, head/neck, extremities, eyes, ears, nose, throat, cognitive status and general appearance.
- A brief physical examination will include, at a minimum, assessments of the general appearance, pulmonary, cardiovascular, gastrointestinal and eyes.
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

### **8.2.2 Vital Signs**

Vital signs will be measured at the time points specified in the Schedule of Activities (Section 1.3).

- Height (at Screening only) and weight will be measured and recorded.
- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed 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 (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at

intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

### 8.2.3 Electrocardiograms

All types of ECGs will be recorded using the same ECG device (Holter recorder). The Holter recorder will be connected to a provided laptop which will allow to print out safety ECGs locally or upload digital ECGs for centralized reading.

#### Safety ECGs

- Triplicate 12-lead ECGs will be obtained as outlined in the SoA using an ECG machine (Holter recorder) that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTcF intervals. At the time of the ECG measurements for the QT/QTc analysis, the Holter recorder can be used for safety ECG and for triplicate digital ECGs.
- The safety ECG should be performed after at least 10 minutes rest in a supine position prior to blood sampling and will be read locally by a physician for real time monitoring. When a clinically significant finding is identified, see Section 7.1 for details regarding discontinuation criteria.

#### Holter ECG for QT/QTc Evaluation

- Holter ECGs will be obtained as outlined in the SoA.
- Holter ECGs should be recorded for approximately 24 hours on C1D-1, and from at least 1 hour before until 8 hours after the first dose on C1D1 and C1D8. The participants should be put in a supine position at least 15 minutes prior to blood sampling, to allow 10 minutes rest and 5 minutes ECG extraction. Triplicate digital ECGs will be extracted from continuous Holter ECGs at predose (-45, -30, -15min), 1h, 2h, 4h, 6h and 8h on C1D1 and C1D8. The data will be archived in digital format using a central ECG vendor and will be analyzed by a specialized central laboratory.

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If the participant discontinue treatment before C3D1(+/- 7 days), CCI

When a clinically significant finding is identified, see Section 7.1 for details regarding discontinuation criteria.

### 8.2.5 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 SoA. All samples will be clearly identified.

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 the local laboratory.

The Sponsor or designee 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 or designated organization.

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 eCRF. The laboratory reports will be filed with the source documents.

Pregnancy testing ( $\beta$ -HCG from serum sample at Screening and from urine or serum sample for all other cycles) will be conducted at the timepoints specified in the SoA.

### 8.2.6 Suicidal Ideation and Behavior Risk Monitoring

Not applicable

## 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.

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

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the Safety Follow-up Visit at the time points specified in the SoA (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 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 AEs of Special Interest (as defined in Section 8.3.8) 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 SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators within 15 days.

An Investigator or sub-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 the safety reports and confirm completion of this review. This information will be filed in the Investigator's Site File, and the IRB/IEC will be notified, if appropriate, according to applicable local laws/regulations and site SOPs.

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 female partners of male participants will be collected after the start of study intervention and until 30 days after the last dose.

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 M1069.
- 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 be withdrawn from the study.

### **8.3.6 Cardiovascular and Death Events**

Death and cardiovascular events (meeting the SAE definition) will be reported as per the reporting guidelines specified in [Appendix 4](#).

The following disease-related events (DREs) are common in participants with cancer and can be serious/life-threatening:

- Because these events are typically associated with the disease under study, it will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded on the applicable eCRF page within the appropriate time frame.

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

- The Investigator considers that there is a reasonable possibility that the event was related to study intervention.

Data from preclinical investigations in albino rats have suggested a potential for adverse retinal findings associated with administration of M1069. To evaluate the ophthalmological impact on study participants, the following ophthalmological findings are considered Adverse Events of Special Interest and should be reported within 24 hours to the Sponsor:

## 8.4 Treatment of Overdose

For this study, any dose of M1069 greater than the maximum dose in the study or in the program that is considered safe and well tolerated within a 24-hour time period will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

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

## 8.5 Pharmacokinetics

Whole blood samples of approximately 6 mL per collection for measurement of plasma concentrations of M1069. Collection times are specified in Table 2 of the SoA.

The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration. In addition, the actual date and time (24-hour clock time) of the study intervention administration prior to sample collection should be recorded in the eCRF. The sampling timing may be altered with the recommendation of SMC during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations, to add 24h post-dose sampling for QD dosing) to ensure appropriate monitoring.

