Clinical Trial Protocol

Clinical Trial Protocol Number	MS200647-0008
Title	A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of MSB0011359C in subjects with metastatic or locally advanced solid tumors with expansion to selected indications in Asia
Trial Phase	I
Coordinating Investigator	PPD
Sponsor	**For sites in Japan:** Merck Biopharma Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany) PPD **For all countries except Japan:** Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany **Medical Responsible:** PPD PPD Merck Biopharma Co., Ltd. Tel: PPD Fax: PPD
Clinical Trial Protocol Version	03 March 2020/Version 7.0 including Amendments 1.0 to 6.0
Replaces Version	21 June 2019/Version 6.0

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original protocol	16-Oct-2015
2.0	Amendment 1.0	04-Jan-2016
3.0	Amendment 2.0	29-Apr-2016
4.0	Amendment 3.0	29-Sep-2016
5.0	Amendment 4.0	18-Apr-2017
6.0	Amendment 5.0	21-Jun-2019
7.0	Amendment 6.0	03-Mar-2020

Protocol Version [7.0] (03 March 2020)

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

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
Table 1 Schedule of Assessments: Dose Escalation Part (footnote g) Table 2 Schedule of Assessments: Dose Expansion Part (footnote g)	Removal of vital signs assessments at 30-, 60-, and 120-minutes post-infusion and addition of text for vital signs assessments for re-initiated subjects.	As per the current Investigator's Brochure (Version 5) the incidence of infusion-related reactions was low and no Grade 3 infusion-related reactions were reported in 2 Phase I studies. The newer MSB0011359C studies have removed the 30- and 60-minute vital sign assessments post-infusion. For re-initiated subjects, text added to clarify if there are no infusion-related reactions after the first infusion, then the 30-, 60-, and 120-minute post-infusion vital sign assessments may be waived.
Table 1 Schedule of Assessments: Dose Escalation Part (footnote q) Table 2 Schedule of Assessments: Dose Expansion Part (footnote r) 6.4 Non-investigational Medicinal Products to be Used 6.5.4 Special Precautions	Removed the 2-hour observation period post end of infusion.	As per the current Investigator's Brochure (Version 5) the incidence of infusion-related reactions was low and no Grade 3 infusion-related reactions were reported in 2 Phase I studies. The 2-hour observation post end of infusion is not necessary.
CCI [redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
7.1.3 Rechallenge	Re-initiation period corrected for constancy in the protocol text.	Text in Section 7.1.3 updated to state re-initiation course of 12 months is allowed to maintain constancy in the protocol text.
7.7.1 Anti-drug antibody Analysis	Included details for anti-drug antibody testing.	Text included describing the anti-drug antibody testing and that confirmed positive antibodies may be tested for the presence of neutralizing antibodies.
	Minor editorial and document formatting updates have been made throughout the protocol.	

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List of Abbreviations

ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from the time of dosing extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from the time of dosing to the time of the last observation
β-HCG	β-human chorionic gonadotropin
BOR	best overall response
BTC	biliary tract cancer
CC	cholangio cell carcinoma
CI	confidence interval
CNS	central nervous system
C_{max}	maximum serum concentration observed postdose
C_{min}	minimum serum concentration observed postdose
CR	complete response
CRO	Contract Research Organization

CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte antigen-4
DLT	dose-limiting toxicity
EC	esophageal cancer
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EORTC QLQ-BIL21	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cholangiocarcinoma and Gallbladder Cancer Module
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core instrument
EORTC QLQ-HCC18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Hepatocellular Carcinoma Module
EORTC QLQ-OES18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Esophageal Module
EORTC QLQ-STO22	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Gastric Module
ESCC	esophageal squamous cell cancer
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GBC	gallbladder cancer
GC	gastric cancer
GCP	Good Clinical Practice
HAHA	human antihuman antibody
HBV	hepatitis B virus
HCC	hepatocellular carcinoma

HCV	hepatitis C virus
HDV	hepatitis D virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
CCI	[redacted]
IRC	Independent Endpoint Review Committee
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
irSD	immune-related stable disease
LDH	lactate dehydrogenase
MAHA	mouse antibody against human antibody
MedDRA	Medical Dictionary for Regulatory Activities
MoA	mechanism of action

mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drugs
ORR	objective response rate
OS	overall survival
PBMC(s)	peripheral blood mononuclear cell(s)
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
Ph Eur	European Pharmacopeia
PGIS	Patient Global Impression of Severity
PK	pharmacokinetics
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RF	rheumatoid factor
SAE	serious adverse event
SAP	statistical analysis plan

SMC	Safety Monitoring Committee
SpO_2	Oxygen saturation
$t_{1/2}$	terminal half-life
T4	thyroxine
TEAE	treatment-emergent adverse event
TGFβ	transforming growth factor-beta
TGFβRII	transforming growth factor-beta receptor II
Treg	regulatory T cells
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USP	United States Pharmacopeia
VAC	carcinoma of Vater's ampular
WBC	white blood cell

1 Synopsis

Trial title	A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of MSB0011359C in subjects with metastatic or locally advanced solid tumors with expansion to selected indications in Asia
Trial number	MS200647-0008
Sponsor	**For sites in Japan:** Merck Biopharma Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany) PPD **For all countries except Japan:** Merck KGaA, Frankfurter Str. 250 64293 Darmstadt, Germany
Phase	I
Trial under IND	☒ yes ☐ no
FDA "covered trial"	☒ yes ☐ no
Trial center(s)/country(ies)	**Dose Escalation Part:** Up to 2 sites in Japan. **Expansion Part:** Up to 30 sites in Japan, Korea and Taiwan.
Planned trial period **(first enrollment-last subject out)**	**Dose Escalation Part:** First subject in: First quarter (Q1) 2016 Last subject out: Q4 2020 **Expansion Part:** First subject in: Q4 2016 (Q2 2016 for hepatocellular carcinoma [HCC]) Last subject out: Q4 2020 **End of Trial:** If the trial is not terminated prematurely, the end of the trial is defined as 1 year after the last subject receives the last dose of MSB0011359C. **Analysis cut-off dates:** The primary data cut-off date for the dose escalation part is 3 months after the last subject

	in the dose escalation part received the first dose of MSB0011359C. The primary data cut-off for the analysis of each expansion cohort separately will be 6 months after the last subject in the cohort started treatment. The final data cut-off is 1 year after the last subject has received the last dose of MSB0011359C.

Trial objectives

Primary objective:

The primary objective of the trial is to determine the safety, tolerability and maximum tolerated dose (MTD) administered as monotherapy of MSB0011359C in subjects with metastatic or locally advanced solid tumors.

Secondary objectives:

The secondary objectives are:

- To characterize the pharmacokinetics (PK) profile of MSB0011359C
- To evaluate the immunogenicity of MSB0011359C and its relationship to drug exposure
- To assess the best overall response (BOR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

CCI [redacted]

Trial design and plan

This Phase I, open-label trial consists of 2 parts: a dose escalation part (Part A) and an expansion part (Part B). This trial will be conducted to investigate the safety and tolerability of MSB0011359C in subjects with metastatic or locally advanced solid tumors in Asia. This trial also has an expansion part to investigate the safety and efficacy of MSB0011359C in Asian patients with gastric cancer (GC), esophageal squamous cell cancer (ESCC) and biliary tract cancer (BTC), and in Japanese patients with HCC.

Dose escalation (Part A):

The dose escalation part will use a standard 3+3 scheme with the planned doses of 3 mg/kg, 10 mg/kg, and 20 mg/kg administered once every 2 weeks. For each dose level, DLTs are assessed during the first 3 weeks (21 days after administration of MSB0011359C). The criteria for moving from one dose level to another do not allow escalation to the next cohort in cases where more than 1 subject in a cohort experiences a DLT. If 1 of 3 subjects in a cohort experiences a DLT, this cohort will be automatically expanded to 6 subjects. The MTD is defined as the highest dose where no more than 1 subject out of 6 subjects experiences a DLT. Thus, the MTD cohort should accrue at a total of 6 subjects. After the cohort with the dose selected for the expansion part has completed the DLT evaluation period, an additional 3 subjects may be enrolled if a total of 6 subjects have not yet been treated at the dose level for the purpose of additional safety evaluation.

A DLT is defined as any Grade ≥ 3 adverse event (AE) (with certain exceptions as described in the protocol) suspected to be related to MSB0011359C by the Investigator and/or Sponsor occurring during the DLT evaluation period (defined as 21 days after administration of MSB0011359C) and confirmed by the Safety Monitoring Committee (SMC) to be relevant for the IMP treatment.

At each dose level, subjects will receive MSB0011359C as a 1-hour intravenous infusion once every 2 weeks until progressive disease (PD) has been confirmed by a subsequent scan, unacceptable toxicity, or occurrence of any criterion for withdrawal from the trial or the IMP as outlined in this protocol. In order to mitigate potential infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) (eg, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] intravenous or oral equivalent) approximately 30 to 60 minutes prior to each dose of MSB0011359C is mandatory for the first 2 infusions. Premedication is optional and at the discretion of the Investigator after the second infusion. If Grade 2 infusion reactions are seen during the first two infusions, then premedication should not be stopped. Steroids as premedication are not permitted.

Expansion (Part B):

The expansion part consists of an HCC cohort and other cohort indications including GC, ESCC, and BTC.

For the HCC cohort, 3 subjects will be enrolled at 3 mg/kg once the 3 mg/kg dose level in the dose escalation part of the trial has been cleared by the SMC. Six subjects will be enrolled at 10 mg/kg once the 10 mg/kg dose level in the dose escalation part of the trial has been cleared by the SMC. The purpose of the HCC cohort is to further assess the safety of MSB0011359C in subjects with HCC.

After confirmation of tolerability at 20 mg/kg in the dose escalation part, the MSB0011359C dose for further investigation is 1200 mg and enrollment of GC, ESCC, and BTC subjects into the expansion cohorts will begin to determine the safety and clinical activity of MSB0011359C. These indications were chosen as they offer the potential for transformative treatment with ability to establish an initial proof of concept of antitumor activity of MSB0011359C with good feasibility.

Subjects in the expansion cohorts will receive MSB0011359C as a 1-hour intravenous infusion once every 2 weeks until PD has been confirmed by a subsequent scan, unacceptable toxicity, or occurrence of any criterion for withdrawal from the trial or the IMP as outlined in this protocol.

Subjects will be monitored and assessed for safety and efficacy parameters at regular intervals throughout the trial.

Planned number of subjects

Dose escalation part: Up to 18 subjects with metastatic or locally advanced solid tumors.

Expansion part: Up to 169 subjects (30, 30, up to 100, and 9 subjects in the GC, ESCC, BTC, and HCC cohorts, respectively).

The total sample size at the end of the trial (based on the dose escalation part and the expansion part) is expected to be up to approximately 187 subjects.

Diagnosis and key inclusion and exclusion criteria

Key inclusion criteria for the dose escalation include:

1. Able and willing to give written informed consent and has signed the appropriate written informed consent form (ICF), prior to performance of any trial activities.
2. Eligible male and female subjects aged ≥ 20 years.
3. Histologically or cytologically proven metastatic or locally advanced solid tumors, for which no effective standard therapy exists or standard therapy has failed.
4. ECOG performance status of 0 to 1 at trial entry.
5. Life expectancy ≥ 12 weeks as judged by the Investigator.
6. Adequate hematological function defined by white blood cell (WBC) count ≥ 3×10^9/L with absolute neutrophil count (ANC) ≥ 1.5×10^9/L, lymphocyte count ≥ 0.5×10^9/L, platelet count ≥ 75×10^9/L, and Hgb ≥ 9 g/dL (in absence of blood transfusion).
7. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × ULN, an AST level ≤ 2.5 × ULN, and an ALT level ≤ 2.5 × ULN. For subjects with liver involvement in their tumor, AST ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and bilirubin ≤ 3.0 is acceptable.
8. Adequate renal function defined by an estimated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula or by measure of creatinine clearance from 24-hour urine collection.

Key inclusion criteria for the expansion cohorts are:

1. Able and willing to give written informed consent and has signed the appropriate written ICF, prior to performance of any trial activities.
2. Eligible male or female subjects aged ≥ 20 years.
3. Subjects must have one of the following:

- **GC:** Histologically or cytologically confirmed recurrent or refractory unresectable stage IV gastric or gastro-esophageal junctional adenocarcinoma (according to American Joint Committee on Cancer/Union Internationale Contre le Cancer 7th edition) for which no standard therapy exists or standard therapy has failed.
- **ESCC:** Histologically or cytologically confirmed esophageal squamous cell cancer for which no standard therapy exists or standard therapy has failed.
- **BTC, second line:** Histologically or cytologically confirmed biliary tract cancer. Must have failed or are intolerant to one line of systemic treatment. Patients who received adjuvant chemotherapy and had evidence of disease recurrence within 6 months of completion of the adjuvant treatment are also eligible.
- **HCC, second line or later, or sorafenib intolerant:** Histologically confirmed HCC. Must be unresectable or have advanced disease not amenable to curative resection. Must have had progression following at least 1 line of prior sorafenib therapy (must have received at least 14 days of sorafenib at least 400 mg per day) or previously considered to be sorafenib intolerant.

  Additional inclusion criteria for HCC subjects include subjects with no allergies to contrast and able to tolerate computed tomography (CT) or magnetic resonance imaging (MRI) contrast in the opinion of the Investigator.

4. Availability of tumor (primary or metastatic) archival material or fresh biopsies within 28 days before first administration of IMP is mandatory. If no archival material is available and only one lesion is amenable for biopsy and it is the only target lesion, the Medical Monitor should be consulted for subject eligibility. CCI [redacted]
5. Disease must be measurable with at least 1 unidimensionally measurable lesion by RECIST 1.1.

Key exclusion criteria:

1. Concurrent treatment with non-permitted drugs.
2. Prior therapy with any antibody/drug targeting T cell coregulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) antibody (consult Medical Monitor if necessary), or anti-4-1BB antibody, is not allowed (consult with Medical Monitor as needed), inclusive of intrahepatic, localized administration of such agents.
3. Prior therapy with any antibody/drug targeting TGFβ or TGF receptor.

4. Anticancer treatment within 21 days before the start of trial treatment, eg, cytoreductive therapy, radiotherapy (with the exception of palliative bone-directed radiotherapy), immune therapy, or cytokine therapy.
5. Anticancer treatment with antibody within 28 days before the start of trial treatment.
6. Major surgery within 28 days before the start of trial treatment (excluding prior diagnostic biopsy).
7. Systemic therapy with immunosuppressive agents within 7 days before the start of trial treatment; or use of any investigational drug within 28 days before the start of trial treatment.

Investigational Medicinal Product

Dose/mode of administration/dosing schedule:

For the dose-escalation cohorts and the HCC cohort, the dose of MSB0011359C will be calculated based on the weight of the subject determined on the day prior to or the day of each drug administration. A flat dose of 1200 mg MSB0011359C will be used for all subjects in the expansion cohort (except for the HCC cohort) after confirming the tolerability of MSB0011359C at 20 mg/kg.

MSB0011359C will be administered once every 2 weeks as a 1-hour (-10/+20 minutes, ie, over 50 to 80 minutes) intravenous infusion.

In order to mitigate potential infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) (eg, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] intravenous or oral equivalent) approximately 30 to 60 minutes prior to each dose of MSB0011359C is mandatory for the first 2 infusions. Premedication is optional and at the discretion of the Investigator after the second infusion. If Grade 2 infusion reactions are seen during the first two infusions, then premedication should not be stopped. Steroids as premedication are not permitted.

Reference therapy

Dose/mode of administration/dosing schedule:

Not applicable

Planned trial and treatment duration per subject

Subjects will receive MSB0011359C until progression has been confirmed by a subsequent scan, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs as outlined in this protocol.

In the case of complete response (CR), partial response (PR) or stable disease (SD), subjects should continue treatment through the end of 12 months at the discretion of the Investigator and in consultation with the Medical Monitor. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor. For subjects who achieve a CR, PR, or SD on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, 1 re-initiation course of treatment at the same dose and schedule and treatment duration up to

12 months is allowed at the discretion of the Investigator and agreement of the trial Medical Monitor. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial MSB0011359C therapy. In the case of PD, subjects should continue treatment through their next tumor assessment, if they meet the criteria described in this protocol. If there is further evidence of PD thereafter, trial treatment should be discontinued; however continued treatment is possible in consultation with the Medical Monitor.

Primary endpoints:

The primary endpoints for the dose escalation part of the trial are:

- Occurrence of DLTs during the first 3 weeks (21 days) of treatment in the dose escalation part
- Number, severity and duration of treatment-emergent AEs (TEAEs) according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03)
- Number, severity, and duration of treatment-related AEs for all dose groups/indications according to CTCAE v4.03.

Secondary endpoints:

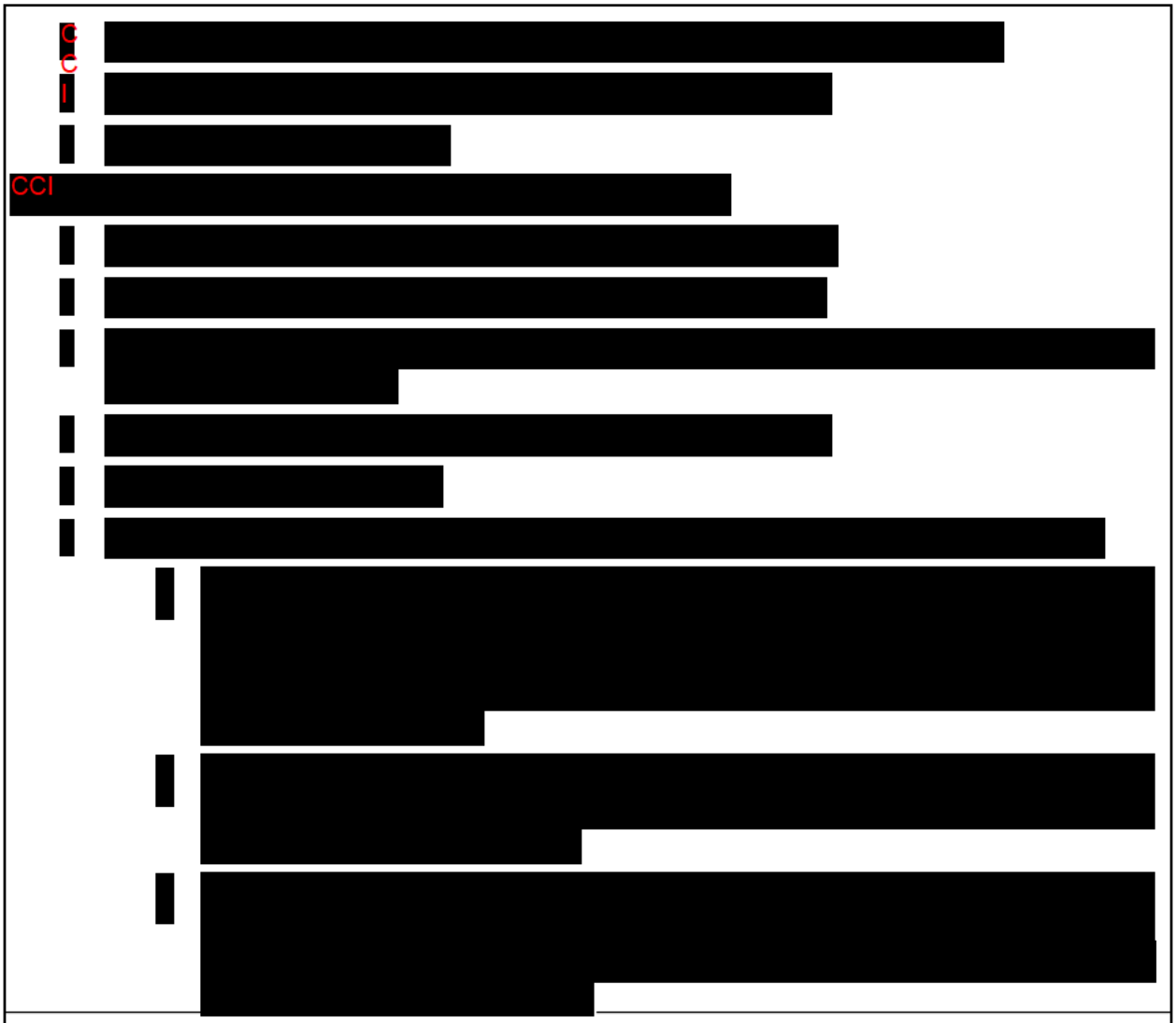
The secondary endpoints for the dose escalation part of the trial are:

- MSB0011359C PK profile (for dose escalation), including area under the concentration-time curve (AUC), maximum serum concentration observed postdose (C_{max}), minimum serum concentration observed postdose (C_{min}) and terminal half-life ($t_{1/2}$)
- Serum titers of anti-MSB0011359C antibodies
- BOR according to RECIST 1.1 per investigator assessments.

The secondary endpoints for the expansion part of the trial are:

- BOR according to RECIST 1.1 as adjudicated by the Independent Review Committee (IRC)
- BOR according to RECIST 1.1 per investigator assessments
- Duration of response according to RECIST as adjudicated by the IRC
- Disease control rate according to RECIST 1.1 as adjudicated by the IRC
- PFS time according to RECIST 1.1 as adjudicated by the IRC
- OS time.

CCI [redacted]



Pharmacokinetics:

- AUC from the time of dosing to the time of the last observation (AUC_{0-t}) – dose escalation only
- AUC from the time of dosing extrapolated to infinity ($AUC_{0-\infty}$) – dose escalation only
- C_{max} observed postdose
- C_{min} observed postdose
- Terminal half-life ($t_{1/2}$) – dose escalation only

CCI [redacted]

Statistical methods:

The sample size for the dose escalation part of the trial is not based on any statistical assumptions; rather, it follows the "3+3 rule", a well-established methodology in the design of dose-finding trials in oncology.

This trial plans for 3 cohorts (3, 10 and 20 mg/kg) of 3 subjects to be treated at each escalating dose level and with typical DLT driven expansions to 6 subjects and at the MTD. The expected total sample size in the dose escalation part of the trial will be up to 18 subjects as DLT evaluable subjects.

For the purpose of assessing safety, after the 3 mg/kg cohort in the escalation has cleared SMC evaluation, the 3 mg/kg HCC cohort may initiate and enroll 3 subjects. This is followed by the initiation and enrollment of 6 subjects in the 10 mg/kg HCC cohort, after the 10 mg/kg escalation cohort clears SMC evaluation.

For the expansion cohorts of subjects with GC, ESCC, and BTC, the primary secondary efficacy endpoint is the BOR, as adjudicated by the IRC, and will be evaluated by confirmed objective response rate (ORR) according to RECIST 1.1 based on IRC assessment. The ORR will be determined as the proportion of patients with confirmed BOR of PR or CR.

Thirty subjects will be enrolled in each cohort. The goal of these cohorts is an exploration of initial clinical activity and viewed as hypothesis-generating, not intended as a test of a hypothesis. The sample size in these cohorts is a practical number in order to obtain preliminary estimates of efficacy. The confirmed ORR according to RECIST 1.1 as adjudicated by the IRC will be determined as the proportion of subjects with confirmed BOR of PR or CR. A 95% exact (Clopper-Pearson) confidence interval will be calculated for the ORR. The total sample size for the trial (dose escalation and expansion) is expected to be up to approximately 187 subjects.

For BTC, up to 100 subjects will be enrolled in total for the purpose of assessing additional safety data and efficacy based on the BOR, if 5 or more of first 20 BTC subjects have a response (that is an ORR of at least 25%).

Statistics for continuous variables may include means, medians, ranges, and appropriate measures of variability. Qualitative variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by confidence intervals. The results of the safety evaluations will be tabulated and displayed by dose level/expansion cohort. CCI [redacted]

CCI [redacted] Descriptive statistics will be examined for indications of dose-related toxicity.

Listings will be produced upon completion of each dose escalation cohort of subjects and the decision as to whether to proceed with dose escalation, dose reduction or to enroll another cohort at the same dose level will be determined by reviewing these data. Full details of the planned analyses will be described in the trial Statistical Analysis Plan, separately for the dose escalation part and the expansion part.

Schedule of Assessments

Table 1 Schedule of Assessments: Dose Escalation Part

Measure	Screening Assessments	Treatment Part (-3 / +1 days)[a]											Discontinuation/ End-of-Treatment Visits[w]	Safety Follow-up Visit[w]	Long-Term Follow-up[b]
		V1	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10			
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13			
	Day -28 to First Treatment	D1	D2	D8	D15	D22	D29	D43	D43-50	D57	D71	D85	Until Progression	Up to 7/28 Days (+/- 5 days) after Decision of Discontinuation/ Last Treatment[c, d]	10 Weeks (+/- 2 weeks) after Last Treatment	Every 12 weeks (+/- 2 weeks)
Written informed consent	X					X										
Inclusion/exclusion criteria	X	X														
Medical history	X															
Cancer disease history	X															
Prior anticancer drug/radiotherapy/ procedures	X															
Other prior medications	X															
Demographic data	X															
HBV, HCV, and HIV testing	X															
Ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity	X															
Physical examination[t,x]	X	X	X	X	X	X	X	X		X	X	X	6-weekly[u]	x/X	X	

Table 1 Schedule of Assessments: Dose Escalation Part

Measure	Screening Assessments	Treatment Part (-3 / +1 days)[a]											Discontinuation/ End-of-Treatment Visits[w]	Safety Follow-up Visit [w]	Long-Term Follow-up [b]
		V1	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10			
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13			
	Day -28 to First Treatment	D1	D2	D8	D15	D22	D29	D43	D43-50	D57	D71	D85	Until Progression	Up to 7/28 Days (+/- 5 days) after Decision of Discontinuation/ Last Treatment [c, d]	10 Weeks (+/- 2 weeks) after Last Treatment	Every 12 weeks (+/- 2 weeks)
Dermatological assessment[e]	X				X		X	X		X	X	X	6-weekly up to/including Week 25, then every 12 weeks	x/X	X	
SpO_2	X	X			X		X	X		X	X	X	2-weekly	X	X	
12 lead ECG[f]	X	X/X	X	X	X/X		X	X				X	6-weekly normal ECGs[u]	-/X	X	
Vital signs including weight and height (height at screening only)[g]	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	x/X	X	
ECOG PS[h]	X	X	X	X	X		X	X		X	X	X	2-weekly	x/X	X	
Enrollment (if eligible)[i]	X															
Hematology/ hemostaseology[j]	X	X	X	X	X	X	X	X		X	X	X	2-weekly	x/X	X	
Core serum chemistry[k]		X	X	X		X	X			X	X		2-weekly			
Full serum chemistry[k]	X				X			X				X	6-weekly	x/X	X	
Serum electrophoresis	X											X		-/X		
Urinalysis[l]	X				X			X				X	6-weekly[u]	x/X	X	
β-HCG pregnancy test (if applicable)[m]	X	X					X			X		X	4-weekly	-/X	X	
FSH (if applicable)	X															

Table 1 Schedule of Assessments: Dose Escalation Part

Measure	Screening Assessments	Treatment Part (-3 / +1 days)[a]											Discontinuation/ End-of-Treatment Visits[w]	Safety Follow-up Visit[w]	Long-Term Follow-up[b]
		V1	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10			
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13			
	Day -28 to First Treatment	D1	D2	D8	D15	D22	D29	D43	D43-50	D57	D71	D85	Until Progression	Up to 7/28 Days (+/- 5 days) after Decision of Discontinuation/ Last Treatment[c, d]	10 Weeks (+/- 2 weeks) after Last Treatment	Every 12 weeks (+/- 2 weeks)
Tumor evaluation/ staging (CT Scan/MRI/ other)[b, n, o, v]	X							X				X	6-weekly	-/X		X[b]
Documentation of AEs[w]	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	x/X[w]	X[w]	
Documentation of concomitant medications, and procedures	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	x/X	X	X
ACTH, ANA, and RF	X															
Free T4 and TSH	X				X			X				X	6-weekly	-/X	X	
PK sampling	See Table 3															
ADA sampling	See Table 3															
Soluble factors	See Table 3															
TGFβ	See Table 3															
Tumor tissue or archived surgical specimen (optional)	See Table 3															
CCI [redacted]	CCI [redacted]															
CCI [redacted]	C															
Pretreatment and IMP administration[q]		X			X		X	X		X	X	X	2-weekly			

Table 1 Schedule of Assessments: Dose Escalation Part

Measure	Screening Assessments	Treatment Part (-3 / +1 days)[a]											Discontinuation/ End-of-Treatment Visits[w]	Safety Follow-up Visit [w]	Long-Term Follow-up [b]
	Day -28 to First Treatment	V1	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10	Until Progression	Up to 7/28 Days (+/- 5 days) after Decision of Discontinuation/ Last Treatment [c, d]	10 Weeks (+/- 2 weeks) after Last Treatment	Every 12 weeks (+/- 2 weeks)
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13				
		D1	D2	D8	D15	D22	D29	D43	D43-50	D57	D71	D85				
Hospitalization on first 2 doses[r]		X			X											
DLT assessment[s]		X	X	X	X	X										
Survival follow-up																X

ACTH=adrenocorticotropic hormone; ADA=anti-drug antibody; AE=adverse events; ANA=antinuclear antibody; β-HCG=β-human chorionic gonadotropin; CT=computer tomography; DLT=dose-limiting toxicity; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FSH=follicle stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IMP=investigational medicinal product; MRI=magnetic resonance imaging; PD=progressive disease; PK=pharmacokinetics; RF=rheumatoid factor; SpO_2=Oxygen saturation; TGFβ=transforming growth factor beta; TSH=thyroid stimulating hormone, T4=thyroxine.

Unless stated otherwise in a footnote, all procedures and samples should occur prior to trial drug administration.

a A time window of up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all procedures (except Day 2 and the Day 43-50 visit). The biweekly 14-day schedule should be strictly adhered to, returning to the target date even if the previous visit was off schedule. The Day 43-50 visit is to accommodate collection of tumor biopsy material and associated PK and CCI (see Table 3).

b Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression (CT/MRI scans every 12 weeks) until PD. In addition, subjects will be followed every 12 weeks for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 1 year after the last subject receives the last dose of trial drug. After completion of the Follow-up period the appropriate electronic Case Report Form section for Trial Termination must be completed.

c Any subject who experiences an AE that mandates discontinuation of trial treatment should have a discontinuation visit within 7 days after the decision to discontinue trial treatment.

d Tumor evaluation at the End-of-Treatment visit should only be performed if no disease progression has been documented previously. If another antineoplastic therapy is administered before the end of the 28-day period, the End-of-Treatment visit should be conducted before the start of new therapy if possible.

e Assessments for skin lesions or rash with biopsy of suspicious lesions. Dermatological consults should be requested as needed.

f ECG to be taken before dosing and as soon as possible after completion of the infusion. If only a single "X", then only ECG before dosing is required. All ECGs will be conducted according to local procedure and will NOT be digitally uploaded.

g Vital signs should be assessed predose (within 15 minutes of start of infusion), then every 15 (±2) minutes after the start of infusion, and 15 (±5), 30 (±5), 60 (±5), 120 (±10), and 360 (±150) minutes after the end of infusion for the first 2 infusions. If there were no clinically significant changes in vital signs during the first 2 infusions, then the vital signs schedule for subsequent infusions will be predose (within 15 minutes of start of infusion), 30 (±5) and 60 (-5/+15) minutes after the start of infusions. For re-initiated subjects, vital signs should be assessed predose (within 15 minutes of start of the infusion), 30 (±5) and 60 (-5/+15) minutes after the start of infusion, and 30 (±5), 60 (±10),

and 120 (±10) minutes after the end of the infusion. If the re-initiated subject does not have an infusion-related reaction during the first infusion the vital sign assessments at 30 (±5), 60 (±10), and 120 minutes after the end of the infusion may be waived for subsequent infusions.

h If the Screening ECOG PS was performed within 3 days prior to Cycle 1 Day 1, it does not have to be repeated at Cycle 1 Day 1.

i Enrollment will be done after the confirmation of fulfilling all Screening inclusion criteria without matching any exclusion criterion. In the case of new clinical laboratory abnormalities detected prior to the first dose, the eligibility of the subject should be reconsidered with the guidance of Medical Monitor.

j Hematology (including complete blood count) and hemostaseology assessments are detailed in Table 8. Follicle-stimulating hormone at Screening, if applicable. Complete blood count results must also be drawn and reviewed within 48 hours prior to dose administration. For subjects experiencing signs of anemia including, but not limited to, a significant drop in Hgb value (especially Hgb < 8 g/dL), routine monitoring of Hgb, red blood cells, and hematocrit should be performed weekly.

k Full chemistry (which includes core chemistry) and core serum chemistry samples are detailed in Table 8. Samples for core chemistry results must be drawn and reviewed within 48 hours prior to dose administration.

l A full urinalysis is required at Screening and the End-of-Treatment visit and basic urinalysis at each visit indicated prior to administration of study drug. If urinalysis (full or basic) is positive for protein, sediment will be evaluated.

m β-HCG must be determined from serum at Screening and from either urine or serum sample thereafter. Results of the most recent pregnancy test should be available prior to next dosing. Pregnancy testing is applied for women of childbearing potential. Woman are considered of childbearing potential unless they are postmenopausal (defined by continuous amenorrhea excluding the amenorrhea caused by the administration of anticancer therapy) for at least 12 months, are surgically sterile or have increased FSH levels indicating menopause.

n Tumor evaluations during Screening must be performed within 28 days prior to Cycle 1 Day 1 in order to document the baseline status of the tumor disease using RECIST 1.1 target and nontarget lesions. The subsequent tumor evaluations have a time window of 5 days prior to dosing (-5 days). In case a tumor response according to RECIST 1.1 is documented during the course of the trial, confirmation of the response should be performed according to RECIST 1.1 after 6 weeks.

o Brain CT/MRI scan (either, with contrast preferred) is required at Screening if not performed within the previous 6 weeks. Thereafter, brain CT/MRI scan should be done if clinically indicated by development of new specific symptoms. A bone scan should be done at Screening and beyond as clinically indicated. Bone metastases detected at Screening need to be followed at the subsequent tumor evaluation visits.

C [redacted]

q In order to mitigate potential infusion-related reactions, all subjects must receive premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of MSB0011359C (eg, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] intravenous or oral equivalent) for the first 2 infusions. Premedication is optional and at the discretion of the Investigator after the second infusion. If Grade 2 infusion reactions are seen during the first two infusions, then premedication should not be stopped. Steroids as premedication are not permitted. MSB0011359C should be administered at the cohort prescribed dose by intravenous infusion over 1 hour (-10 minutes/+20 minutes, ie, over 50 to 80 minutes). The first 2 doses of MSB0011359C for any subject will be accompanied by overnight evaluation of at least 24 hours in an in-patient setting.

r In-patient admission with periodic ECG and vital sign monitoring for a minimum of 24 hours. After 24 hours, investigator will decide the discharge of the subject based on the monitoring results and the results of in-person examination.

s The observation period for DLTs refers to the first 21 days of IMP treatment in the dose escalation part for all subjects with data used for implementing the dose-escalation algorithm for determination of the MTD.

t At each visit, eye signs and symptoms should be checked. If clinically relevant findings, then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days.

u After 6 months, this will be assessed every 12 weeks and after a year, this will be assessed every 6 months.

v Tumor evaluation will be assessed every 12 weeks after 12 months.

w See Section 7.4.1.3 for definition of the AE reporting period and Section 7.4.1.6 for monitoring of subjects with AEs.

x After Day 1, the physical examination will be a directed physical examination indicated by subject's symptoms.

Table 2 Schedule of Assessments: Expansion Part

Measure	Screening Assessments	Treatment Part (-3 / +1 days)[a]												Discontinuation/ End-of-Treatment Visits [w]	Safety Follow-up Visit [w]	Long-Term Follow-up [b]
		V1[x]	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10				
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13				
	Day -28 to First Treatment	D1	D2[cc]	D8[cc]	D15	D22[cc]	D29	D43	D43-50[cc]	D57	D71	D85	Until Progression	Up to 7/28 Days (+/- 5 days) after Decision of Discontinuation/ Last Treatment[c, d]	10 Weeks (+/- 2 weeks) after Last Treatment	Every 12 weeks (+/- 2 weeks)
Written informed consent	X															
Inclusion/exclusion criteria	X	X														
Medical history	X															
Cancer disease history	X															
Prior anticancer drug/ radiotherapy/procedures	X															
Other prior medications	X															
Demographic data	X															
HBV, HCV, and HIV testing	X															
Ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity	X															
Physical examination [s,u]	X	X	X	X	X	X	X	X		X	X	X	6-weekly[t]	x/X	X	
Dermatological assessment[e]	X				X		X	X		X	X	X	6-weekly up to/including Week 25, then every 12 weeks	x/X	X	
SpO_2	X	X			X		X	X		X	X	X	2-weekly	X	X	

Table 2 Schedule of Assessments: Expansion Part

Measure	Screening Assessments	Treatment Part (-3 / +1 days)[a]											Discontinuation/ End-of-Treatment Visits[w]	Safety Follow-up Visit[w]	Long-Term Follow-up[b]
		V1[x]	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10			
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13			
	Day -28 to First Treatment	D1	D2[cc]	D8[cc]	D15	D22[cc]	D29	D43	D43-50[cc]	D57	D71	D85	Until Progression	Up to 7/28 Days (+/- 5 days) after Decision of Discontinuation/ Last Treatment[c, d]	10 Weeks (+/- 2 weeks) after Last Treatment	Every 12 weeks (+/- 2 weeks)
12 lead ECG[f]	X	X/X	X	X	X/X		X	X				X	6-weekly normal ECGs[t]	-/X	X	
Vital signs including weight and height (height at screening only)[g]	X	X			X	X	X	X	X	X	X	X	2-weekly	x/X	X	
ECOG PS[h]	X	X	X	X	X		X	X		X	X	X	2-weekly	x/X	X	
Enrollment (if eligible)[i]	X															
Hematology/ hemostaseology[j]	X	X	X	X	X	X	X	X		X	X	X	2-weekly	x/X	X	
Core serum chemistry[k]		X	X	X		X	X			X	X		2-weekly			
Full serum chemistry[k]	X				X			X				X	6-weekly	x/X	X	
Urinalysis[l]	X				X			X				X	6-weekly[t]	x/X	X	
β-HCG pregnancy test (if applicable)[m]	X	X					X			X		X	4-weekly	-/X	X	
FSH (if applicable)	X															
CCI [redacted]	[redacted]							[redacted]				[redacted]	[redacted]	[redacted]		[redacted]
Documentation of AEs[w]	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	x/X[w]	X[w]	
Documentation of concomitant medications, and procedures	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly	x/X	X	X
ACTH, ANA, and RF	X															

Table 2 Schedule of Assessments: Expansion Part

Measure	Screening Assessments	Treatment Part (-3 / +1 days)[a]												Discontinuation/ End-of-Treatment Visits[w]	Safety Follow-up Visit[w]	Long-Term Follow-up[b]
		V1[x]	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10				
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13				
	Day -28 to First Treatment	D1	D2[cc]	D8[cc]	D15	D22[cc]	D29	D43	D43-50[cc]	D57	D71	D85	Until Progression	Up to 7/28 Days (+/- 5 days) after Decision of Discontinuation/ Last Treatment[c, d]	10 Weeks (+/- 2 weeks) after Last Treatment	Every 12 weeks (+/- 2 weeks)
Free T4 and TSH	X				X			X				X	6-weekly	-/X	X	
EBV testing[p]	X															
PK sampling	See Table 3															
ADA sampling	See Table 3															
Soluble factors[cc]	See Table 3															
TGFβ[cc]	See Table 3															
Tumor tissue or archived surgical specimen / paired biopsy[cc]	See Table 3															
CCI [redacted]	[redacted]															
[redacted]	[redacted]															
Pretreatment and IMP administration[r]		X			X		X	X		X	X	X	2-weekly			
Expansion: GC, ESCC and BTC [y]																
Patient-reported Outcomes (PGIS and EORTC QLQ-C30, QLQ-STO22,[z] QLQ-OES18,[aa] QLQ-BIL21,[bb] and QLQ-HCC18 [bb])	X	X			X		X	X		X	X	X	2-weekly up to Week 25	x/X	X	

Table 2 Schedule of Assessments: Expansion Part

Measure	Screening Assessments	Treatment Part (-3 / +1 days)[a]												Discontinuation/ End-of-Treatment Visits [w]	Safety Follow-up Visit [w]	Long-Term Follow-up [b]
		V1[x]	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10				
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13				
	Day -28 to First Treatment	D1	D2[cc]	D8[cc]	D15	D22[cc]	D29	D43	D43-50[cc]	D57	D71	D85	Until Progression	Up to 7/28 Days (+/- 5 days) after Decision of Discontinuation/ Last Treatment[c, d]	10 Weeks (+/- 2 weeks) after Last Treatment	Every 12 weeks (+/- 2 weeks)

ACTH=adrenocorticotropic hormone; ADA=anti-drug antibody; AE=adverse events; ANA=anti-nuclear antibody; β-HCG=β-human chorionic gonadotropin; CT=computer tomography; DLT=dose-limiting toxicity; EBV=epstein barr virus; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core instrument; EORTC QLQ-STO22=stomach cancer module; EORTC QLQ-OES18=esophageal cancer module; EORTC QLQ-BIL21=cholangiocarcinoma and gallbladder cancer module; EORTC QLQ-HCC18= hepatocellular carcinoma module; FSH=follicle stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IMP=investigational medicinal product; MRI=magnetic resonance imaging; PD=progressive disease; PGIS=Patient Global Impression of Severity; PK=pharmacokinetics; RF=rheumatoid factor; SpO_2=Oxygen saturation; TGFβ=transforming growth factor beta; TSH=thyroid stimulating hormone, T4=thyroxine.