The quantification of M1069 in plasma will be performed using a validated method. Concentrations will be used to evaluate the PK of M1069. Remaining samples collected for analyses of M1069 concentration may also be used for CCI assessment of metabolites of M1069, or CCI and transporters, or safety or efficacy aspects related to concerns arising during or after the study.

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

The following M1069 PK parameters will be calculated, when appropriate (see Table 10). A non-compartmental analysis (NCA) will be performed to estimate these PK parameters for M1069. Other PK parameters might be added based on emerging data. Details will be included in the Integrated Analysis Plan.

Considering the confounding effects from caffeine on PK-Pd relationship, caffeine intake is prohibited 48-hour before the dosing until after collection of the PK samples on C1D1 and C1D8. The daily caffeine intake information should be recorded in the diary.

**Table 10**                      **Assessment of Plasma Pharmacokinetic Parameters**

Symbol	Definition
$AUC_{0-t_{last}}$	The AUC from time zero (= dosing time) to the time of the last quantifiable concentration ( $t_{last}$ ).
$AUC_{0-t_{last}}/Dose$	The dose normalized $AUC_{0-t_{last}}$ .
$AUC_{\tau}$	The AUC over the dosing interval $\tau$ .
$AUC_{\tau}/Dose$	The dose normalized $AUC_{\tau}$ .
$AUC_{0-\infty}$	The AUC from time zero (= dosing time) up to infinity with extrapolation of the terminal phase.
$AUC_{0-\infty}/Dose$	The dose normalized $AUC_{0-\infty}$ .
$CL/F$	The apparent total body clearance following extravascular administration.
$C_{max}$	Maximum observed concentration.
$C_{max}/Dose$	The dose normalized $C_{max}$ .
$C_{trough}$	The concentration observed at the end of a dosing interval immediately before next dosing.
LI	The linearity index after repeated administration.
$R_{acc}(AUC_{0-8})$	The accumulation ratio of $AUC_{0-8}$ after repeated administration.
$R_{acc}(C_{max})$	The accumulation ratio of $C_{max}$ after repeated administration.
$t_{1/2}$	The terminal half-life.
$t_{max}$	The time to reach the $C_{max}$ in a dosing interval.
$V_z/F$	The apparent volume of distribution during the terminal phase following extravascular administration.

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8.7

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- CCI [REDACTED]

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- CCI [REDACTED]

[REDACTED]

CCI [REDACTED]

[REDACTED]

## 8.9 Immunogenicity Assessments

Not applicable.

## 8.10 Health Economic

Not applicable.

## 9 Statistical Considerations

All analyses will be prepared by dose level and will be described in detail in the Integrated Analysis Plan (IAP).

There is no formal family-wise type I error control for this study, as such all analyses are considered descriptive.

## 9.1 Statistical Hypotheses

This is an exploratory study. No formal statistical hypothesis will be tested, and all analyses are considered descriptive.

CCI

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 9.3 Populations for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock (except for the DLT analysis set). For the DLT analysis set the decision is taken by the SMC.

<b>Analysis Set</b>	<b>Description</b>
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's study intervention status in the study.
Safety (SAF)	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
DLT	<p>The DLT Set will include all participants who received at least one dose of study intervention and meet at least one of the following criteria:</p> <ul style="list-style-type: none"> <li>• Experienced at least one DLT during the DLT period, regardless of the administered number of doses of study intervention/completion in the DLT period.</li> <li>• Received at least 80% of the planned cumulative dose during the DLT period.</li> <li>• Additionally, participants who did not receive at least 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.</li> </ul> <p>The final decision on evaluability for dose escalation analysis will be made by the SMC (e.g. considering relevant deviations from dosing schedule).</p>
PK	All participants, who receive at least one dose of study intervention and provide at least one measurable post-dose concentration. Participants will be analyzed per the actual study intervention they received.
Pd	<p>All participants, who receive at least one dose of study intervention, have no important events affecting Pd and provide at least one measurable PD endpoint post-dose.</p> <p>Participants will be analyzed per the actual study intervention they received. All PD analyses will be based on this analysis population.</p>

## 9.4 Statistical Analyses

In general, continuous variables will be summarized using number of participants (n); mean, standard deviation; median, 25<sup>th</sup> Percentile to 75<sup>th</sup> Percentile (Q1-Q3), minimum, and maximum. If there are less than 5 observations available only mean and the observed data will be given.