Unless stated otherwise in a footnote, all procedures and samples should occur prior to trial drug administration.

a A time window of up to 3 days before or 1 day after the scheduled visit day (-3 / +1 days) will be permitted for all procedures (except Day 2 and the Day 43-50 visit). The bi-weekly 14-day schedule should be strictly adhered to, returning to the target date even if the previous visit was off schedule. The Day 43-50 visit is to accommodate collection of tumor biopsy material and associated PK and [redacted] (see Table 3).

b Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression (CT/MRI scans every 12 weeks) until PD. In addition, subjects will be followed every 12 weeks for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 1 year after the last subject receives the last dose of trial drug. After completion of the Follow-up period, the appropriate electronic Case Report Form section for Trial Termination must be completed.

c Any subject who experiences an AE that mandates discontinuation of trial treatment should have a discontinuation visit within 7 days after the decision to discontinue trial treatment.

d Tumor evaluation at the End-of-Treatment visit should only be performed if no disease progression has been documented previously. If another antineoplastic therapy is administered before the end of this 28-day period, the End-of-Treatment visit should be conducted, if possible, prior to the start of this new therapy.

e Assessments for skin lesions or rash with biopsy of suspicious lesions. Dermatological consults should be requested as needed.

f ECG to be taken before dosing and as soon as possible after completion of the infusion. If only a single "X", then only ECG before dosing is required. All ECGs will be conducted according to local procedure and will NOT be digitally uploaded.

g Vital signs should be assessed predose (within 15 minutes of start of infusion), then every 15 (±2) minutes after the start of infusion, and 15 (±5), 30 (±5), 60 (±5), 120 (±10), and 360 (±150) minutes after the end of infusion for the first 2 infusions. If there were no clinically significant changes in vital signs during the first 2 infusions, then the vital signs schedule for subsequent infusions will be predose (within 15 minutes of start of infusion), 30 (±5) and 60 (-5/+15) minutes after the start of infusion. For re-initiated subjects, vital signs should be assessed predose (within 15 minutes of start of the infusion), 30 (±5) and 60 (-5/+15) minutes after the start of infusion, and 30 (±5), 60 (±10), and 120 (±10) minutes after the end of the infusion. If the re-initiated subject does not have an infusion-related reaction during the first infusion the vital sign assessments at 30 (±5), 60 (±10), and 120 minutes after the end of the infusion may be waived for subsequent infusions.

h If the Screening ECOG PS was performed within 3 days prior to Cycle 1 Day 1, it does not have to be repeated at Cycle 1 Day 1.

i Enrollment will be done after the confirmation of fulfilling all Screening inclusion criteria without matching any exclusion criterion. In the case of new clinical laboratory abnormalities detected prior to the first dose, the eligibility of the subject should be reconsidered with the guidance of Medical Monitor.

j Hematology (including complete blood count) and hemostaseology assessments are detailed in Table 8. Follicle-stimulating hormone at Screening, if applicable. Complete blood count results must also be drawn and reviewed within 48 hours prior to dose administration according to the schedule in the above table. For subjects experiencing signs of anemia including, but not limited to, a significant drop in Hgb value (especially Hgb < 8 g/dL), routine monitoring of Hgb, red blood cells, and hematocrit should be performed weekly.

k Full chemistry (which includes core chemistry) and core serum chemistry samples are detailed in Table 8. Samples for core chemistry results must be drawn and reviewed within 48 hours prior to dose administration according to the schedule in the above table.

l A full urinalysis is required at Screening and the End-of-Treatment visit and basic urinalysis at each visit indicated prior to administration of trial drug. If urinalysis (full or basic) is positive for protein, sediment will be evaluated.

m β-HCG must be determined from serum at Screening and from either urine or serum sample thereafter. Results of the most recent pregnancy test should be available prior to next dosing. Pregnancy testing is applied for women of childbearing potential. Woman are considered of childbearing potential unless they are postmenopausal (defined by continuous amenorrhea excluding the amenorrhea caused by the administration of anticancer therapy) for at least 12 months, are surgically sterile or have increased FSH levels

[redacted]

p Serum VCA-IgG Ab and EBNA IgG examination should be done for gastric cancer cohort.

[redacted]

c In order to mitigate potential infusion-related reactions, all subjects must receive premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of MSB0011359C (eg, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] intravenous or oral equivalent) for the first 2 infusions. Premedication is optional and at the discretion of the Investigator after the second infusion. If Grade 2 infusion reactions are seen during the first two infusions, then premedication should not be stopped. Steroids as premedication are not permitted. MSB0011359C should be administered according to the dose decided from the dose escalation part of the trial by intravenous infusion over 1 hour (-10 minutes/+20 minutes, ie, over 50 to 80 minutes).

s At each visit, eye signs and symptoms should be checked. If clinically relevant findings, then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days.

t After 6 months, this will be assessed every 12 weeks and after a year, this will be assessed every 6 months.

u After Day 1, the physical examination will be a directed physical examination indicated by subject's symptoms.

[redacted]

w See Section 7.4.1.3 for definition of the AE reporting period and Section 7.4.1.6 for monitoring of subjects with AEs.

x Subjects who re-initiate treatment will continue in the trial and will be treated and monitored according to the Schedule of Assessments for the expansion part of the trial starting at Week 1, Day 1.

y Patient-reported outcomes should be completed prior to any study-related procedures at the indicated visits.

z For subjects in the GC expansion cohort only, symptom severity also will be assessed using the EORTC QLQ-STO22, stomach cancer module.

aa For subjects in the ESCC expansion cohort only, symptom severity also will be assessed using the EORTC QLQ-OES18, esophageal cancer module.

bb For subjects in the BTC expansion cohort only, symptom severity also will be assessed using the EORTC QLQ-BIL21 (cholangiocarcinoma and gallbladder cancer module) and the EORTC QLQ-HCC18 (hepatocellular carcinoma module).

[redacted]

Table 3 Schedule of Assessments – Pharmacokinetics Sampling, CCI [redacted]

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]											Discontinuation/ End-of-Treatment Visits	Safety Follow-up Visit	Long-term Follow-up
		V1[l]	V2	V3	V4	V5	V6	V7	V7	V8	V9	V10			
		W1	W1	W2	W3	W4	W5	W7	W7	W9	W11	W13			
	Day -28 to First Treatment	D1	D2[b,l]	D8[l]	D15	D22[l]	D29	D43	D43-50[l]	D57	D71	D85	Until Progression	Up to 7/28 Days (±5 days) after Decision of Discontinuation/ Last Treatment[c]	10 Weeks (±2 weeks) after Last Treatment	Every 12 Weeks (±2 weeks)
Dose Escalation															
PK sampling[d,e]		X/X/ X[d]	X[b]	X	X/X/ X[e]		X/X/ X[e]	X/X/ X[e]	X[f]	X[e]	X[e]	X[e]	6-weekly up to/including Week 25, then every 12 weeks	- /X	X	
ADA sampling (HAHA on the CRF)[g]	X				X		X	X		X	X	X		- /X	X	
Soluble factors[h]		X	X[b]	X	X			X				X		- /X		
TGFβ[h]		X	X[b]	X	X			X				X		- /X		
CCI [redacted]	[redacted]								[redacted]					[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]				[redacted]		[redacted]		
Expansion: HCC[m]															
PK sampling[d, e]		X/X/ X[d]	X[b]	X	X/X/ X[e]		X	X/X/ X[e]	X[f]			X/X/ X[e]	6-weekly up to/including Week 25, then every 12 weeks	- /X	X	
ADA sampling (HAHA on the CRF)	X				X		X	X				X	6-weekly up to/including Week 25, then every 12 weeks	- /X	X	
Soluble factors		X	X[b]	X	X			X				X	6-weekly up to/including Week 25, then every 12 weeks	- /X		

Table 3 Schedule of Assessments – Pharmacokinetics Sampling, CCI [redacted]

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]												Discontinuation/ End-of-Treatment Visits	Safety Follow-up Visit	Long-term Follow-up
	Day -28 to First Treatment	V1[l] W1 D1	V2 W1 D2[b,l]	V3 W2 D8[l]	V4 W3 D15	V5 W4 D22[l]	V6 W5 D29	V7 W7 D43	V7 W7 D43-50[l]	V8 W9 D57	V9 W11 D71	V10 W13 D85	Until Progression	Up to 7/28 Days (±5 days) after Decision of Discontinuation/ Last Treatment[c]	10 Weeks (±2 weeks) after Last Treatment	Every 12 Weeks (±2 weeks)
TGFβ		X	X[b]	X	X			X				X		- /X		
Viral load testing (HBV, HCV)[n]	X	X			X			X				X	6-weekly up to/including Week 25, then every 12 weeks	- /X	X	
Alpha-fetoprotein		X			X			X				X	6-weekly up to/including Week 25, then every 12 weeks	- /X		
CCI [redacted]	[redacted]								[redacted]					[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]				[redacted]		[redacted]		
Expansion: GC, ESCC and BTC																
PK sampling[d, e]		X/X/ X[d]	X[b]	X	X/X/ X[e]		X	X/X/ X[e]	X[f]			X/X/ X[e]	6-weekly up to/including Week 25, then every 12 week	- /X	X	
ADA sampling (HAHA on the CRF)[g]	X				X		X	X				X	6-weekly up to/including Week 25, then every 12 weeks	- /X	X	

Table 3 Schedule of Assessments – Pharmacokinetics Sampling, CCI [redacted]

Measure	Screening Assessments	Treatment Phase (-3 / +1 days)[a]												Discontinuation/ End-of-Treatment Visits	Safety Follow-up Visit	Long-term Follow-up
	Day -28 to First Treatment	V1[l] W1 D1	V2 W1 D2[b,l]	V3 W2 D8[l]	V4 W3 D15	V5 W4 D22[l]	V6 W5 D29	V7 W7 D43	V7 W7 D43-50[l]	V8 W9 D57	V9 W11 D71	V10 W13 D85	Until Progression	Up to 7/28 Days (±5 days) after Decision of Discontinuation/ Last Treatment[c]	10 Weeks (±2 weeks) after Last Treatment	Every 12 Weeks (±2 weeks)
Soluble factors		X	X[b]	X	X			X				X	6-weekly up to/including Week 25, then every 12 weeks	- /X		
TGFβ		X														
CCI [redacted]																
[redacted]																

ADA=anti-drug antibody; BTC=biliary tract cancer; CRF=case report form; ESCC=esophageal squamous cell carcinoma; GC=gastric cancer; HAHA=human antihuman antibody; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; PD=progressive disease; PK=pharmacokinetics; TGFβ=transforming growth factor beta.

Unless stated otherwise in a footnote, all procedures and samples should occur prior to trial drug administration.

a A time window of up to 3 days before or 1 day after the scheduled visit day (-3 / +1 days) will be permitted for all procedures (except Day 2 and the Day 43-50 visit). The bi-weekly 14-day schedule should be strictly adhered to, returning to the target date even if the previous visit was off schedule.

b The Day 2 PK and CCI [redacted] samples must be drawn at least 24 hours after the Day 1 end of infusion, preferably > 30 hours after end of infusion. The exact time of each draw must be recorded. A protocol deviation will be defined by a sample not being drawn or by a predose sample being drawn after start of dosing.

c If another antineoplastic therapy is administered before the end of this 28-day period, the End-of-Treatment visit should be conducted, if possible, prior to the start of this new therapy.

d Blood samples for PK analysis should be drawn on Day 1 prior to dosing, immediately after completion of the infusion, and 4 hours after the start of the infusion.

e Samples for PK analysis to be taken before infusion (as close to the start of the infusion as possible), immediately after the completion of infusion, and 2 to 8 hours after the end of infusion (the later the better). If only 1 blood sample is scheduled at a visit, this is to be taken prior to the IMP administration. The exact time of each draw must be recorded. A protocol deviation will be defined by a sample not being drawn.

f A PK sample should be collected as close as possible to the time of mandatory/optional Week 7 biopsy as possible (ie, same day).

g An ADA sample should be taken prior to infusion, and the actual time of sample collection should be recorded.

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l Subjects who re-initiate treatment will continue in the trial and will be treated and monitored according to the Schedule of Assessments for the expansion part of the trial starting at Week 1, Day 1.

m No re-initiated HCC subjects as all completed/discontinued study.

n Subjects who are HBV positive should be tested for HBV viral load assessed according to the HCC schedule. Subjects with a previous history of HCV infection who have sustained viral response should have HCV viral load assessed at the Investigator's discretion according to the HCC schedule. Subjects who are HCV antibody positive at Screening should have HCV viral load assessed according to the HCC schedule.

2 Sponsor, Investigators and Trial Administrative Structure

The Sponsor of this clinical trial with MSB0011359C is Merck Biopharma Co., Ltd. (affiliate of Merck KGaA, Darmstadt, Germany) in Japan. In addition, Merck KGaA, Darmstadt, Germany, sponsors this clinical trial in Korea and Taiwan.

Trial Organization in Japan

Refer to the Trial Organization in Japan supporting document.

PPD

2.1 Investigational Sites

Dose escalation part: The trial will be conducted in up to 2 sites in Japan.

Expansion part: The trial will be conducted in up to 30 sites in Japan, Korea and Taiwan.

2.2 Trial Coordination/Monitoring

The Sponsor will coordinate the trial and will provide the support of CROs for some activities of the trial. Sponsor functional groups will perform oversight of the activities performed by the CROs.

The Sponsor will supply the trial medication of MSB0011359C to the sites. Packaging and distribution of clinical supplies will be performed by the Clinical Trial Supplies department of the Sponsor and the contracted manufacturing organization.

Safety laboratory assessments will be performed locally by investigational sites. Pharmacokinetics (PK), CCI CCI assessments will be performed centrally under the responsibility of the Sponsor.

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

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

The department of Global Biostatistics will supervise the statistical analyses (with the exception of the PK data analyses) which will be outsourced to a CRO.

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

Signature pages for the Protocol Lead and the Coordinating Investigator, as well as a list of Sponsor responsible persons, are in Appendix 4.

2.2.1 Safety Monitoring Committee

To ensure subjects' safety during the dose escalation and expansion parts of the trial, a Safety Monitoring Committee (SMC) will review the safety data on a regular basis. The SMC consists of permanent members from the Sponsor and/or CRO (at least the Medical Responsible, the Global Drug Safety Product Leader, and the Biostatistician for the expansion part), the Coordinating Investigator, and an external expert with expertise in the management of cancer patients. The SMC will evaluate the safety data from the dose levels 1 and 3 mg/kg and PK data from the dose level 1 mg/kg of EMR200647-001 as well before Study EMR200647-008 will be started at the 3 mg/kg dose level. During the dose escalation part of the trial, the SMC will evaluate the safety information of all the treated subjects, including those who started the treatment but did not complete the dose-limiting toxicity (DLT) evaluation period, and available PK data and will decide on the DLTs relevant for the treatment and will decide by consensus on dose escalation or suspension of enrollment and/or declaration of the maximum tolerated dose (MTD), with the final adjudication being a Sponsor prerogative. Treatment-related adverse events leading to a delay in dosing will be considered as well for the decision to go to the next dose level.

The SMC will recommend an MSB0011359C dose for the expansion part of the trial and may consider the MTD plus overall AEs, PK and any supporting information such as biomarker data. During the expansion part of the trial, the SMC will monitor on an ongoing basis (eg, when 15 subjects have been enrolled and treated for at least 4 weeks), all safety information of the participating subjects and will decide by consensus on continuation, modification, or suspension of the trial or of a particular expansion cohort. The SMC may modify the frequency of meetings as deemed appropriate by the SMC during the course of the trial. The specific working procedures will be described in an SMC charter, which will be established prior to the start of recruitment.

2.2.2 Central Reader and Independent Endpoint Review Committee

A central facility will read and interpret all radiographic scans for subjects enrolled in the expansion cohorts (for dose escalation, radiographic scans will be read locally). The data for all

images will be transferred from trial sites to the central reading center for evaluation. Scans will be evaluated at the central facility in accordance with Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1, see Eisenhauer 2009) and secondarily using modified RECIST (mRECIST) for subjects in the hepatocellular carcinoma (HCC) cohort. The imaging data will be transferred to the Sponsor or designee at regular intervals. A manual from the vendor will be provided to each trial site. The results of the central read will not be available in real time and will not be used for trial subject management. Local interpretation of radiographic scans will be used by the Investigator for real-time trial subject management decisions.

For subjects enrolled in the expansion cohorts, an Independent Endpoint Review Committee (IRC) will perform a blinded determination as to whether the criteria for tumor response or progression according to RECIST 1.1 have been met. The role of the IRC will be to review radiographic image findings and physical findings for the determination of the time point overall response and date of disease progression according to RECIST 1.1 for each subject. The full membership, mandate, and processes of the IRC will be detailed in the IRC charter. The results from the IRC will not be available in real-time and will not be used for trial subject management. The Investigator will determine tumor response or progression according to RECIST 1.1 for real-time trial subject management decisions.

3 Background Information

3.1 Investigational Medicinal Product

The Investigational Medicinal Product (IMP) for the present trial is M7824 (MSB0011359C).

MSB0011359C is a bifunctional fusion protein that combines an anti-programmed death ligand 1 (PD-L1) antibody and the soluble extracellular domain of transforming growth factor beta (TGFβ) receptor type II as a TGFβ neutralizing "trap" into a single molecule. This anti-PD-L1/TGFβ-Trap molecule is designed to target 2 major mechanisms of immunosuppression in the tumor microenvironment. The molecule contains the identical anti-PD-L1 antibody, avelumab (international nonproprietary name for MSB0010718C), currently in Phase II/III clinical development by the Sponsor. The MSB0011359C drug product is a genetic recombination drug manufactured by Chinese hamster ovary cells, transfected with an expression vector coding for this fusion protein.