Categorical variables will be summarized using frequency counts 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.

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

Except for the analysis of DLTs, all analyses will be performed on the Safety Analysis population.

#### 9.4.1 Efficacy Analyses

Endpoint	Category	Statistical Analysis Methods/Further Estimand Attributes
OR	Main	<p>Objective response rate will be determined as the proportion of participants with a confirmed objective response of PR or CR. Confirmation of response according to RECIST v1.1 will be required no sooner than 6 weeks after the initial documentation of CR or PR.</p> <p>The 95% two-sided Confidence interval for the ORR will be calculated using the Clopper Pearson method.</p>
DoR, PFS	Main	<p>Kaplan-Meier estimates (product-limit estimates) will be presented for the analysis of DoR and PFS together with a summary of associated statistics (median, survival time and survival rate estimates at 3, 6, 12 months and every 6 months thereafter if applicable) including the corresponding 2-sided 95% CIs.</p> <p>DoR is defined, for participants with an objective response, 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. The censoring rules for DoR are as described below for PFS.</p> <p>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. PFS 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 2 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</p>

Endpoint	Category	Statistical Analysis Methods/Further Estimand Attributes
		assessments will be censored at the date of the start of study intervention.
CCI		

CI = Confidence interval, CR = Complete response, DoR = Duration of response; PD = Pharmacodynamic, PFS = Progression-free survival, PR = Partial response; OR = Objective response; ORR = Objective response rate, RECIST = Response Evaluation Criteria in Solid Tumors.

## 9.4.2 Safety Analyses

Except for the analysis of DLTs (a primary endpoint), all safety analyses will be performed on the Safety Analysis population.

Endpoint	Category	Statistical Analysis Methods/Further Estimand Attributes
DLT	Main	Bayesian logistic regression analysis as described in <a href="#">Appendix 8</a> . At end of dose escalation analysis and main analysis, the number and proportion of participants experiencing DLTs will be reported by dose level, based on observations during the first study intervention cycle. Posterior probabilities (2.5%, 25%, 50%, 75%, 95% and 97.5% quantiles) for DLT probabilities at selected doses will be estimated from the Bayesian logistic regression model.
DLT	Sensitivity	2 parameter frequentist modeling (without prior).
AEs, Treatment-Related Adverse Event	Main	TEAEs are defined as AEs emerging or worsening after start of treatment until 30 days after end of treatment. Adverse events will be coded according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded by the Investigator using the NCI-CTCAE (Version 5) toxicity grades. Treatment-related AEs will be

		defined as any AE considered as related to M1069 according to Investigator. Incidence of TEAEs and treatment-related AEs summarized by SOC and PT.
Deaths	Main	Counts and percentages.
Changes in laboratory measurements and vital signs	Main	Summary statistics and line plots. 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.
CCI		

AE = Adverse event, DLT = Dose-limiting toxicity, IAP = Integrated analysis plan, MedDRA = Medical Dictionary for Regulatory Activities, NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, PT = Preferred Term, SOC = System Organ Class, TEAE = Treatment-emergent adverse event.

### 9.4.2.1 Dose Escalation

Analyses to decide on dose escalation will be performed on the DLT set and will be based on concentration available safety, preliminary PK and available Pd data. To support the decision on dose escalation, the SMC will receive results of a Bayesian dose toxicity model, including the recommendation of the next dose level. This Bayesian two-parameter logistic regression model (Neuenschwander 2008) is further specified in [Appendix 8](#). For each SMC meeting, the model will be updated with the number of DLTs and evaluable participants per dose level. The following dose levels are foreseen: 150, 300, 450, 600, and 700 mg BID. If deemed necessary based on obtained pharmacological data, higher dose levels than 700 mg BID with an increase by 15% may be recommended by the SMC. Participants will receive study intervention twice daily with a food restriction for 2 hours before and 1 hour after dose administration. However, the SMC may decide to investigate different doses, dosing regimen and dosing conditions (see Section 6.6.2).

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 dosing of M1069 to once daily instead of twice daily. In such a case the dose toxicity model will be extended, or a separate model will be set up.

The MTD will be defined by the SMC. The target DLT probability for the MTD suggested by the Bayesian model is 30%. The prerequisites for the MTD suggestion from the model are described in the [Appendix 8](#).