CCI [redacted] derived suppressor cells, T cells, and tumor (Hotchkiss 2014; Souza-Fonseca-Guimaraes 2013).

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PD-L1. Blocking the axis restores the effector function in these T cells. Additionally, in the tumor microenvironment, myeloid cells, macrophages, parenchymal cells, and T cells upregulate PD-L1.

TGFβ has growth inhibitory effects on normal epithelial cells, functioning as a regulator of epithelial cell homeostasis, and it acts as a tumor suppressor during early carcinogenesis. As tumors progress toward malignancy, the growth inhibitory effects of TGFβ on the tumor are lost via mutation in one or more of the TGFβ pathway signaling components or through oncogenic reprogramming (Lebrun 2012). Upon loss of sensitivity to TGFβ inhibition, the tumor continues to produce high levels of TGFβ, which then serve to promote tumor growth (Lebrun 2012). The TGFβ cytokine is overexpressed in various cancer types with correlation to tumor stage (Lebrun 2012; Wrzesinski 2007). Many types of cells in the tumor microenvironment produce TGFβ, including the tumor cells themselves, immature myeloid cells, regulatory T cells, and stromal fibroblasts; these cells collectively generate a large reservoir of TGFβ in the extracellular matrix. TGFβ signaling contributes to tumor progression by promoting metastasis, stimulating angiogenesis, and suppressing innate and adaptive antitumor immunity (Lebrun 2012). As a broadly immunosuppressive factor, TGFβ directly down regulates the effector function of activated cytotoxic T cells and natural killer (NK) cells and potently induces the differentiation of naïve CD4+ T cells to the immunosuppressive regulatory T cells (Treg) phenotype (Wrzesinski 2007). In addition, TGFβ polarizes macrophages and neutrophils to a wound-healing phenotype that is associated with production of immunosuppressive cytokines (Hao 2012). As a therapeutic strategy, neutralization of TGFβ activity has the potential to control tumor growth by restoring effective antitumor immunity, blocking metastasis, and inhibiting angiogenesis.

Inhibition of TGFβ by soluble TGβRII reduced malignant mesothelioma tumors in a manner that was associated with an increase in CD8+ T cell antitumor effects (Suzuki 2004). CCI [redacted]

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Recently, nivolumab has shown clinical activity in HCC (out of 39 evaluable patients, 2 experienced complete response [CR] and 7 experienced partial response [PR]) with an acceptable safety profile (El-Khoueiry 2015).

A Phase II study of a small molecule kinase inhibitor of TGF signaling, LY2157299, revealed a subgroup of alpha-fetoprotein (AFP) responders in sorafenib failures or sorafenib intolerant HCC patients who had a substantial and significant increase in overall survival (OS) compared with the non-AFP responders, with median OS of 93.1 weeks versus 29.6 weeks, respectively, suggesting possible clinical activity of a TGF inhibitor in HCC (Faivre 2014).

MSB0011359C, is comprised of an extracellular domain of the human TGFβ receptor TGFβRII covalently joined via a glycine/serine linker to the C terminus of each heavy chain of the fully human IgG1 anti-PD-L1 antibody, avelumab. Given the emerging picture for PD-1/PD-L1 class, in which responses are apparent but with room for increase in effect size, it is assumed that co-targeting a complementary immune modulation step will improve tumor response. A similar TGF-targeting agent, fresolimumab, which is a monoclonal antibody targeting TGFβ1, 2 and 3, showed initial evidence of tumor response in a Phase I trial in subjects with melanoma. The objective response was observed in 1 of 28 subjects with 6 subjects showing stable disease (Morris 2014). CCI [redacted]

A reasonable safety profile is anticipated when targeting these pathways. The safety of the PD-1 / PD-L1 class continues to emerge but appears to be substantially less adverse compared with the cytotoxic T lymphocyte antigen-4 (CTLA-4) class of T cell checkpoint inhibitors (Dolan 2014; Sznol 2015). Two TGFβ inhibiting biologics have been administered in clinical trials and showed an acceptable human safety profile in humans that did not include immune-related events.

Fresolimumab was studied in Phase I trial in subjects with cancer (28 with melanoma, 1 with renal cell carcinoma). No DLTs were observed and 15 mg/kg, the highest dose tested, was determined to be safe (Morris 2014). The major AE was emergent skin tumors and hyperkeratosis. In a small trial of idiopathic pulmonary fibrosis, the most common AE was fatigue (Lonning 2011). In a study of 16 subjects with focal segmental glomerulosclerosis, the only AE was pustular rash in 2 subjects (Trachtman 2011). Transforming growth factor-β1 monoclonal antibody (TβM1), an antibody inhibiting the TGFβII receptor, was well tolerated when studied at doses as high as 240 mg with diarrhea as the only DLT event (Cohn 2014). Notably, one event of low hemoglobin (Hgb) was observed in the high dose group CCI [redacted] Overall, evidence suggests non-overlapping toxicity profiles for anti-PD-L1 and anti-TGFβ agent classes. There is a theoretical potential of immune-related adverse events (irAEs) that would be the consequence of a double blockade of negative regulatory loops of the immune system; however, taken together, CCI [redacted]

The anti-PD-L1 moiety of MSB0011359C is identical to the anti-PD-L1 antibody, avelumab, currently in Phase II/III clinical trials conducted by the Sponsor. The safety profile is described in the IB for avelumab and is briefly summarized here (refer to the current avelumab IB). As of a cut-off date of 05 November 2014, overall 558 subjects have received at least 1 dose of avelumab. In general, the safety analysis suggests an acceptable safety profile with most events either in line with those expected in subjects with advanced solid tumors or with similar class effects of monoclonal antibodies blocking the PD-1/PD-L1 axis. Infusion-related reactions including hypersensitivity and irAEs/autoimmune disorders have been identified as important risks for avelumab and thus considered potential risks for MSB0011359C. Management algorithms include steroids, other immune-suppressants, study drug interruption/discontinuation, and supportive management. Anti-PD-L1 has shown an overall rate of infusion reactions of approximately 10% (Grade 3/4 approximately 0.4% [fell to 0.2% with mandatory premedication]; no Grade 5).

A brief summary of safety experience with the PD-1 inhibitors nivolumab (Opdivo®) and pembrolizumab (Keytruda®) is given here, based on prescribing information (refer to current label information for updated information). For pembrolizumab the section on Warnings and Precautions includes adverse reactions of immune-mediated pneumonitis (2.9%), immune-mediated colitis (1%), immune-mediated hepatitis (0.5%), immune-mediated hypophysitis (0.5%), renal failure (0.5%) and immune-mediated nephritis (0.7%), immune-mediated hyperthyroidism (1.2%) and hypothyroidism (8.3%), and a variety of other immune-mediated adverse reactions occurring in less than 1% of patients. In addition, a warning for embryofetal toxicity is provided. For nivolumab, the section on Warning and Precautions includes adverse reactions of immune-mediated pneumonitis (2.2%) with fatal immune-mediated pneumonitis in 0.9% (5/574), immune-medicated colitis (2.2%), immune-mediated hepatitis (1.1%), immune-mediated nephritis and renal dysfunction (0.7%), immune-mediated hyperthyroidism (3%) and hypothyroidism (8%) and a variety of other immune-mediated adverse

reactions occurring in less than 1% of patients. In addition, a warning for embryofetal toxicity is provided.

Safety experience with various TGFβ targeting agents described in the literature suggests no overlapping immune-related profile with compounds of the anti-PD-1/anti-PD-L1 class. In Phase I trials, the experience with a molecule with a highly similar mechanism to the MSB0011359C TGFβ trap moiety, the anti-TGFβ-1 and 3 antibody fresolimumab, showed no dose limiting toxicity up to 15 mg/kg and no immune related events (Morris 2014). There were no DLTs and the only major AEs were skin lesions, mainly keratoacanthomas, some with atypical features, one event of squamous cell carcinoma, plus hyperkeratosis of the skin. Immune events were not reported. A syndrome known as Ferguson-Smith disease is caused by mutations in TGFβ is associated with the formation of keratoacanthomas, similar to the findings described for fresolimumab (Goudie 2011). Therefore, it is plausible that skin tumors observed during fresolimumab treatment may be related to TGFβ inhibition. TβM1, a neutralizing antibody against TGFβ-1, was well tolerated when studied as high as 240 mg with diarrhea as the only DLT event. Notably, one event of low Hgb was observed in the high dose group. CCI [redacted]. Trabedersen, an antisense oligonucleotide that inhibits TGFβ2 expression, was associated with thrombocytopenia that was moderate (Oettle 2011). Finally, TGFβ is known to play a role in wound repair (Leask 2004).

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3.2.2 Pharmacokinetics/Immunogenicity Findings

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3.3.3 Disease Background

3.3.3.1 Gastric Cancer

Gastric cancer (GC) remains the third leading cause of cancer-related deaths worldwide and is especially frequent in East Asia, including Japan (Ferlay 2015). Patients with advanced disease at diagnosis still remain with poor prognosis despite improvements in treatment. The relative 5-year survival rate of GC was reported to be around 60% in Japan (Matsuda 2011). Ramucirumab, an anti-epidermal growth factor receptor antibody was recently approved in Japan. The combination of ramucirumab with paclitaxel significantly increases overall survival compared with placebo plus paclitaxel. Recent progression of the treatment strategy with immune-checkpoint inhibitors showed antitumor activities in many kinds of tumors. PD-1 plays an important role as an immune-checkpoint molecule. Some clinical trials of anti-PD-1/PD-L1 monoclonal antibody are under investigation for GC. Pembrolizumab, a monoclonal antibody against PD-1 showed favorable antitumor effects in advanced GC (Bang 2015). The TGFβ1 is also considered a target of anticancer therapy. The association between expression of TGFβ and prognosis in GC has been reported. Patients with TGFβ1 expression had worse prognosis after surgical therapy compared to those without expression of TGF-β1 in the tumor (median survival of 16.1 months of patients with TGFβ1 expression versus 37.1 months of patients without TGFβ1 expression, $p = 0.034$) (Ananiev 2011). GC is considered to be a good target indication of MSB0011359C.

3.3.3.2 Esophageal Squamous Cell Cancer

Esophageal cancer (EC) is one of the common cancers in the world (Zhang 2013). The incidence of EC appears to be increasing due to the increase of adenocarcinoma in the Western countries. Globally, the most prevalent form of EC is esophageal squamous cell carcinoma (ESCC) (Arnold 2015). ESCC is the most common histological type in Asian countries, including Japan with over 95% of EC. In 2014, mortality was estimated at 11,700 in Japan (Matsuda 2014). Esophageal cancer continues to have a poor prognosis with a relative 5-year survival of 30% (Matsuda 2011). PD-L1, the ligand of PD-1, is known to frequently overexpress in EC. Pembrolizumab, a monoclonal antibody against PD-1 has demonstrated antitumor effects in advanced EC (Doi 2015). One ESCC patient was also observed to have a durable response on avelumab (internal data). Association between serum TGFβ1 level and the prognosis in patients with ESCC was also reported (Sun 2007). In patients with decreased serum TGFβ1 levels after radiotherapy, the 1-year survival rate was 61.02% compared with 17.86% in patients with increased serum TGFβ1 levels ($p < 0.01$). ESCC is also considered to be a good target indication of MSB0011359C.

3.3.3.3 Biliary Tract Cancer

Biliary tract cancer (BTC) is more common in East Asia and Latin America than in other continents. The incidence of BTC in 2011 was reported to be 23,606 (male: 12,250, female: 11,356) in Japan (Doi 2015). Biliary tract cancer includes gallbladder cancer (GBC), cholangio

cell carcinoma (CC) and carcinoma of Vater's ampular (VAC). CC is classified into intrahepatic CC and extrahepatic CC. The proportion of each cancer in BTC in Japan was reported as follows: GBC: 37.0%; CC: 48.9%; and VAC: 14.1% (Miyakawa 2009). Despite recent progress in diagnostic procedures, most cases are advanced at initial diagnosis and are treated by chemotherapy. The survival data of the unresectable patients is poor (1-year survival: GBC: 11%; CC: 25%; VAC: 38%). Even if surgery can be performed, 5-year survival rates remain low as a result of relapse (GBC: 41.6%; CC: 33.1%; VAC: 52.8%) (Miyakawa 2009). Results of several studies showed that both PD-L1 and TGFβ were related to tumor progression or malignancy of BTC. A higher tumor-related PD-1 expression was associated with a poorer histological differentiation and a more advanced primary tumor node metastasis stage in intrahepatic cholangiocarcinoma ($p < 0.05$) (Ye 2009). Another study showed that immunohistochemical TGFβ correlated with tumor progression and poor prognosis. TGFβ immune activity was significantly higher in advanced than in early GBC ($p = 0.02498$) (Kitamura 2003). These data provide a strong rationale for continuing the development of MSB0011359C in BTC.

3.3.3.4 Hepatocellular Carcinoma

Hepatocellular carcinoma is the seventh most common cancer with 782,000 new cases occurring globally in 2012 (IARC 2012). More than 70% (50% in China alone) of all new cases of liver cancer were diagnosed in Asia (Ashtari 2015). Chronic hepatitis B virus (HBV) infection is the main cause of HCC in Asia. In Japan, the prevalence of hepatitis C virus (HCV) infection is higher than HBV infection unlike other Asian countries.

The treatment strategy for HCC is determined based on its stage and liver function. Surgery and radiofrequency ablation are the standard therapies for early stage HCC. For intermediate stage, transcatheter arterial chemoembolization is selected. Most HCC are diagnosed at an advanced stage. Sorafenib is the standard 1st line systemic chemotherapy for advanced HCC based on the clinical trial data (Llovet 2008; Cheng 2012). However, the prognosis of advanced HCC remains poor and there are no approved standard therapies beyond sorafenib.

Recently, nivolumab was shown to have clinical activity in HCC (of the 39 evaluable patients, 2 experienced CR and 7 experienced PR) with an acceptable safety profile (El-Khoueiry 2015).

A Phase II study of a small molecule kinase inhibitor of TGF signaling, LY2157299, revealed a subgroup of AFP responders in sorafenib failures or sorafenib intolerant HCC patients who had a substantial and significant increase in overall survival (OS) compared with the non-AFP responders, with median OS of 93.1 weeks versus 29.6 weeks, respectively, suggesting possible clinical activity of a TGF inhibitor in HCC (Faivre 2014). Hepatocellular carcinoma is also considered a good target indication of MSB0011359C.

3.4 Summary of the Overall Benefit and Risk

The risk-benefit ratio has been carefully considered in the planning of the trial. CCI [redacted] n SMC

is planned for the ongoing assessment of the risk-benefit ratio. The trial will be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit ratio and would render continuation of the trial unjustifiable. The following are considered important risks of exposure to MSB0011359C:

- Infusion-related reactions including hypersensitivity
- irAEs/autoimmune disorders
- Anemia
- Rash with hyperkeratosis, keratoacanthoma, and squamous cell carcinoma of the skin
- Alterations in wound healing or repair of tissue damage
- Embryofetal toxicities
- Mild to moderate mucosal bleeding events.

Respective safety measures comprise inclusion/exclusion criteria for participation in clinical trials with MSB0011359C, guidance for prevention, monitoring, and medical management of important risks, as well as guidance on trial treatment interruption or discontinuation.

3.4.1 Infusion-related Reactions/Hypersensitivity

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As of 05 November 2014, from the EMR100070-001 trial with the parent avelumab antibody, 1 subject (2.0%) in the dose escalation cohort reported an infusion-related reaction event (Grade 2) and 49 (10.2%) of the 480 subjects in the expansion cohorts experienced at least 1 episode of an infusion-related reaction when receiving avelumab monotherapy. Most of the events were Grade 1 (8 subjects, 1.7%) or Grade 2 (36 subjects, 7.5%) in intensity, and Grade 3 (3 subjects, 0.6%) or Grade 4 events (2 subjects, 0.4%) were less frequent. No Grade 5 events have been reported. Most of the infusion-related reaction events had an onset after the first (30 subjects, 6.3%) or second (16 subjects, 3.3%) avelumab infusion. In 8 subjects (1.7%), avelumab treatment was discontinued because of infusion-related reaction events.

Risk mitigation measures for potential infusion-related reactions/hypersensitivity include:

- Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of MSB0011359C is mandatory (eg, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] intravenous or oral equivalent) for the first 2 infusions. Premedication is optional and at the discretion of the Investigator after the second infusion. If Grade 2 infusion reactions are seen during the first two infusions, then premedication should not be stopped. Steroids as premedication are not permitted.
- Special precautions for monitoring of subjects and management of infusion-related reactions/hypersensitivity as described in Section 6.5.4.1 and Section 6.5.4.2.
- Infusion-related reactions/hypersensitivity (any grade) are considered as important identified risks and adverse events of special interest (AESI) requiring expedited reporting from the Investigator to the Sponsor. For nonserious AESIs, an AESI Report Form has to be completed; for serious events, an SAE Report Form has to be used (see Section 7.4.1.4).

3.4.2 Immune-related Adverse Events/Autoimmune Disorders

Immune-related AEs/autoimmune disorders are events that are related to the pharmacology of checkpoint inhibitors and can be explained by an immune-phenomenon after other etiologies have been ruled out. Relevant clinical safety experience has been generated with the parent anti-PD-L1 avelumab antibody.

- As of 05 November 2014, a cumulative review revealed 56 cases of potential irAEs out of 480 subjects (11.7%) treated in the expansion part of trial EMR100070-001 and 4 cases out of 50 subjects (8.0%) treated in the dose-escalation part of trial EMR100070-001. A customized Medical Dictionary for Regulatory Activities (MedDRA) query was used for data retrieval from the clinical database with predefined preferred terms of potential irAEs.
- Of 69 potential irAEs reported, 13 were SAEs (18.8%) and 56 were nonserious AEs (81.1%). In the majority of the cases, there was a plausible temporal association between the event onset and the drug administration. Of these 69 events, 46 events (66.7%) were assessed as treatment-related by the Investigator and 23 events (33.3%) were assessed as not treatment-related by the Investigator.
- Twenty-six events were assessed as Grade 1, 29 events as Grade 2, 11 events as Grade 3, 2 events as Grade 4, and 1 event (pneumonitis) as Grade 5 (note: 2 more events of autoimmune hepatitis had a fatal outcome; however, they were assessed as Grade 3 with a subsequent fatal liver failure).
- Based on the irAE cases that have been observed with avelumab, all trial investigators will be trained to be made aware of the frequency and severity of the observed events and to proactively administer steroid treatment for any suspicion of irAEs.

Based on clinical experience with avelumab and with other agents blocking the PD-1/PD-L1 pathway, irAEs/autoimmune disorders are an important identified risk and AESI for MSB0011359C. Risk management measures similar to the lead program include:

- Instructions for trial treatment discontinuation or interruption in case of irAEs/autoimmune disorders (see Section 6.5.4.3).
- Guidance for the medical management of irAEs/autoimmune disorders including specific guidance with regard to the affected organ/body system (see Section 6.5.4.3).
- irAEs/autoimmune disorders (any grade) are considered as AESIs requiring expedited reporting from the Investigator to the Sponsor. For nonserious AESIs, an AESI Report Form has to be completed; for serious events, an SAE Report Form has to be used.
- Regular laboratory tests on parameters indicative for autoimmune disorders, such as thyroid stimulating hormone (TSH), will be performed as detailed in the Schedules of Assessments (see Table 1 and Table 2).
- To help monitor for autoimmune effects, baseline ophthalmology examination including slit lamp inclusive of the anterior segment and including visual acuity. If clinically relevant eye signs or symptoms occur during the trial, then an appropriate ophthalmology examination should be obtained within 2 days including slit lamp evaluation inclusive of the anterior segment and with visual acuity.