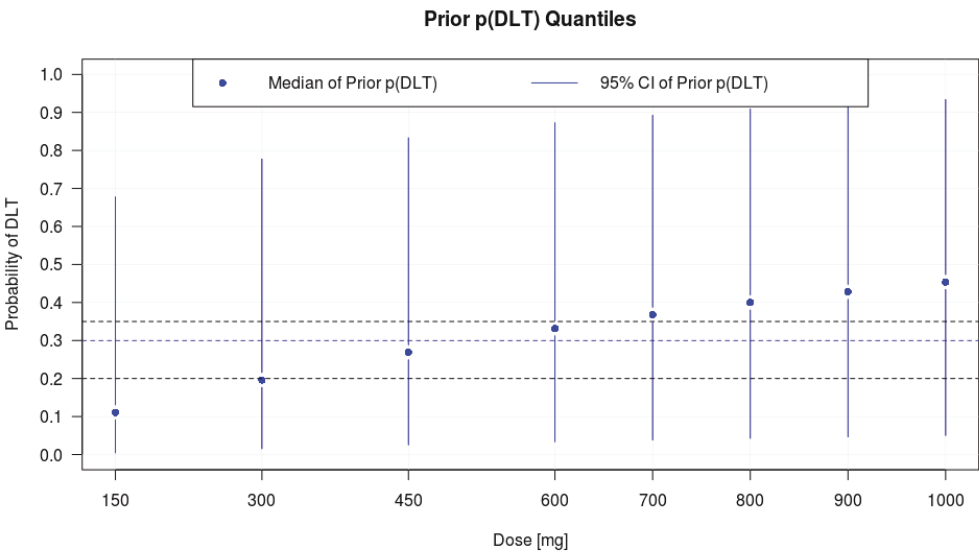
Analyses for the Bayesian dose escalation will be performed on the DLT set. Usually, decisions on dose escalation are taken once all participants of the most recent cohort have completed the DLT period or dropped out. In exceptional cases, however, the SMC may decide on the next cohort earlier, i.e., before the last participant of a cohort has finished the DLT period (considering the model recommendation). Per definition of the DLT 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 (if criteria for the Dose escalation set are fulfilled).

Details on analyses for SMCs will be described in the SMC IAP.

Before first dosing, the assumed relationship between dose level and toxicity is specified through the prior distribution. The prior distribution chosen for this trial corresponds to the following:

Probability for DLT	150 mg	300 mg	450 mg	600 mg	700 mg
Prior mean	CCI				
Prior median					

DLT = Dose-limiting toxicity.



Details of the model, including the prior distribution are described in [Appendix 8](#).

CCI

CCI  
CCI

### 9.4.3.1 Pharmacokinetic Profile

Estimation of Individual PK Parameters:

- Pharmacokinetic parameters will be calculated using standard non-compartmental methods and the actual administered dose.
- Non-compartmental computation of PK parameters will be performed using the computer program Phoenix® WinNonlin® version 6.3, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).
- The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.1 or higher) may be used to produce tables, listings and figures and in the calculation of PK Parameters if appropriate.

Pharmacokinetic analyses will be specified in the IAP finalized before database lock. More details on the PK parameters planned to be analyzed are described in Section 8.5.

CCI

### 9.4.4 Sequence of Analyses

The SMC will review available data during study conduct. The cutoff 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 the 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 Cycle 1. 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, cutoff can be earlier (after the DLT period of the first 2 participants are finished or they experienced a DLT).

Primary Analysis: The cutoff for the primary analysis will be LSLV or 13 weeks after LSFD, whichever comes first.

Follow-up analyses to report further efficacy and safety data will be done once the End of Study has been reached.

Additional analysis during the study might be conducted, e.g., for publication or decision making purposes.

More details will be described in the IAP.