3.4.3 Anemia

CCI [redacted] Inclusion criteria for the study will require adequate entry Hgb value. Respective hematological parameters will be monitored every week up to Week 5 and then every 2 weeks thereafter. Risk management measures are provided in Section 6.5.4.4. CCI [redacted]

3.4.4 Alterations in Wound Healing or Repair of Tissue Damage

Alternations of wound healing and tissue damage repair are considered as an important potential risk given the TGFβ mechanism. Management should be discussed with the Medical Monitor on a case-by-case basis. In general, a 2 week delay from treatment is recommended following minor surgery and a 4 week delay for major surgery, but cases should be discussed with the Medical Monitor.

3.4.5 Rash with Hyperkeratosis/Keratoacanthoma/Squamous Cell Carcinoma of the Skin

Phase I information from a TGF antibody showed excess acanthomas, some with atypical features, and one confirmed squamous cell carcinoma (Morris 2014). A genetic disorder in the TGF pathway is also known to be associated with skin tumors (Goudie 2011). Based on this information, skin tumors are considered a potential risk. Monitoring will include skin assessments as defined in the Schedules of Assessments (see Table 1 and Table 2). Management should be discussed with the Medical Monitor on a case-by-case basis. Dermatological consults should be requested as needed. Rash with hyperkeratosis/keratoacanthoma/squamous cell carcinoma of the skin are considered as an important identified risk and AESIs requiring expedited reporting from the Investigator to the Sponsor. Any suspicious lesion should be biopsied. For nonserious AESIs, an AESI Report Form has to be completed; for serious events, an SAE Report Form has to be used (see Section 7.4.1.4).

3.4.6 Embryofetal Toxicity

Embryofetal toxicities are a known risk of the PD-1/PD-L1 targeting class. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Based on its mechanism of action (MoA), MSB0011359C may cause fetal harm when administered to a pregnant female and conferred as an important potential risk. An appropriate contraception warning is provided in this clinical protocol. Subjects with pregnancy or in lactation period are prohibited from enrolling in clinical trials.

3.4.7 Mild to Moderate Mucosal Bleeding Events

Mucosal bleeding events of mild to moderate severity were observed in participants treated with M7824 in ongoing studies and are a potential risk for M7824. Events may include epistaxis, hemoptysis, gingival bleeding, or hematuria amongst others. In general, these reactions resolve without discontinuation of treatment.

3.4.8 Potential Benefit

A direct benefit is considered unlikely for participants in this Phase I trial, especially in the low doses of the dose escalation part; therefore only subjects with malignancies for which no standard effective therapy exists or subjects having experienced a failure of standard therapy are eligible for this part of the trial. However, preliminary results from the EMR100070-001 trial with the parent avelumab antibody demonstrate promising clinical antitumor activity. CCI [redacted]

In conclusion, the risk-benefit ratio of treatment with MSB0011359C in the targeted trial population appears positive given the poor prognosis of subjects with advanced malignancies with no standard treatment options.

This clinical study will be conducted in compliance with the clinical study protocol, standards stipulated in Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law; and "Ministerial Ordinance on Standards for the Implementation of Clinical Studies on Pharmaceutical Product (GCP).

4 Trial Objectives

4.1 Primary Objective

The primary objective of the trial is to determine the safety, tolerability and MTD administered as monotherapy of MSB0011359C in subjects with metastatic or locally advanced solid tumors.

4.2 Secondary Objectives

The secondary objectives are:

- To characterize the PK profile of MSB0011359C
- To evaluate the immunogenicity of MSB0011359C and its relationship to drug exposure
- To assess the best overall response (BOR) according to RECIST 1.1 (Eisenhauer 2009).

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5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a Phase I, open-label, dose escalation trial to investigate the safety, tolerability, PK, biological and clinical activity of MSB0011359C (M7824) in subjects with metastatic or locally advanced solid tumors with expansion cohorts in selected indications (GC, ESCC, BTC and HCC) in Asia (see Figure 1).

5.1.1 Overall Study Design

5.1.1.1 Dose Escalation

The dose escalation part of this trial will investigate the safety and tolerability of MSB0011359C. It is composed of a standard "3+3" dose escalation design for which 3 to 6 subjects will be enrolled at each dose level depending on the occurrence of DLTs (see Section 5.1.3.3), followed by expansion in cohorts of subjects with GC, ESCC, BTC and HCC (see Figure 1). The dose escalation part and the HCC expansion part of the trial will be conducted in Japan only.

Cohorts of 3 to 6 subjects with metastatic or locally advanced solid tumors, for which no standard effective therapy exists or a standard therapy has failed, will receive MSB0011359C at escalating dose levels (3 mg/kg, 10 mg/kg and 20 mg/kg) once every 2 weeks (see Section 5.1.3.2). The dose range and schedule for this trial were developed based on safety considerations as well as on CCI and experience with the parent avelumab antibody. Up to 18 subjects with metastatic or locally advanced solid tumors are planned for the dose escalation part.

At each dose level, subjects will receive MSB0011359C as a 1-hour (-10 minutes/+20 minutes, ie, over 50 to 80 minutes) intravenous infusion once every 2 weeks until PD has been confirmed by a subsequent scan, unacceptable toxicity, or occurrence of any criterion for withdrawal from the trial or the investigation medicinal product (IMP; see Section 5.5).

Subjects who have experienced CR, PR or SD should be treated through the end of 12 months, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor. For subjects who achieve CR, PR, or SD on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the study, 1 re-initiation course of treatment at the same dose and schedule and treatment duration up to 12 months is allowed at the discretion of the Investigator and agreement of the trial Medical Monitor (see Section 5.1.6).

Assessment of safety parameters will focus on potential acute side effects that include allergic reactions/hypersensitivities during and immediately following infusion, in the worst case

anaphylaxis, which could develop as consequence of an immunogenicity response and might be pronounced due to the immunostimulatory properties of MSB0011359C, promoting an immune response against itself.

Evaluation of safety will also include the incidence and severity of potential irAEs, which may manifest after weeks of treatment (Attia 2005; Calabro 2010; Di Giacomo 2010; Kaehler 2010; Phan 2003; Wolchok 2010). Such immune-mediated AEs may include pneumonitis, colitis, hepatitis, hypophysitis, nephritis, and thyroiditis (hypo- or hyperthyroidism). The spectrum of hypothetical irAEs also includes formation of auto-antibodies such as antinuclear antibodies (ANAs).

Other important risks of the compound include anemia, rash with hyperkeratosis, keratoacanthoma, and squamous cell carcinoma of the skin, as well as alterations in wound healing or repair of tissue damage.

All DLTs will be monitored centrally, and the decision to escalate to the next dose level will be determined by the SMC as outlined in Section 2.2.1.

5.1.1.2 Expansion Cohorts

After determination of the MTD in the dose escalation part, an MSB0011359C dose for further investigation will be selected and enrollment in the expansion cohorts of GC, ESCC and BTC will begin (Figure 1).

After completion of DLT evaluation at 3 mg/kg and 10 mg/kg in the dose escalation part, enrollment in the HCC expansion cohort will start at 3 mg/kg and 10 mg/kg, respectively. Three subjects will be enrolled at 3 mg/kg once the 3 mg/kg dose level in the dose escalation part of the trial has been cleared by the SMC. Six subjects will be enrolled at 10 mg/kg once the 10 mg/kg dose level in the dose escalation part of the trial has been cleared by the SMC. The purpose of the HCC cohort is to further assess the safety of MSB0011359C in subjects with HCC.

Subjects in the expansion cohorts will receive MSB0011359C as a 1-hour intravenous infusion once every 2 weeks until PD has been confirmed by a subsequent scan, unacceptable toxicity or occurrence of any criterion for withdrawal from the trial or the IMP (see Section 5.5).

Subjects who have experienced CR, PR or SD should continue treatment through the end of 12 months after confirmation, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor. In the case of PD, subjects should continue treatment through their next tumor assessment, if they meet the criteria described in Section 5.5.1. If there is further evidence of PD thereafter, trial treatment should be discontinued; however, continued treatment is possible in consultation with the Medical Monitor. For subjects who achieve a CR, PR, or SD on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the study, 1 re-initiation course of treatment at the same

dose and schedule and treatment duration up to 12 months is allowed at the discretion of the Investigator and agreement of the trial Medical Monitor (see Section 5.1.6).

For subjects in the GC expansion cohort only, symptom severity will be assessed using 3 patient-reported outcomes questionnaires:

- Patient Global Impression of Severity (PGIS)
- Select items from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core instrument (EORTC QLQ-C30)
- Select items from the EORTC QLQ-STO22 (stomach cancer module)

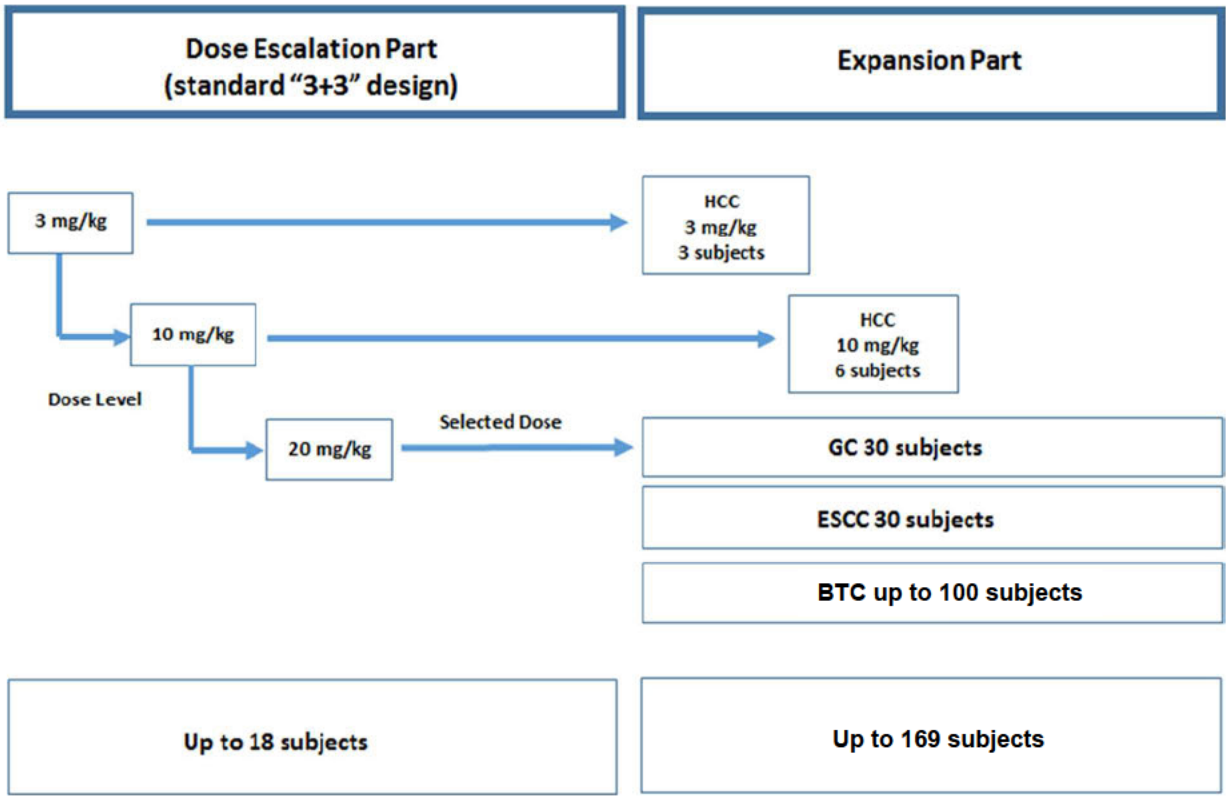
For subjects in the ESCC cohort only, symptom severity will be assessed using 3 patient-reported outcomes questionnaires:

- PGIS
- Select items from the EORTC QLQ-C30
- Select items from the EORTC QLQ-OES18 (esophageal cancer module)

For subjects in the BTC cohort only, symptom severity will be assessed using 4 patient-reported outcomes questionnaires:

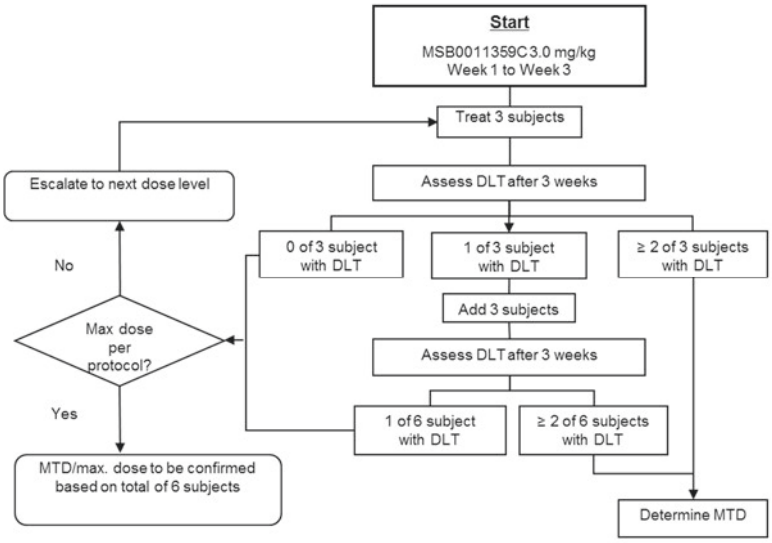
- PGIS
- Select items from the EORTC QLQ-C30
- Select items from the EORTC QLQ-BIL21 (cholangiocarcinoma and gallbladder cancer module)
- Select items from the EORTC QLQ-HCC18 (hepatocellular carcinoma module)

Figure 1 Schematic of Study Design



BTC=biliary tract cancer; ESCC=esophageal squamous cell cancer; GC=gastric cancer; HCC=hepatocellular carcinoma.

Figure 2 Dose Escalation Schematic



DLT=dose-limiting toxicity; max=maximum; MTD=maximum tolerated dose

5.1.2 Trial Medication Administration and Schedule

Subjects will receive intravenous infusion of MSB0011359C over 1 hour (- 10 minutes/+20 minutes, ie, over 50 to 80 minutes) once every 2 weeks. In order to mitigate potential infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) (eg, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] intravenous or oral equivalent) approximately 30 to 60 minutes prior to each dose of MSB0011359C is mandatory for the first 2 infusions. Premedication is optional and at the discretion of the Investigator after the second infusion. If Grade 2 infusion reactions are seen during the first two infusions, then premedication should not be stopped. Steroids as premedication are not permitted.

The trial treatment schedules are provided in the Schedules of Assessments (see Table 1 and Table 2).

The formulation and packaging information of MSB0011359C is provided in Section 6.1 and Section 6.6.

5.1.3 MSB0011359C Dose Escalation

The dose escalation part of the study is expected to enroll up to 18 subjects. Eligible subjects will be patients with metastatic or locally advanced solid tumors who have failed standard therapies or who have no standard effective therapy available.

5.1.3.1 Starting Dose

The starting dose of MSB0011359C will be 3 mg/kg.

5.1.3.2 Dose Escalation

The dose escalation will use a standard 3+3 scheme with the following planned doses:

- 3 mg/kg
- 10 mg/kg
- 20 mg/kg

The DLT period is defined as 21 days after the start of therapy. The first subject of each cohort will be observed for at least 5 days before the second subject can be treated. Thereafter, within each cohort, 48 hours must pass before a new subject can initiate dosing. Once the 3 or 6 subjects have passed the 21-day DLT evaluation period, the SMC will review the safety and available PK data to decide upon further dose escalation. Pharmacokinetics data from the previous cohort will be required for SMC review (eg, when the SMC is reviewing safety data from the 10 mg/kg cohort, available PK data from the 3 mg/kg cohort); however, PK data from the cohort under review will not be required).

For each dose level, DLTs are assessed during the first 3 weeks (Figure 1). The criteria for moving from one dose level to another do not allow escalation to the next cohort in cases where more than 1 subject in a cohort experience a DLT. If 1 of 3 subjects in a cohort experiences a DLT, this cohort will be expanded to 6 subjects with the SMC meeting after the 6th subject completes the DLT evaluation period.

The MTD is defined as the highest dose where no more than 1 subject out of 6 subjects experiences a DLT. Thus, the MTD cohort should accrue a total of 6 subjects (Figure 2).

After completion of the DLT evaluation at 3 and 10 mg/kg in the dose escalation part, enrollment in the HCC expansion cohort will start at 3 and 10 mg/kg, respectively.

After determination of the MTD in the dose escalation part, an MSB0011359C dose for further investigation will be selected and enrollment in the expansion cohorts of subjects with GC, ESCC, and BTC will begin (Figure 1).

The DLT criteria will not apply to any of the expansion cohorts.

5.1.3.3 Dose-Limiting Toxicity

A DLT is defined as any Grade ≥ 3 AE, with the exceptions described hereafter, assessed as related to IMP by the Investigator and/or Sponsor (ie, Grade ≥ 3 adverse drug reaction [ADR]; grading

according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.03 [CTCAE v4.03]) occurring in the DLT evaluation period (21 days after first administration of MSB0011359C) confirmed by the SMC to be relevant for the IMP treatment. The SMC recognizes that in the absence of prior human experience with MSB0011359C, a conservative approach will be adopted in ascribing the relevance of the treatment-related toxicity to IMP. Treatment-related SAEs will be ascribed as related to drug except where a clear relationship to the underlying disease or recognized comorbidities is evident.

A DLT is defined as the following:

Any Grade ≥ 3 AE that is related to MSB0011359C, occurring during the DLT evaluation period (21 days after administration of MSB0011359C), **except** for those listed below. Also, elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 3 times the upper limit of normal (ULN) and a concomitant elevation of bilirubin 2 times the ULN attributable to study drug constitutes a DLT.

- Grade 3 infusion-related reactions resolving within 6 hours from the end of infusion and controlled with medical management.
- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management.
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1.
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis.
- Grade 3 Hgb decrease (< 8.0 g/dL) that resolves to at least 9 g/dL within 14 days or the changes in the associated RBC parameters resolve within 14 days without blood transfusion or erythroid growth factor use.
- Malignant skin lesion that is local and can be resected with negative resection margin.

Dose-limiting toxicities that require treatment discontinuation are described in Section 5.1.7.2.

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

5.1.4 Expansion Cohorts

After completion of DLT evaluation at 3 and 10 mg/kg in the dose escalation part, enrollment in the HCC expansion cohort will start at 3 and 10 mg/kg, respectively.

After confirmation of tolerability at 20 mg/kg in the dose escalation part, the MSB0011359C dose for further investigation is 1200 mg in the expansion cohorts of subjects with GC, ESCC, and BTC after confirmation by the SMC.

5.1.5 Planned Number of Subjects

The planned number of the evaluable subjects for this trial is derived from the dose escalation "3+3" design and the expansion cohort sizes:

CCI [redacted]

[redacted]

The final sample size, however, may vary depending on the total number of dose levels to be escalated and tested, and the subject replacement for DLT evaluations if applicable.

In the event that rapid recruitment in the expansion phase impacts supply of IMP, the screening of new subjects for any cohort may be temporarily paused with 24 hours' notice to investigators.

5.1.6 Planned Treatment Duration

The trial duration for a subject is estimated to be up to 2 years. This includes:

- Up to 28-day Screening period (decision will be made in this period for subjects' trial inclusion if all eligibility criteria are met).
- 21-day DLT evaluation period.
- 12-month treatment duration period until confirmed PD, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 5.5).
- End-of-Treatment visit 28 days (± 5 days) after the last dose of MSB0011359C administration.
- Safety follow-up period 10 weeks (± 2 weeks) after the last administration of MSB0011359C.
- Long-term follow-up period: Subjects without PD at the End-of-Treatment visit will be followed up for disease progression (computed tomography [CT]/magnetic resonance imaging [MRI] scans every 12 weeks) until PD.
- Planned first subject in (dose escalation): First Quarter (Q1) 2016. Planned date last subject out (dose escalation): Q4 2020. Planned date last subject out (after expansion and follow-up): Q4 2020.