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## 11 Appendices

### Appendix 1 Abbreviations

A <sub>2A</sub> /2 <sub>B</sub>	Adenosine Receptor 2A/2B
ADL	Activity of daily living
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CCI	
BID	Twice daily
BLRM	Bayesian 2-parameter logistic regression model
C	Cycle
CIOMS	Council for International Organizations of Medical Sciences
CR	Complete Response
CREB	cAMP response element-binding protein,
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
CYP	Cytochrome P450
D	(Study) Day
DDI	Drug-drug interaction
DL	Dose level
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DRE	Disease-related event
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

EOSI	End of Study Intervention
ETDRS	Early Treatment Diabetic Retinopathy Study
EZ-line	Ellipsoid line
FDA	U.S. Food and Drug Administration
FFPE	Formalin-fixed Paraffin-embedded
FIH	First in Human
FSH	Follicle-stimulating hormone
FU	Follow-up
GI	Gastrointestinal
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Human equivalent dose
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-severely Toxic Dose
HRT	Hormonal replacement therapy
IAP	Integrated Analysis Plan
IMP	Investigational Medicinal Product
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone releasing system
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
INR	International Normalized Ratio
IRB	Institutional Review Board

LAM	lactational amenorrhoea method
LSFD	Last Subject First Dose
LSLV	Last Subject Last Visit
MD	Mean Deviation
MedRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NOAEL	No observed adverse effect level
NTI	Narrow therapeutic index
CCI	
OR	Objective response
ORR	Objective response rate
CCI	
PD	Progressive disease
Pd	Pharmacodynamic
PFS	Progression-free survival
PK	Pharmacokinetics
P-gp	P-glycoprotein
PGx	Pharmacogenetic
PR	Partial Response
PT	Preferred Term
QD	Once daily
QSP	Quantitative system pharmacology
QTcF	QT interval in the ECG, corrected by Fridericia formula
RDE	Recommended Dose for Expansion
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
CCI	
SMC	Safety Monitoring Committee

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SmPC	Summary of Product Characteristics (European Union)
SoA	Schedule of Activities
SoC	System Organ Class
STD	Severely toxic dose
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse events.
TME	Tumor microenvironment
Tregs	Regulatory T-cells
USPI	Prescribing Information (United States)
VEGF	Vascular endothelial growth factor
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 and answer all questions on the study.

Participants will be informed that their participation is voluntary.

Participants or their legally-authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; the Japanese ministerial ordinance on GCP 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 sign a new ICF.

### Data Protection

The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Rescreened participants will be assigned a new participant number. 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 study will be conducted at approximately 3 study sites in North America, including approximately 2 study sites in the US. 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 registries: 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 will be a SMC member. The SMC may modify the frequency of meetings as deemed appropriate during the study. See Section 6.6 for more details.

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

- IQVIA central laboratory services (Q2S)
- Clinical data management study design and programming
- Clinical ancillary supplies services
- Clinical data management
- Clinical operations
- Feasibility
- Global site services
- Medical monitoring
- Operational planning
- Pharmacovigilance and Drug safety services
- Project financial analysts
- Project management
- Project vendor management.

- Catalent is responsible for drug supply and distribution responsibilities (e.g., use of regional distribution centers).
- The IRT (interactive response technology) will be used to trigger supply/re-supply of IMP to sites, assign unique participant numbers, allocate participants to study intervention group at enrollment visit, and to provide study intervention to participants at each study intervention visit.
- ERT (eResearchTechnology, Inc) (ECG) monitoring will be performed as specified in the SoA for end of study central QTc analysis.
- The Sponsor is responsible for supply and manufacture of M1069 and for study oversight.
- 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 questions.

## **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 CSR 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.

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff who had been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study intervention and therefore may be disclosed as required to other clinical Investigators, to the US Food and Drug Administration, and to other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study. No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement.

## **Data Quality Assurance**

All participant study data will be recorded on printed or electronic eCRFs 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 eCRF. Details for managing eCRFs are in the Data Management Plan.

The Investigator will maintain accurate documentation (source data) that supports the information in the eCRF.

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 eCRF 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 eCRFs 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:

#### WOCBP:

A woman is of childbearing potential (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.

#### Postmenopause:

Postmenopause is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement ( $> 40$  IU/L or mIU/mL) is required.
- A female on HRT and whose menopausal status are 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.

#### Permanent sterilization:

For this study, permanent sterilization includes:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

For individuals 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.