Subjects who have experienced a CR, PR or SD should continue treatment through the end of 12 months after confirmation, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor. In the case of PD, subjects should continue treatment through their next tumor assessment, if they meet the criteria described in Section 5.5.1.

For subjects who achieve a CR, PR, or SD on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, 1 re-initiation course of treatment at the same dose and schedule and treatment duration up to 12 months is allowed at the discretion of the Investigator and agreement of the trial Medical Monitor. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial MSB0011359C therapy. Prior to re-initiation of the trial treatment, malignant disease needs to be radiologically re-staged to assess all known sites of the disease and to establish a new baseline for subsequent tumor measurements. Relevant safety laboratory results must be available and verified prior to re-initiating of treatment. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the Schedule of Assessments for the expansion part of the trial starting at Week 1, Day 1 (see Table 2).

Moreover, any ADRs should be followed until they resolve, return to Baseline, or stabilization or are irreversible, or when the subject starts a new anticancer therapy (see Section 7.1.5 for details).

5.1.7 Dose Modification and Adverse Drug Reactions Requiring Treatment Discontinuation

5.1.7.1 Dose Modification

The dose of MSB0011359C will be calculated based on the weight of the subject determined on the day prior to or the day of each drug administration.

Each subject will stay on the MSB0011359C dose level assigned in the trial unless treatment needs to be stopped. Dosing modifications (changes in infusion rate) and dose delays are described in Section 5.1.7.2 and Section 6.5.4 and subsections. There are no dose reductions.

5.1.7.2 Adverse Drug Reactions Requiring Treatment Discontinuation

Certain ADRs, defined in this trial as any AE assessed as related to MSB0011359C by the Investigator and/or Sponsor, may require permanent treatment discontinuation of MSB0011359C (listed below). For certain ADRs assessed to be immune-related, Table 5 criteria may supersede this section. These criteria may allow the subject to continue on study if medically indicated after consultation with Medical Monitor.

Any Grade 4 ADRs require permanent treatment discontinuation except for single laboratory values out of normal range that do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management.

Any Grade 3 ADRs require treatment discontinuation <u>except</u> for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management.

- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to ≤ Grade 1.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis. The trial Medical Monitor should be consulted for such Grade ≥ 3 amylase or lipase abnormalities. If the amylase or lipase abnormality not associated with symptoms or clinical manifestations of pancreatitis has not resolved to Grade ≤ 1 within the subsequent 2 cycles (28 days), the subject should permanently discontinue treatment with MSB0011359C.
- Grade 3 Hgb decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor use does not require treatment discontinuation. During the 21-Day DLT period, a Grade 3 Hgb decrease (< 8.0 g/dL) will require treatment discontinuation, unless it resolves to at least 9 g/dL within 14 days or the changes in the associated RBC parameters resolve within 14 days without blood transfusion or erythroid growth factor use.
- Increases in Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 3 that resolves to ≤ 2 by cycle Day 1 of the next cycle (infusions should not be given if the ECOG PS is ≥ 3 on the day of IMP administration and should be delayed until ECOG PS ≤ 2).
- Keratoacanthoma and squamous cell carcinoma of the skin. Any suspicious skin lesion should be biopsied and be surgically removed. The Study Medical Monitor should be consulted.
- Grade 3 or 4 dematological irAEs, treatment should be delayed and treatment started according to Table 5, if condition improves to Grade 1, treatment may be resumed. If ≥ 2 consecutive doses are missed, the Medical Monitor should be consulted.
- Grade 3 or 4 symptomatic endocrinopathies (eg, thyroiditis or hypophysitis), treatment should be delayed and treatment started according to Table 5, if condition improves to Grade 1, treatment may be resumed. If ≥ 2 consecutive doses are missed, the Medical Monitor should be consulted
- Other immune-related ADRs, see Table 5.

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle but is manageable and/or not clinically relevant, the ADR should be discussed with the medical monitor. Based on the discussion, it is possible that the infusion will be given on the following cycle. If at the end of the following cycle, the event has not resolved to Grade 1,

another discussion should occur with Medical Monitor to consider permanently discontinuing treatment with MSB0011359C.

- Upon the second occurrence of the same Grade 2 ADR in the same subject (except for fatigue and hormone insufficiencies that can be managed by replacement therapy), continuation of treatment with MSB0011359C has to be discussed with the medical monitor and may lead to permanently discontinuation.
- Infusion-related reactions and hypersensitivity reactions (Grades 1 to 4) should be handled according to the guidelines provided in Section 6.5.4.1 and Section 6.5.4.2, respectively.
- Anemia should be handled according to the guidelines provided in Section 6.5.4.4.
- If immune-related ADRs, see Table 5.

5.1.8 Analysis Cut-Off Dates

After the end of the dose escalation part of the trial, a full analysis for safety and PK/CCI [redacted] data will be made. The primary data cut-off date for the dose escalation part is 3 months after the last subject in the dose escalation part received the first dose of MSB0011359C.

The primary data cut-off for the analysis of each expansion cohort separately will be 6 months after the last subject in that cohort started treatment.

The final data cut-off is 1 year after the last subject has received the last dose of MSB0011359C.

5.2 Discussion of Trial Design

This is a Phase I, open-label, dose escalation trial with an expansion part in cohorts of subjects with GC, ESCC, BTC and HCC. An open-label, unblinded design is appropriate for a dose escalation trial with expansion cohorts in advanced cancer subjects since subjects have exhausted treatment options.

In this trial, the assessment of the safety and tolerability of the IMP with the determination of the MTD (in the dose escalation part only) is set to be the primary objective. The determination of the MTD is one of the first major steps in the development of a compound entering early clinical development because it might be determined that the highest tolerable dose is important in future clinical development in order to achieve the best efficacy to risk ratio for subjects. The MTD will be determined using a standard "3+3 subjects" dose-escalation design based on DLT assessments, which is commonly used in first-in-man oncology trials (Crowley 2006). The aim of this design is to maximize the protection to subjects and reduce the chances of more subjects to be exposed to possible drug toxicities; however, at the end of the dose-escalation part, it is intended to fill cohorts as described in Section 5.1.1 to identify a reasonable dose for the expansion part. All these assessments will be correlated to PKCCI [redacted] parameters to potentially aid selection of the most meaningful dose for the expansion cohorts or future studies.

A reasonably safe starting dose of 3 mg/kg has been chosen taking also into account the information from the clinical experience with the parent monoclonal antibody, avelumab, and the predicted lack of overlapping immune-related safety profile with TGFβ inhibition, as previously discussed. Initial dose setting follows the principle that the starting dose should be pharmacologically active but also reasonably safe to use. This initial dose estimation algorithm is proposed in ICH S9: CCI [redacted]

The dose to be used in the expansion part of the trial will be determined based on the data from the dose escalation part. The parameters considered for selection of the dose to be used in expansion part will include safety profile, PK, pharmacodynamics, and antitumor efficacy. In addition to determining the MTD, the trial will serve to explore biologic and clinical parameters after exposure to MSB0011359C. Due to a limited understanding of the interaction of the immune system and tumors in cancer subjects, there can be no certainty that the doses to be examined will be associated with relevant antitumor activity, although preliminary results with the parent avelumab antibody suggest promising clinical antitumor activity. The selection of the dose to be used for further clinical evaluation will be based on the best current scientific knowledge.

The target population for the dose escalation part comprises subjects with metastatic or locally advanced solid tumors who have exhausted standard treatment options. There will be 4 cohorts of subjects with GC, ESCC, BTC and HCC in the expansion part. In order to obtain a trend of biological/clinical activity, to assess target engagement based on tumor tissue samples and to collect further safety data, a treatment expansion at a meaningful dose level to be identified during the dose-escalation part to ensure further development in selected settings is justified.

The tests and analyses to examine the biologic effects of MSB0011359C dosing will include the assessment of markers of immune activation known to show typical changes after treatment with therapies blocking immune checkpoints. CCI [redacted] CCI [redacted].

5.2.1 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

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

5.3.1 Inclusion Criteria

For inclusion in the trial, all of the following inclusion criteria must be fulfilled.

5.3.1.1 Inclusion Criteria for Dose Escalation

1. Able and willing to give written informed consent and has signed the appropriate written informed consent form (ICF), prior to performance of any trial activities.
2. Eligible male or female subjects aged ≥ 20 years.
3. Histologically or cytologically proven metastatic or locally advanced solid tumors, for which no effective standard therapy exists or standard therapy has failed.
4. ECOG PS of 0 to 1 at trial entry.
5. Life expectancy ≥ 12 weeks as judged by the Investigator.
6. Adequate hematological function defined by white blood cell (WBC) count ≥ 3×10^9/L with absolute neutrophil count (ANC) ≥ 1.5×10^9/L, lymphocyte count ≥ 0.5×10^9/L, platelet count ≥ 75×10^9/L, and Hgb ≥ 9 g/dL (in absence of blood transfusion).
7. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × ULN, an AST level ≤ 2.5 × ULN, and an ALT level ≤ 2.5 × ULN. For subjects with liver involvement in their tumor, AST ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and bilirubin ≤ 3.0 is acceptable.
8. Adequate renal function defined by an estimated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula or by measure of creatinine clearance from 24-hour urine collection.
9. Highly effective contraception (that is, methods with a failure rate of less than 1% per year) for both male and female subjects if the risk of conception exists (Note: The effects of the trial treatment on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use highly effective contraception, defined in Appendix 2 or as stipulated in national or local guidelines). Highly effective contraception must be used 30 days prior to first trial treatment administration, for the duration of trial treatment, and at least for 4 months after stopping trial treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this trial, the treating physician should be informed immediately.
10. Woman of childbearing potential must have a negative serum pregnancy test at screening visit and a negative serum or urine pregnancy test at Day 1 before dosing, if applicable.

5.3.1.2 Inclusion Criteria for Expansion Cohorts

1. Able and willing to give written informed consent and has signed the appropriate written ICF, prior to performance of any trial activities.
2. Eligible male or female subjects aged ≥ 20 years.

3. Subjects must have one of the following:

   - **GC:** Histologically or cytologically confirmed recurrent or refractory unresectable stage IV gastric or gastro-esophageal junctional adenocarcinoma (according to American Joint Committee on Cancer/Union Internationale Contre le Cancer 7th edition) for which no standard therapy exists or standard therapy has failed.
   - **ESCC:** Histologically or cytologically confirmed esophageal squamous cell cancer for which no standard therapy exists or standard therapy has failed.
   - **BTC, second line:** Histologically or cytologically confirmed biliary tract cancer. Must have failed or are intolerant to one line of systemic treatment. Patients who received adjuvant chemotherapy and had evidence of disease recurrence within 6 months of completion of the adjuvant treatment are also eligible.
   - **HCC,** second line or later, or sorafenib intolerant: Histologically confirmed HCC. Must be unresectable or advanced disease not amenable to curative resection. Must have had progression following at least 1 line of prior sorafenib therapy (must have received at least 14 days of sorafenib at least 400 mg per day) or previously considered to be sorafenib intolerant.

     Uninfected, HCV and HBV infected subjects are eligible. Subjects infected with HBV must be treated and on a stable dose of entecavir, tenofovir, or lamivudine (adefovir or interferon not allowed) at study entry and with planned monitoring and management according to appropriate labeling guidance. Any prior HCV therapy for curative intent must be completed prior to entry; if subjects reach stable disease, CR or PR of at least 3 months duration and are considered medically stable, then HCV small molecule treatments are allowable in the judgement of the Investigator and in consultation with the Medical Monitor and following appropriate labeling guidance for initiation, monitoring, and management.

     Additional inclusion criteria for HCC subjects include:

     - Child-Pugh A or B7
     - Albumin $\geq$ 2.8 g/dL
     - International normalized ratio (INR) < 1.7
     - Prothrombin time < 4 seconds over control
     - Hepatic function defined by a total bilirubin level $\leq$ 3 mg/dL and AST and ALT levels $\leq$ 5 $\times$ ULN
     - Adequate hematological function defined by WBC count $\geq$ 2.5 $\times$ 10^9/L with ANC $\geq$ 1.5 $\times$ 10^9/L, lymphocyte count $\geq$ 0.5 $\times$ 10^9/L, platelet count $\geq$ 50 $\times$ 10^9/L, and hemoglobin $\geq$ 9 g/dL (in absence of blood transfusion)
     - Subjects with no allergies to contrast and able to tolerate CT or MRI contrast in the opinion of the Investigator.

4. Availability of tumor (primary or metastatic) archival material or fresh biopsies within 28 days before first administration of IMP is mandatory. If no archival material is available and only one lesion is amenable for biopsy and it is the only target lesion, the Medical Monitor should be consulted for subject eligibility). Tumor biopsies and tumor archival material must be suitable for CCI [redacted] as described in the Laboratory Manual.
5. Disease must be measurable with at least 1 unidimensionally measurable lesion by RECIST 1.1.
6. ECOG PS of 0 to 1 at trial entry.
7. Life expectancy ≥ 12 weeks as judged by the Investigator.
8. For subjects with GC, ESCC, or BTC, adequate hematological function defined by WBC count ≥ 3 × 10^9/L with ANC ≥ 1.5 × 10^9/L, lymphocyte count ≥ 0.5 × 10^9/L, platelet count ≥ 75 × 10^9/L, and Hgb ≥ 9 g/dL (in absence of blood transfusion).
9. For subjects with GC, ESCC, or BTC, adequate hepatic function defined by a total bilirubin level ≤ 1.5 × ULN, an AST level ≤ 2.5 × ULN, and an ALT level ≤ 2.5 × ULN.
10. Adequate renal function defined by an estimated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula or by measure of creatinine clearance from 24-hour urine collection.
11. Highly effective contraception (that is, methods with a failure rate of less than 1% per year) for both male and female subjects if the risk of conception exists (Note: The effects of the trial treatment on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use highly effective contraception, defined in Appendix 2 or as stipulated in national or local guidelines). Highly effective contraception must be used 30 days prior to first trial treatment administration, for the duration of trial treatment, and at least for 4 months after stopping trial treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this trial, the treating physician should be informed immediately.
12. Woman of childbearing potential must have a negative serum pregnancy test at screening visit and a negative serum or urine pregnancy test at Day 1 before dosing, if applicable.

5.3.2 Exclusion Criteria

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

1. Concurrent treatment with non-permitted drugs (see Section 6.5.2).
2. Prior therapy with any antibody/drug targeting T cell coregulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, anti-CTLA-4 antibody (consult Medical Monitor if necessary), or anti-4-1BB antibody is not allowed, inclusive of intrahepatic, localized administration of such agents.

3. Prior therapy with any antibody/drug targeting TGFβ/TGFβ receptor.

4. Anticancer treatment within 21 days before the start of trial treatment, eg, cytoreductive therapy, radiotherapy involving more than 30% of the bone marrow (with the exception of palliative bone directed radiotherapy), immune therapy, or cytokine therapy.

5. Anticancer treatment with antibody within 28 days before the start of trial treatment.

6. Major surgery within 28 days before the start of trial treatment (excluding prior diagnostic biopsy).

7. Systemic therapy with immunosuppressive agents within 7 days before the start of trial treatment; or use of any investigational drug within 28 days before the start of trial treatment.

8. Previous malignant disease other than the target malignancy to be investigated in this trial with the exception of cervical carcinoma in situ and superficial or non-invasive bladder cancer (treated with curative intent) within the last 5 years or basal cell or squamous cell carcinoma in situ within the last 3 years.

9. Rapidly progressive disease which, in the opinion of the Investigator, may predispose to inability to tolerate treatment or trial procedures.

10. Subjects with active central nervous system (CNS) metastases causing clinical symptoms or metastases that require therapeutic intervention are excluded. Subjects with a history of treated CNS metastases (by surgery or radiation therapy) are not eligible unless they have fully recovered from treatment, demonstrated no progression for at least 2 months, and do not require continued steroid therapy. Subjects with CNS metastases incidentally detected during Screening which do not cause clinical symptoms and where no therapeutic intervention is needed should be discussed with the Sponsor.

11. Receipt of any organ transplantation, including allogeneic stem-cell transplantation, but with the exception of transplants that do not require immunosuppression (eg, corneal transplant, hair transplant).

12. Significant acute or chronic infections including, among others:

    - Positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome
    - Except for the HCC cohort, HBV infection (HBV surface antigen positive or HBV core antibody positive with reflex to positive HBV DNA) or HCV infection (positive HCV antibody with reflex to positive HCV RNA)
    - Subjects with active tuberculosis (history of exposure or history of positive tuberculosis test; plus presence of clinical symptoms, physical or radiographic findings)

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

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

    - Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg of prednisone or equivalent per day.

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

14. Interstitial lung disease or its history.

15. Known history of hypersensitivity reactions to MSB0011359C or its products, or known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v4.03), any history of anaphylaxis, or recent, within 5 months, history of uncontrolled asthma.

16. Persisting toxicity (except alopecia and vitiligo) related to prior therapy Grade > 1 NCI-CTCAE v4.03; however, sensory neuropathy Grade ≤ 2 is acceptable.

17. Pregnancy or currently in lactation. Subject is not eligible even if lactation is suspended.

18. Known alcohol or drug abuse.

19. Clinically significant cardiovascular/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 II), or serious cardiac arrhythmia.

20. Clinically relevant diseases (eg, inflammatory bowel disease) and/or uncontrolled medical conditions, which, in the opinion of the Investigator, might impair the subject's tolerance or ability to participate in the trial.

21. Any psychiatric condition that would prohibit the understanding or rendering of informed consent.

22. Legal incapacity or limited legal capacity.

23. Vaccine administration within 4 weeks of IMP administration. Vaccination with live vaccines while on trial is prohibited. Administration of inactivated vaccines is allowed (eg, inactivated influenza vaccines).

Additional exclusion criteria for subjects in the HCC cohort include:

24. Any prior or current ascites that requires paracentesis for control; or history of variceal bleeding; or history of hepatic encephalopathy; or history of obstructive jaundice.

25. Hepatitis D virus (HDV) co-infection with HBV (if HBV surface antigen or HBV DNA positivity at Screening, then must check for HDV status).

26. Chemoembolization or radioembolization within 28 days prior to IMP administration.

5.4 Criteria for Initiation of Trial Treatment

The inclusion and exclusion criteria will be checked at the Screening visit. Eligible subjects will be enrolled before treatment start after verification of fulfilling all inclusion criteria without matching any exclusion criterion.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Trial Treatment

Subjects will be withdrawn from trial treatment for any of the following reasons:

- Confirmed PD per RECIST 1.1: Subjects should continue treatment beyond the initial determination of PD, through their next tumor assessment, provided:

a. There are no new Grade 2 or greater symptoms or significant worsening of existing symptoms.

b. There is no decrease in ECOG PS.

c. In the opinion of the Investigator, the subject does not require new anticancer therapy.

- Subjects should be discontinued from treatment thereafter if further evidence of PD; however, continued treatment is possible in consultation with the Medical Monitor.
- Occurrence of an exclusion criterion, which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor.
- Therapeutic failure requiring urgent additional cancer therapy.
- Occurrence of any Grade ≥ 3 ADRs or repetitive Grade 2 ADRs as defined in Section 5.1.7.2.
- Occurrence of AEs, at the Investigator's discretion.

- Pregnancy.
- Use of prohibited concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from the IMP.
- Non-adherence/noncompliance to the trial protocol or trial requirements (see Section 6.9).
- Withdrawal of consent.
- Participation in any other trial.

For subjects who miss ≥ 2 consecutive doses for medical reasons, the Medical Monitor should be consulted.

Subject Replacement

For the dose escalation part, subjects with the following events during the DLT observation period (see Section 5.1.3.3 and Section 5.5.2) will be considered non-completers and have to be replaced:

- Deviation in MSB0011359C administration of greater than -3 days or +1 day due to reasons other than DLT.
- Other condition that DLT is not evaluable (eg, use of non-permitted medicines as detailed in Section 6.5.2).

5.5.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial.