## Contraception Guidance:

<b>CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:</b>
<p><b>Highly Effective Methods That Have Low User Dependency</b></p> <p>Implantable progestogen-only hormone contraception associated with inhibition of ovulation</p> <p>IUD</p> <p>IUS</p> <p>Bilateral tubal occlusion</p> <p>Azoospermic partner (vasectomized or due to a medical cause)</p> <p>Azoospermia is a highly effective contraceptive method provided the partner is the sole sexual partner of the 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.</p> <p>Documentation can come from the site personnel's review of the individual's medical records, medical examination, or medical history interview.</p>
<p><b>Highly Effective Methods That Are User Dependent</b></p> <p>Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation</p> <p>Oral</p> <p>Intravaginal</p> <p>Transdermal</p> <p>Injectable</p> <p>Progestogen-only hormone contraception associated with inhibition of ovulation</p> <p>Oral</p> <p>Injectable</p> <p>Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.</p>
<p><b>Barrier Methods (to be used in addition to a highly effective method)</b></p> <p>Male or female condom with or without spermicide</p> <p>Cap, diaphragm, or sponge with spermicide]</p>
<p>Notes:</p> <ul style="list-style-type: none"> <li>Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants.</li> <li>Highly effective methods are those with a failure rate of &lt;1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.</li> <li>"Hormonal contraception may be susceptible to interaction with the study intervention(s), which may reduce the efficacy of the contraceptive method. As such, 1) barrier methods (male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide) in addition to hormonal contraception or 2) a non-hormonal intrauterine device must be used".</li> <li>If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.</li> <li>Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure from friction).</li> </ul>

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

### 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, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- 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 a SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or a SAE if they fulfill 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, or expected progression, signs, or symptoms of the disease/disorder being studied.
- 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 his/her condition and/or unless the outcome is fatal within the AE reporting period, as defined in Section 8.3.1.

## Other Adverse Events to be Reported Using a Specialized Procedure or Form:

- Any case of overdose, whether or not associated with an AE (serious or non-serious), must be recorded in the eCRF and reported to the Sponsor in an expedited manner using the SAE and Overdose Report Form.
- Pregnancies and their outcomes must be reported to the Sponsor using the Pregnancy Report Form. In case of an abnormal outcome, the SAE report form (when the subject sustains an event) and the Parent-Child/Fetus Adverse Event Report Form (when the child/fetus sustains an event) must be transmitted to the Sponsor.

## 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).

A SAE is defined as any untoward medical occurrence that, at any dose:	
a)	Results in death
b)	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.	
c)	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 fulfills 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 (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

**d) 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.

**e) Is a congenital anomaly/birth defect**

**f) 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 eCRF.
- As needed, the 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 the 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 eCRF Completion and Monitoring Conventions.

### Assessment of Intensity

The Investigator will assess the intensity of each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. Do not confuse an AE that is assessed as severe with a SAE. Severe is a category used to rate the intensity of an event; both AEs and SAEs can be assessed as severe.

An event is defined as “serious” when it meets at least 1 of the predefined criteria specified in the definition of an SAE, NOT when it is rated as severe.

Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (CTCAE), version 5.0 (publication date: 27 November 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’s 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 a 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 the Sponsor/designee 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.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Sponsor/designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor/designee 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 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 data collection tool, specified below, to report the event within 24 hours.
- The site will enter into the electronic system the SAE data within 24 hours after becoming aware of the event. It is expected that the investigator/sub-investigator signs off this data in the system and any relevant associated data (e.g., additional laboratory tests, medical records, diagnostic reports, histopathological examinations, or consultation with other health care professionals) will be entered 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 Electronic Data Capture 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 eCRF may be required in addition (e.g. medical history, concomitant medication). The data provided will be consistent with the information in the eCRF.

### **Recording and Reporting of DLTs**

- Each event that meets the DLT criteria, as specified in Section 6.6.3, will be recorded in the eCRF 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**

See Section 6.6.3 and Section 6.6.4 for management of liver toxicities.

## Appendix 6 Clinical Laboratory Tests

The protocol-required clinical laboratory test are in the following table. All safety-required clinical laboratory tests will be performed by a local laboratory.