A subject must be withdrawn in the event of any of the following:

- Withdrawal of the subject's consent.
- Participation in any other therapeutic trial during the treatment duration of this trial; however, subjects will continue to be followed for survival.

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

In case of withdrawal from the trial, the assessments scheduled for the last visit (End-of-Treatment visit) should be performed (see Section 7.1.4), if possible, with focus on the most relevant assessments. In any case, the appropriate End-of-Treatment electronic case report form (eCRF) visit must be completed. In case of withdrawal, subjects will be asked to continue safety and survival follow-up, which includes the collection of data on survival and subsequent anticancer therapy. After completion of the Follow-up period or after the End-of-Treatment visit, whatever is applicable, the appropriate eCRF section for Trial Termination must be completed.

If a subject is withdrawn prior to disease progression for any reason in the expansion part of the trial, the subject will not be replaced. For the dose escalation part, subjects with the following events during the DLT observation period will be considered non-completers and have to be replaced: 1) deviation in MSB0011359C administration of greater than -3 days or +1 day due to reasons other than DLT; or 2) other condition that DLT is not evaluable (eg, use of non-permitted medicines).

5.6 Premature Discontinuation of the Trial

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

- New information leading to unfavorable risk-benefit judgment of the IMP(s), eg, due to:
  - Evidence of inefficacy of the IMP(s),
  - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
  - Other unfavorable safety findings.

  (Note: evidence of inefficacy may arise from this trial or from other trials; unfavorable safety findings may arise from clinical or nonclinical examinations, eg, toxicology.)
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of the Sponsor's IMP(s).
- Withdrawal of the IMP(s) from the market for safety reasons (applicable to trials with marketed products only).

After primary analyses are completed, subjects may be offered to enroll into a roll-over trial before planned end of the trial.

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

The whole trial may be terminated or suspended upon request of the Health Authorities.

5.7 Definition of End of Trial

If the trial is not terminated for any reason given in Section 5.6, the end of the trial is defined as 1 year after the last subject receives the last dose of MSB0011359C.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" refers to an active substance or a placebo being tested or used as a reference therapy in a clinical trial, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form. The only IMP used in this trial is MSB0011359C.

There is no placebo or active control arm in this trial.

6.1 Description of Investigational Medicinal Product

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

6.2 Dosage and Administration

Subjects will receive intravenous infusion of MSB0011359C over 1 hour (- 10 minutes/+20 minutes, ie, over 50 to 80 minutes) once every 2 weeks as detailed in the Schedules of Assessments (see Table 1 and Table 2). Modifications of the infusion rate due to infusion-related reactions are described in Section 6.5.4.1. In order to mitigate potential infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) (eg, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] intravenous or oral equivalent) approximately 30 to 60 minutes prior to each dose of MSB0011359C is mandatory for the first 2 infusions. Premedication is optional and at the discretion of the Investigator after the second infusion. If Grade 2 infusion reactions are seen during the first two infusions, then premedication should not be stopped. Steroids as premedication are not permitted. Special precautions for monitoring of subjects and management of infusion-related reactions/hypersensitivity including modifications of the infusion rate and stopping of trial drug are described in Section 6.5.4 and subsections.

The starting dose of MSB0011359C in the dose escalation part is 3 mg/kg (dose escalation according to 3+3 design up to 20 mg/kg is intended) and the treatment cycle will be 2 weeks (14 days). The first subject of each cohort will be observed for at least 5 days before the second subject can be treated. Within each cohort, 48 hours must pass before a new subject can initiate dosing.

During the dose escalation part and for the HCC cohort, the dose of MSB0011359C will be calculated based on the weight of the subject determined on the day prior to or the day of each drug administration. For subsequent administrations, the dose will only be changed in case of weight gain or loss of ≥ 10%.

A flat dose of 1200 mg MSB0011359C will be used for all subjects in the expansion cohort (except for the HCC cohort) after confirming the tolerability of MSB0011359C at 20 mg/kg. Subjects will receive MSB0011359C once every 2 weeks until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 5.5). Subjects who have experienced a CR, PR or SD should continue treatment through the end of 12 months at the discretion of the Investigator and in consultation with the Medical Monitor. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor.

For subjects who achieve a CR, PR, or SD on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, 1 re-initiation course of treatment at the same dose and schedule and treatment duration up to 12 months is allowed at the discretion of the Investigator and agreement of the trial Medical Monitor. Subjects re-initiating treatment should be assessed according to the Schedule of Assessments for the expansion part of the trial (see Table 2).

6.3 Assignment to Treatment Groups

The Investigator or delegate will assign a unique subject identifier number to eligible subjects in chronological order at the time of informed consent signature. Subject identifiers will be comprised of digits representing the trial number, the site number, and the subject number, which is allocated sequentially. Enrollment in the dose escalation and expansion parts will utilize an interactive web response system.

6.4 Non-investigational Medicinal Products to be Used

In order to mitigate potential infusion-related reactions premedication with an antihistamine and with paracetamol (acetaminophen) (eg, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] intravenous or oral equivalent) approximately 30 to 60 minutes prior to each dose of MSB0011359C is mandatory for the first 2 infusions. Premedication is optional and at the discretion of the Investigator after the second infusion. If Grade 2 infusion reactions are seen during the first two infusions, then premedication should not be stopped. This regimen may be modified based on local treatment standards and guidelines as appropriate. Steroids as premedication are not permitted.

As with all monoclonal antibody therapies, there is a risk of allergic reaction including anaphylactic shock. MSB0011359C should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (intravenous antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access. Infusion of MSB0011359C will be stopped in case of Grade ≥ 2 infusion-related, allergic, or anaphylactic reactions. Following MSB0011359C infusions, during the first 2 doses in the escalation phase there will be a minimum 24-hour in-patient observation. Please see the guidelines for handling of infusion-related reaction in Section 6.5.4.1.

If an allergic reaction occurs, the subject must be treated according to the best available medical practice. Guidelines for management of infusion-related reactions and severe hypersensitivity reaction according to the NCI are found in Section 6.5.4.

Further precautions are provided in Section 6.5.4. For prophylaxis of flu-like symptoms, a nonsteroidal anti-inflammatory drug (NSAID), eg, ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each dose of MSB0011359C intravenous infusion.

6.5 Concomitant Medications and Therapies

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

duration and indication of each drug. Nondrug interventions (other than vitamins) and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

6.5.1 Permitted Medicines

Any medications (other than those excluded by the clinical trial protocol) that are considered necessary to protect subject welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

Other drugs to be used for prophylaxis, treatment of anaphylactic reactions, infusion-related reactions, and severe hypersensitivity reactions/flu-like symptoms and irAEs are described in Sections 5.1.7.2, 6.4, and 6.5.4.

Palliative bone directed radiotherapy may be administered during the trial. The assessment of PD will be made according to RECIST 1.1 (Eisenhauer 2009) and not based on the necessity for palliative bone-directed radiotherapy.

6.5.2 Prohibited Medicines

As stated for the exclusion criteria in Section 5.3.2, subjects must not have had chemotherapy, radiotherapy involving more than 30% of the bone marrow (other than palliative bone directed radiotherapy as described in Section 6.5.1) within 21 days before the start of trial treatment, and anticancer treatment with antibody, major surgery, or received another investigational agent within 28 days before the start of trial treatment.

The following treatments must not be administered during the trial:

- Immunotherapy, immunosuppressive drugs (eg, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions, endocrine replacement therapy at low dose prednisone [≤ 10 mg daily] or equivalent, or for the treatment of irAEs or other appropriate short-term steroid use), or other experimental pharmaceutical products. Short-term administration of systemic steroid or other immunosuppressant such as infliximab or mycophenolate (ie, for allergic reactions or the management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are allowed.
- Adefovir.
- Prophylactic use of corticosteroids for infusion-related reactions is prohibited.
- Any live vaccine therapies for the prevention of infectious disease. Administration of inactivated vaccines is allowed (eg, inactivated influenza vaccines).
- Blood transfusions and erythroid growth factors are not allowed during the 21-day DLT window during the escalation part.

If the administration of a non-permitted concomitant drug becomes necessary during the trial, the subject will be withdrawn from trial treatment (the Medical Monitor may be contacted to discuss whether the IMP must be discontinued).

Medications other than those specifically excluded in this trial (as outlined in this section) may be administered for the management of symptoms associated with the administration of MSB0011359C as required. These might include analgesics, antiemetics, antihistamines, diuretics, anti-anxiety medications, and medication for pain management, including narcotic agents.

Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

6.5.3 Other Interventions

The following nondrug therapies must not be administered during the trial (and within 28 days before the start of trial treatment):

- Major surgery (excluding prior diagnostic biopsy).
- Herbal remedies with immunostimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin).
- Subjects should not abuse alcohol or other drugs during the trial.

6.5.4 Special Precautions

For subjects enrolled in the dose escalation part of the trial, in-house observation in a hospitalized setting for at least 24 hours will occur for the first 2 doses administered to each subject. To facilitate PK and CCI [redacted], subjects may remain in-house through an additional 24 hours if necessary. A nurse or physician will communicate with the first subject of each cohort after the first treatment to assess for any side effects on or after Day 5 but before enrolling a subsequent subject. Thereafter, within each cohort, 48 hours must pass before a new subject can initiate dosing.

In the expansion part of the trial, there is no in-house observation and no waiting period between subjects.

At all times during MSB0011359C treatment, immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

Infusion of MSB0011359C will be stopped in case of Grade ≥ 2 hypersensitivity, inflammatory response, or anaphylactic reaction. The treatment recommendations for infusion-related reactions and severe hypersensitivity reactions according to the NCI are outlined in Sections 6.5.4.1 and 6.5.4.2, respectively.

Investigators should also monitor subjects closely for potential irAEs, which may become manifest after several weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of hypothetical irAEs also includes formation of auto-antibodies like ANAs.

6.5.4.1 Infusion-related Reactions

A. Symptoms:
- Fever
- Chills
- Rigors
- Diaphoresis
- Headache.

B. Management (see Table 4)

Table 4 Treatment Modification for Symptoms of Infusion-related Reactions Caused by MSB0011359C

NCI-CTCAE Grade	Treatment Modification for MSB0011359C
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the MSB0011359C infusion rate by 50% and monitor closely for any worsening. • The total infusion time for MSB0011359C should not exceed 120 minutes.
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	• Stop MSB0011359C infusion. • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the MSB0011359C infusion immediately and disconnect infusion tubing from the subject. • Subjects have to be withdrawn immediately from MSB0011359C treatment and must not receive any further MSB0011359C treatment.

IV=intravenous; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs=nonsteroidal anti-inflammatory drugs.

Additional Modifications for Subjects with Grade 2 Infusion-related Reactions

If, in the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 4 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids and the infusion of IMP should be stopped for that day. At the next infusion, the Investigator may consider the addition of H2-blocker antihistamines (eg, famotidine or ranitidine), in addition to premedication, for select subjects. However, prophylactic steroids are NOT permitted. If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, with or without the addition of further medication to premedication, the infusion should be stopped and the subject removed from MSB0011359C treatment.

6.5.4.2 Severe Hypersensitivity Reactions and Flu-like Symptoms

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

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

B. Management
1. Epinephrine injection and intravenous dexamethasone.
2. Patient should be placed on cardiac, blood pressure, heart rate, and oxygen saturation monitor immediately.
3. Alert intensive care unit for possible transfer if required.

For prophylaxis of flu-like symptoms, an NSAID, eg, ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each dose of MSB0011359C IV infusion except for the DLT period (for subjects who experienced a flu-like syndrome in the DLT assessment period, prophylactic use of an NSAID at the next dose is allowed).

6.5.4.3 Immune-related Adverse Events

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

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

Treatment of irAEs should follow guidelines set forth in Table 5.

Table 5 Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over Baseline	Continue MSB0011359C therapy	Close monitoring for worsening symptoms

Colitis: asymptomatic	Symptomatic treatment (eg, loperamide)	Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay MSB0011359C therapy Symptomatic treatment	If improves to Grade 1: Resume MSB0011359C therapy If persists > 5 to 7 days or recur: 0.5 to 1 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume MSB0011359C therapy per protocol. If worsens or persists > 3 to 5 days with oral steroids: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hours; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue MSB0011359C therapy per protocol 1 to 2 mg/kg/day methylprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade 1, then taper over at least 1 month If persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis Permanently discontinue IMP
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (eg, antihistamines, topical steroids) Continue MSB0011359C therapy	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Delay MSB0011359C therapy Consider 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume MSB0011359C therapy If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Covering > 30% body surface area; life threatening consequences	Delay or discontinue MSB0011359C therapy Consider skin biopsy Dermatology consult	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

	1 to 2 mg/kg/day methylprednisolone IV or IV equivalent	Resume MSB0011359C therapy (except in cases of Toxic Epidermal Necrolysis or Stevens-Johnson Syndrome)
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delay of MSB0011359C therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay MSB0011359C therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month and then resume MSB0011359C therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4 Permanently discontinue IMP
Grade 3 to 4 Severe new symptoms; New/worsening hypoxia; life-threatening	Discontinue MSB0011359C therapy Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (eg, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil) Permanently discontinue IMP
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or total bilirubin > ULN to 1.5 x ULN	Continue MSB0011359C therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4

Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Delay MSB0011359C therapy Increase frequency of monitoring to every 3 days	If returns to Baseline: Resume routine monitoring, resume MSB0011359C therapy If elevations persist > 5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume MSB0011359C therapy
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Discontinue MSB0011359C therapy Increase frequency of monitoring to every 1 to 2 days 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines Permanently discontinue IMP

Cardiac irAEs

Myocarditis	Management	Follow-up
CCI [redacted]	CCI [redacted]	CCI [redacted]

Immune-mediated myocarditis	Permanently discontinue MSB0011359C. Guideline based supportive treatment as appropriate as per cardiology consult.[a] Methylprednisolone 1 to 2 mg/kg/day.	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A).

a Local guidelines, or eg. European Society of Cardiology or American Heart Association guidelines

European Society of Cardiology guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines

American Heart Association guidelines website:

http://professional heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

Endocrine irAEs

Endocrine Disorder	Management	Follow-up
Asymptomatic TSH abnormality	Continue MSB0011359C therapy If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary scan Symptomatic with abnormal laboratory/pituitary scan: Delay MSB0011359C therapy 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent Initiate appropriate hormone therapy No abnormal laboratory/ pituitary MRI scan but symptoms persist: Repeat laboratories in 1 to 3 weeks/MRI in 1 month	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections Resume MSB0011359C therapy Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue MSB0011359C therapy Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CT=computed tomography; irAE=immune-related adverse event; IMP=investigational medicinal product; IV=intravenous; LFT=liver function test; LLN=lower limit of normal; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; T4=thyroxine; TSH=thyroid stimulating hormone; ULN=upper limit of normal.

6.5.4.4 Anemia

Risk management measures in addition to routine laboratory tests will include:

- Subjects must enter the trial with Hgb values at least 9 g/dL
- Routine monitoring of Hgb, red blood cells, and hematocrit will be performed every week up to Week 5 and then every 2 weeks thereafter (prior to treatment)
- RBC morphology will be assessed in the case of anemia onset caused by hemolysis, or other unknown causes
- Instructions for trial treatment discontinuation or modification in case of anemia will be provided, briefly described here:

o If decreased Hgb below 8 g/dL does not return to 9 g/dL (the entry criterion at screening) or changes in associated red blood cell parameters during such a Hgb decrease that do not resolve within 14 days without blood transfusion or erythroid growth factor use, the subject is permanently withdrawn from trial treatment (pertains only to the 21-day DLT period). Furthermore, the subject may require additional treatment for anemia.

o Especially if Hgb < 7 g/dL, the Investigator should consider blood transfusion.

o In case of any Hgb < 8 g/dL, the Investigator should use discretion to initiate anemia work up, including Coombs, haptoglobin, indirect bilirubin and peripheral smear, and prothrombin time, activated partial thromboplastin time, INR; Hgb, red blood cells, and hematocrit are to be closely monitored.

- If a subject experiences significant anemia, then the amount of blood to be drawn may be reduced by not taking blood at selected time points for soluble factors and TGFβ. The decision to reduce the time points for these biomarkers will be taken by the Investigator in consultation with the Medical Monitor. This will be documented. Blood will continue to be taken as scheduled for safety analyses, PK, anti-drug antibodies (ADAs).

6.5.4.5 Rash with Hyperkeratosis/Keratoacanthoma/Squamous Cell Carcinoma of the Skin

Monitoring will include skin assessments as defined in the Schedules of Assessments (Table 1 and Table 2), with biopsy of suspicious lesions. Management should be discussed with the Medical Monitor on a case-by-case basis. Dermatological consults should be requested as needed. Hyperkeratotic rash/keratoacanthoma/squamous cell carcinoma will be considered as AESI requiring expedited reporting from the Investigator to the Sponsor.

6.5.4.6 Alterations in Wound Healing or Tissue Damage Repair

Management should be discussed with the Medical Monitor on a case-by-case basis. Dermatological consults should be requested as needed.

6.5.4.7 Dose Interruptions for Adverse Events No Related to Study Drug

In the case of Grade 3 and Grade 4 AEs that are not considered to be related to the study drug, the study treatment may be interrupted based on the Investigator assessment. The subject will be medically treated for the event.

If the AE reduces to a lower tolerable grade, the study treatment may be resumed in the subsequent cycle. If the AE remains the same in spite of medical treatment until the next treatment (second cycle after the AE occurred), the event should be discussed with the Medical Monitor to consider either a possible extension of the dose interruption for up to 1 additional cycle or a permanent withdrawal from the study treatment.

If upon resuming study treatment, the subject experiences the same AE again, this should be discussed again with the medical monitor to assess permanent withdrawal from the study treatment.

Grade 3 and 4 laboratory abnormalities that do not have clinical significance do not require dose interruption.

6.6 Packaging and Labeling of the Investigational Medicinal Product

MSB0011359C freeze-dried formulation is presented at a concentration of 45 mg/vial in USP / Ph Eur type I glass vial closed with a rubber stopper and sealed with an aluminum crimping cap. MSB0011359C liquid formulation is presented at a 10 mg/mL concentration in a USP / Ph Eur type I 50R vial closed with a rubber stopper and sealed with an aluminum crimp seal closure. The stopper is made of elastomer complying with USP and Ph Eur. Vials are filled with 61.2 mL of drug product solution in order to allow an extractable volume of 60 mL.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice guidelines. MSB0011359C will be packed in boxes containing a suitable number of vials. The information on the medication will be in accordance with approved submission documents.

MSB0011359C will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature control devices.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable GMP Guidelines.

6.7 Preparation, Handling and Storage

CCI

CCI

CCI

CCI

Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the manual of preparation.

MSB0011359C must not be used for any purpose other than the trial. The administration of IMPs to subjects who have not been enrolled into the trial is not covered by the trial insurance.

The contents of the MSB0011359C vials are sterile and non-pyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

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

6.8 Investigational Medicinal Product Accountability

The Head of the trial site is responsible for ensuring accountability for the IMP, including reconciliation of drugs and maintenance of drug records. The head of the trial site can delegate the control of and accountability for trial drug to the investigational product storage manager.

- Upon receipt of the IMP, the head of the trial site or the investigational product storage manager will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation provided by the Sponsor and returning it to the Sponsor. A copy will retained by the head of the trial site.

- The dispensing of the IMP will be carefully recorded on the appropriate drug accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the Sponsor's Medical Monitor at each monitoring visit.
- Trial site IMP accountability records will include the following:

- Confirmation of IMP receipt, in good condition and in the defined temperature range.
- The inventory of IMP provided by the Sponsor and prepared at the site.
- The use of each dose by each subject.
- The return to the Sponsor or alternative disposition of unused trial drug.
- Dates, quantities, batch numbers, expiry dates, formulation (for IMP prepared at the site), and the subjects' trial numbers.
  - The Investigator should maintain records that adequately document the following:
  - The subjects received the doses specified by the clinical trial protocol/amendment(s); and
  - The head of the trial site should maintain records that adequately document that all IMP provided by the Sponsor were fully reconciled.