Laboratory Assessments	Parameters			
Hematology	Platelet count		Mean corpuscular volume (MCV)	White Blood Cell Count with Differential: <ul style="list-style-type: none"><li>• Neutrophils</li><li>• Lymphocytes</li><li>• Monocytes</li><li>• Eosinophils</li><li>• Basophils</li></ul>
	Hemoglobin		Mean corpuscular hemoglobin (MCH)	
	Hematocrit			
	Erythrocytes		Reticulocytes	
Biochemistry	Blood Urea Nitrogen/total urea	Potassium	Aspartate aminotransferase	Total bilirubin/indirect bilirubin
	Creatinine	Sodium	Alanine aminotransferase	Total protein
	Glucose	Calcium	Alkaline phosphatase	CRP
	Albumin	Amylase	Lactate dehydrogenase	Ferritin
	Lipase	Magnesium	Uric acid	Creatinine Clearance
Coagulation	aPTT (sec)	PT (sec)	INR	
Routine Urinalysis	<ul style="list-style-type: none"><li>• Specific gravity</li><li>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes by dipstick</li><li>• Microscopic examination (if blood or protein is abnormal).</li></ul>			
Other Screening Tests	<ul style="list-style-type: none"><li>• FSH</li><li>• Serum (at Screening) and highly sensitive urine (during M1069 treatment) hCG pregnancy test (as needed for a WOCBP).</li><li>• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody).</li></ul>			

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Appendix 8      Model for Bayesian Dose Escalation

The Bayesian model results are based on the number of DLTs and evaluable participants per dose level. 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 dose level  $d_j$ , the relationship between dose and probability of toxicity  $P$  (DLT) is defined by:

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

with bivariate normally distributed parameters  $(\alpha, \beta)$ , using the following parameterization:

- Pre-selected dose level  $d_j \in \{150 \text{ mg}, 300 \text{ mg}, 450 \text{ mg}, 600 \text{ mg}, 700 \text{ mg}\}$

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The following toxicity regions will be defined:

	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]	[2]

The model-based recommendation for the next dose level is the dose level 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:

- $1 \times P(\text{Under-Dosing}) + 0 \times P(\text{targeted toxicity}) + 1 \times P(\text{excessive toxicity}) + 2 \times P(\text{unacceptable toxicity})$ .

The model will be provided with the following dose levels: 150, 300, 450, 600, and 700 mg BID. The set of doses can be changed any time by the SMC.

The target DLT probability for the MTD suggested by the Bayesian model 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.:

- CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

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 or change from fasted to fed condition, these will also be documented in the SMC charter prior to the first SMC with patients with the new regimen / fasting status.

Posterior distribution and the recommended next dose level suggested by the model will be calculated using SAS v 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 9      Protocol Amendment History**

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

## Appendix 10 Sponsor Signature Page

**Study Title:** First-in-Human Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M1069 in Participants with Metastatic or Locally Advanced Unresectable Solid Tumors.

**Regulatory Agency Identifying Numbers:** CCI [REDACTED]

**Clinical Study Protocol Version:** 11 November 2021 / Version 2.0

I approve the design of the clinical study:

---

Signature

---

Date of Signature

**Name, academic degree:**

PPD [REDACTED]

**Function/Title:**

PPD [REDACTED]

**Institution:**

Merck Healthcare KGaA

**Address:**

Merck Healthcare KGaA  
Global Clinical Development Immuno-Oncology  
Frankfurter Str. 250 – F135  
64293 Darmstadt  
Germany

**Telephone number:**

CCI [REDACTED]  
[REDACTED]

**Fax number:**

Not Applicable

**E-mail address:**

PPD [REDACTED]

## Appendix 11 Coordinating Investigator Signature Page

**Study Title:** First-in-Human Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M1069 in Participants with Metastatic or Locally Advanced Unresectable Solid Tumors.

**Regulatory Agency Identifying Numbers:** IND CCI

**Clinical Study Protocol Version:** 11 November 2021 / Version 2.0

**Site Number:**

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 on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

---

Signature

---

Date of Signature

**Name, academic degree:**

PPD

**Function/Title:**

PPD

**Institution:**

PPD

**Address:**

PPD

**Telephone number:**

PPD

**Fax number:**

PPD

**E-mail address:**

PPD

## Appendix 12 Principal Investigator Signature Page

**Study Title:** First-in-Human Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Clinical Activity of M1069 in Participants with Metastatic or Locally Advanced Unresectable Solid Tumors

**Regulatory Agency Identifying Numbers:** IND **CCI**

**Clinical Study Protocol Version:** 11 November 2021 / Version 2.0

**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 on 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:** [Insert Name and highest degree or for a single center study, insert from Title Page]

**Function/Title:**

**Institution:** [Insert Name of Institution or for a single center study, insert from Title Page]

**Address:** [Insert Full Mailing Address (e.g., Street, City, postal code, and Country)]

**Telephone number:** [Insert Full number, including country code]

**Fax number:** [Insert Full number, including country code or “Not Applicable”]

**E-mail address:**