The unused IMP must not be discarded or used for any purpose other than the present trial. Any IMP that has been dispensed to a subject must not be re-dispensed to a different subject.

The Sponsor's Monitor will periodically collect and review the IMP accountability forms and where applicable, will check all returns (both unused and used containers) before arranging for their return or authorizing their destruction by the trial site.

At the conclusion or termination of this trial, trial site personnel and the Clinical Trial Monitor will conduct a final product supply inventory on the Investigational Drug Accountability Forms and all unused containers will be destroyed. Instructions for destruction of product will be provided to the site. The Clinical Trial Monitor will be supplied with a copy for filing of the Investigational Drug Accountability Forms. This documentation must contain a record of clinical supplies used, unused, and destroyed and shall include information on:

- all administered units,
- all unused units,
- all destroyed units (during the trial),
- all destroyed units at the end of the trial,
- date of destruction(s),
- name and signature of the head of the trial site or the investigational product storage manager

It must be ensured at each trial site that the IMP is not used

- after the expiry date, and
- after the retest date unless the IMP is reanalyzed and its retest date extended.

This is to be closely monitored by the Clinical Trial Monitor.

6.9 Assessment of Investigational Medicinal Product Compliance

In this trial, subjects will receive IMP (MSB0011359C intravenous infusions) at the investigational site. Well-trained medical staff will monitor and perform the IMP administration. The information of each IMP administration including the date, time, and dose of IMP will be recorded on the eCRF. The Investigator will make sure that the information entered into the eCRF regarding IMP administration is accurate for each subject. Any reason for noncompliance should be documented.

Noncompliance is defined as a subject missing > 1 administration of trial treatment for nonmedical reasons. If 1 treatment administration was missed and the interval between the subsequent treatment and the last administered treatment is longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance are met as well. Continuation of treatment should be discussed with the Medical Monitor.

6.10 Method of Blinding

Not applicable.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose 5% greater than the highest dose included in the clinical trial protocol. Any overdose must be recorded in the trial medication section of the eCRF.

For monitoring purposes, any case of overdose – whether or not associated with an AE (serious or nonserious) – must be reported to the Sponsor's Global Drug Safety department in an expedited manner using the appropriate reporting form (see Section 7.4.1.4).

There are no known symptoms of MSB0011359C overdose to date. The Investigator should monitor closely for AEs should an overdose occur and use his or her clinical judgment in providing symptomatic/supportive care as medically indicated. There is no known antidote for MSB0011359C.

6.13 Medical Care of Subjects after End of Trial

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

Upon withdrawal from the trial, subjects may receive whatever care they and their physicians agree upon. Subjects will be followed for survival and AEs as specified in Section 7.1.5.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

A complete schedule of assessments for the dose escalation part of the trial is provided in Table 1 and for the expansion part in Table 2. Sample collection for PK, CCI [redacted] CCI [redacted], and changes in CCI [redacted] are provided in Table 3.

Prior to performing any study assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent according to the procedure described in Section 9.2.

7.1.1 Screening and Baseline Procedures and Assessments

There is a 21-day washout/recovery period for prior anticancer treatment (eg, cytoreductive therapy, radiotherapy involving more than 30% of the bone marrow [with the exception of palliative bone directed radiotherapy], immune therapy, or cytokine therapy except for erythropoietin) and 28 days for prior anticancer treatment with antibody, major surgery before the start of trial treatment (Section 5.3.2). Hematology, hemostaseology and chemistry laboratory samples must be drawn and reviewed within 48 hours prior to dose administration.

During the Screening period and before any trial-related investigations and assessments are started, the subjects will be asked to sign the relevant ICFs. The subjects' information that will be documented during Screening includes the demographic information (birth date, sex, ethnicity, and race) and the complete medical history, including the history of the tumor disease and prior anticancer therapies, previous medications (prior 30 days to signing of ICF), concomitant medications, and baseline medical condition (the information of concomitant medications and AEs will be monitored throughout the trial treatment period). Moreover, an Emergency Medical Support card will be handed out at the baseline assessments visit.

During Screening, subjects will undergo a complete physical examination, recording vital signs, including body weight and height (height only at Screening), 12-lead electrocardiogram (ECG), dermatological assessment, ophthalmology examination including slit lamp inclusive of the anterior segment and including visual acuity, and a determination of the ECOG PS (Appendix 1).

The Screening laboratory examination includes hematology, hemostaseology, full serum chemistry, serum electrophoresis (for dose escalation part only), and full urinalysis. Adrenocorticotropic hormone (ACTH), ANA, rheumatoid factor (RF), free thyroxine (T4), and TSH will also be assessed at Screening.

During Screening, a serum β-human chorionic gonadotropin (β-HCG) pregnancy test will be performed for females of child bearing potential and blood HBV, HCV and HIV testing will be performed for all Screening subjects as these conditions are trial entry exclusion criteria. Females who are postmenopausal (age-related amenorrhea $\geq$ 12 consecutive months and if needed increased FSH > 40 mIU/mL [in the postmenopausal range]), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening. Serum VCA-IgG Ab and EBNA IgG examination will done in the GC expansion cohort.

- The tumor evaluation (type/staging, etc.) will be performed using CT scan or MRI (if MRI is used, CT of chest is mandatory) as well as tumor markers or any other established methods (see Section 7.2.5 for details). Brain CT/MRI scan (either, with contrast preferred) is required if not performed within the previous 6 weeks. Bone scans should be performed as clinically indicated.

Collection of tumor tissues or archived surgical specimen will also be done during this period, if applicable (optional for the dose escalation part). Subjects in the expansion cohorts are required to provide tumor tissue samples, see Section 5.3.1 and Section 7.6.1.3 for details.

Baseline samples for ADAs (the term for ADA on the CRF is human antihuman antibodies [HAHA]), CCI blood samples for optional CCI, and for CCI CCI should be collected.

For subjects in the GC, ESCC, and BTC expansion cohorts only, patient-reported outcome questionnaires (PGIS, EORTC QLQ-C30, EORTC QLQ-BIL21, EORTC QLQ-HCC18, EORTC QLQ-OES18, and EORTC QLQ-STO22) will be administered and completed by the subjects at Screening to collect baseline data about their symptom severity.

7.1.2 Treatment Period

For this protocol, a cycle is defined as 14 days. In this trial, the treatment will be given until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the trial or IMP occurs (see Section 5.5). Subjects who have experienced a CR, PR or SD should continue treatment through the end of 12 months after confirmation, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Medical Monitor. In the case of PD, subjects should continue treatment through their next tumor assessment, if they meet the criteria described in Section 5.5.1.

For subjects who achieve CR, PR, or SD on MSB0011359C therapy and then subsequently develop disease progression after stopping therapy, but prior to the end of the trial, 1 re-initiation course of treatment at the same dose and schedule and treatment duration up to 12 months is allowed at the discretion of the Investigator and agreement of the trial Medical Monitor. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial MSB0011359C therapy. Prior to re-initiation of the trial treatment, malignant disease needs to be radiologically re-staged to assess all known sites of the disease and to establish a new baseline for subsequent tumor measurements. Relevant safety laboratory samples must be drawn and results available and verified prior to re-initiating of treatment. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the Schedule of Assessments for the expansion part of the trial (see Table 2).

Subjects will be asked to visit the investigational site according to the Schedules of Assessments (see Table 1 and Table 2). A time window of up to 3 days before or 1 day after the scheduled visit day (-3/+1 days) will be permitted for all trial procedures (except on Day 2 and the Day 43 to 50 visit). In addition, the tumor evaluation (see Section 7.3) has a tumor assessment visiting time window of 5 days prior to dosing (-5 days). Furthermore, if any Screening procedures are conducted within 3 days prior to Day 1 of trial treatment (Week 1, Day 1), the assessments scheduled on Week 1, Day 1 do not need to be repeated except for the evaluation of AEs and concomitant medications.

7.1.2.1 Dose Escalation Part Treatment Period

For the dose escalation part, in-house observation in a hospitalized setting with periodic ECG and vital sign monitoring for at least 24 hours will occur for the first 2 MSB0011359C doses administered to each subject. After 24 hours, investigator will decide the discharge of the subject based on the monitoring results and the results of in-person examination. The first subject of each cohort will be observed for at least 5 days before the second subject can be treated. Subsequent subjects may receive first dosing at no less than 48 hour intervals between subjects.

During the treatment period, the following assessments will be performed (see Table 1 and Table 3 for the detailed schedule):

- DLTs will be assessed during the first 21 days of trial treatment for each dose level of the dose-escalation part (see Section 5.1.3.2).
- For subjects who wish to continue participation following the completion of their DLT period, another written consent is required.
- AEs and concomitant medications will be documented at each trial visit.
- ECOG PS will be assessed prior to trial treatment on Day 1 (unless the Screening ECOG PS was performed within 3 days prior to Day 1) and according to Table 1 thereafter.

- Physical examination will be performed prior to trial treatment on Day 1 (Week 1). After Day 1, a directed physical examination indicated by subject's symptoms will be performed according to Table 1.
- At each visit, eye signs and symptoms should be checked. If clinically relevant findings, then an appropriate ophthalmology examination (including slit lamp evaluation inclusive of the anterior segment and with visual acuity) should be obtained within 2 days.
- Dermatological assessment.
- Oxygen saturation (SpO_2) will be measured.
- Vital signs including body weight, will be assessed prior to trial treatment according to Table 1.
- 12-lead ECG will be assessed prior to and as soon as possible after infusion according to Table 1.
- The laboratory hematology and hemostaseology tests will be assessed according to Table 1. Complete blood count results must be drawn and reviewed within 48 hours prior to dose administration.
- Full serum chemistry (includes core chemistry) and core serum chemistry will be assessed prior to trial treatment according to Table 1. Samples for core chemistry results must be drawn and reviewed within 48 hours prior to dose administration.
- Serum electrophoresis at Week 13 (Visit 10).
- A basic urinalysis will be performed prior to trial treatment as detailed in Table 1.
- A serum β-HCG pregnancy test will be required at Screening, urine or serum β-HCG pregnancy test will be performed prior to each administration of the study drug every 4 weeks (if applicable). If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.
- The tumor evaluation (see Section 7.3) will be performed at Week 7, and then once every 6 weeks, with a tumor assessment visiting time window of 5 days prior to dosing.
- PK samples will be drawn as detailed in Table 3.
- Free T4 and TSH will be measured prior to trial treatment according to Table 1.
- ADA samples will be drawn as detailed in Table 3. The term for ADA on the CRF is human antihuman antibodies (HAHA)
- Soluble factors will be drawn as detailed in Table 3 and as described in Section 7.6.1.2.
- Samples for TGFβ determination will be drawn as detailed in Table 3.
- Blood samples for gene expression evaluation will be collected according to Table 3 (prior to IMP administration where applicable).

- For subjects undergoing the optional Week 7 biopsy, the biopsy should be performed within 7 days after the Week 7 IMP administration (Table 3).

7.1.2.2 Expansion Part Treatment Period

During the treatment period, the following assessments will be performed (see Table 2 and Table 3 for the detailed schedule):

- For subjects in the GC, ESCC, and BTC expansion cohorts only, patient-reported outcome questionnaires (PGIS, EORTC QLQ-C30, EORTC QLQ-BIL21, EORTC QLQ-HCC18, EORTC QLQ-OES18, and EORTC QLQ-STO22) will be completed prior to any study-related procedures as indicated in Table 2.
- AEs and concomitant medications will be documented in each study visit.
- ECOG PS will be assessed prior to trial treatment on Day 1 (unless the Screening ECOG PS was performed within 3 days prior to Day 1) and according to Table 2 thereafter.
- Any new concomitant procedures will be documented in each study visit. For any biopsies or other procedures resulting in tissue acquisition, official pathology reports must be filed and available for review if requested.
- Physical examination will be performed prior to trial treatment on Day 1 (Week 1). After Day 1, a directed physical examination indicated by subject's symptoms will be performed according to Table 2.
- At each visit, eye signs and symptoms should be checked. If clinically relevant findings, then an appropriate ophthalmology examination (including slit lamp evaluation inclusive of the anterior segment and with visual acuity) should be obtained within 2 days.
- Dermatological assessment.
- SpO_2 will be measured.
- Vital signs, including body weight, will be assessed prior to trial treatment according to Table 2.
- 12-lead ECG will be assessed prior to and as soon as possible after infusion according to Table 2.
- The laboratory hematology and hemostaseology tests will be assessed according to Table 2. Complete blood count results must be drawn and reviewed within 48 hours prior to dose administration. For subjects experiencing signs of anemia including, but not limited to, a significant drop in Hgb value (especially Hgb < 8 g/dL), routine monitoring of Hgb, red blood cells, and hematocrit should be performed weekly.
- Full serum chemistry (includes core chemistry) and core serum chemistry will be assessed prior to trial treatment according to Table 2. Samples for core chemistry results must be drawn and reviewed within 48 hours prior to dose administration.

- A basic urinalysis will be performed prior to trial treatment as detailed in Table 2.
- A serum β-HCG pregnancy test will be required at Screening, urine or serum β-HCG pregnancy test will be performed prior to each administration of the study drug every 4 weeks (if applicable). If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.
- The tumor evaluation (see Section 7.3) will be performed at Week 7, and then once every 6 weeks, with a tumor assessment visiting time window of 5 days prior to dosing.
- Tumor biopsies at Week 7 (Days 43 to 50, see Table 3).
- PK samples will be drawn as detailed in Table 3.
- Free T4 and TSH will be measured prior to trial treatment according to Table 2.
- ADA samples will be drawn as detailed in Table 3. The term for ADA on the CRF is human antihuman antibodies (HAHA).
- Soluble factors will be drawn as detailed in Table 3 and as described in Section 7.6.1.2.
- Samples for TGFβ determination will be drawn as detailed in Table 3.
- Samples will be collected for viral load testing (HBV, HCV) and AFP from subjects in the HCC cohort as detailed in Table 3.
- Blood samples for gene expression evaluation will be collected according to Table 3 (prior to study drug administration where applicable).

7.1.3 Rechallenge

One re-initiation course of treatment at the same dose and schedule and treatment duration up to 12 months is allowed at the discretion of the Investigator and agreement of the Medical Responsible for the following:

- Participants who are experiencing stable disease, a PR, or CR at the time of discontinuation, and then subsequently develop disease progression after stopping therapy, but prior to the end of the study.

OR

- Participants who are discontinued due to an AE that are subsequently well managed or resolved after stopping therapy, but prior to the end of the study.

Prior to re-initiation, the Investigator will need to confirm that the benefit of re-initiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation. For participants with only stable disease at the time of discontinuation, the Investigator should confirm that no other reasonable treatment options are available. In addition, to be eligible for re-initiation,

the participant must not have previously withdrawn consent for this trial and should have been followed up with regular eCRF documented evaluation scans up to re-initiation of treatment.

Prior to re-initiation of the study intervention, malignant disease must be radiologically restaged within 28 days of dosing to assess all known disease sites. Additionally, relevant safety laboratory assessments, including both full hematology and full chemistry results within 2 weeks, must be available and verified. The clinical Investigator will determine whether additional evaluation and work up are required on a case-by-case basis.

Participants who re-initiate treatment should stay on study and should be treated and monitored according the Schedule of Activities for the rest of the study.

7.1.4 End-of-Treatment

7.1.4.1 Discontinuation Visit

Any subject who experiences an AE that mandates discontinuation of trial treatment should have a discontinuation visit within 7 days after the decision to discontinue trial treatment (see Table 1 and Table 2). For all these subjects, the discontinuation visit consists of:

- Documentation of AEs and concomitant medications.
- Physical examination including vital signs and body weight.
- Dermatological assessment.
- SpO_2 will be measured.
- Laboratory hematology, hemostaseology, full serum chemistry, and basic urinalysis.
- ECOG PS will be assessed.

7.1.4.2 End-of-Treatment Visit

The End-of-Treatment visit is scheduled 4 weeks (28±5 days) after the last administration of MSB0011359C but before any new therapy is started, if possible, whichever occurs earlier. The End-of-Treatment visit will comprise a full assessment for safety, immunogenicity, and tumor response as appropriate, which will include the following (refer to Table 1, Table 2, and Table 3):

- For subjects in the GC, ESCC, and BTC expansion cohorts only, patient-reported outcome questionnaires (PGIS, EORTC QLQ-C30, EORTC QLQ-BIL21, EORTC QLQ-HCC18, EORTC QLQ-OES18, and EORTC QLQ-STO22) will be completed prior to any study-related procedures as indicated in Table 2.
- AEs, concomitant medications.
- Vital signs and body weight.
- Physical examinations.

- Dermatological assessment.
- SpO_2 will be measured.
- 12-lead ECG will be assessed.
- The laboratory hematology, hemostaseology, full serum chemistry, serum electrophoresis tests (for dose escalation part only), and full urinalysis.
- ECOG PS will be assessed.
- Urine β-HCG pregnancy test (in females of childbearing potential).
- Tumor evaluation (only to be performed, if no disease progression was documented previously).
- Free T4 and TSH.
- PK sample.
  - ADA sample (see Section 7.7.1). The term for ADA on the CRF is human antihuman antibodies (HAHA)
  - Soluble factors will be drawn as described in Section 7.6.1.2 and Table 3.
  - Samples for TGFβ determination as described in Table 3.
  - Blood samples for gene expression evaluation for subjects with PD.
  - Samples for viral load testing (HBV, HCV) and AFP (for HCC cohort only).
  - If the therapy is discontinued due to regrowth of the tumor, then a repeat biopsy at the end of treatment is advisable (optional). A PK sample should be collected as close as possible to the time of the biopsy (ie, same day).

7.1.5 Post-Treatment Follow-up

7.1.5.1 Safety Follow-up Visit

All subjects will have a subsequent visit scheduled 10 weeks (±2 weeks) after the last administration of MSB0011359C. The visit will include the following full assessment of safety parameters (refer to Table 1, Table 2, and Table 3):

- For subjects in the GC, ESCC, and BTC expansion cohorts only, patient-reported outcome questionnaires (PGIS, EORTC QLQ-C30, EORTC QLQ-BIL21, EORTC QLQ-HCC18, EORTC QLQ-OES18, and EORTC QLQ-STO22) will be completed prior to any study-related procedures as indicated in Table 2.
- AEs that are deemed attributable to trial drug by the Investigator and concomitant medications (including further anticancer therapy) will be documented.
- Vital signs and body weight will be measured.

- Physical examination will be performed.
- Dermatological assessment.
- SpO_2 will be measured.
- ECOG PS will be assessed.
- 12-lead ECG will be assessed.
- Laboratory testing consisting of the following will be assessed:
  - Hematology, hemostaseology, full serum chemistry, and full urinalysis
  - Free T4, and TSH levels.
    - PK sample will be collected.
    - ADA sample. The term for ADA on the CRF is human antihuman antibodies (HAHA)
    - Samples for viral load testing (HBV, HCV; HCC cohort only).
- A urine β-HCG pregnancy test (in women of child bearing potential) will be conducted.

7.1.5.2 Long-term Follow-up/Trial Termination

All SAEs ongoing at the End-of-Treatment visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up" or started a new anticancer therapy. In addition, all trial drug-related SAEs occurring after End-of-Treatment visit and ongoing at the Safety Follow-up visit have to be followed up in the same manner.

Subjects without PD at the End-of-Treatment visit will be followed up for disease progression (CT/MRI scans every 12 weeks) until PD.

After the End-of-Treatment visit, subjects will be followed quarterly (±14 days) for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 1 year after the last subject receives the last dose of MSB0011359C.

After completion of the Follow-up period or at discontinuation of the trial, whatever is applicable / comes first, the appropriate eCRF section for Trial Termination must be completed.

7.1.6 Blood Consumption for Clinical Assessments

The overall amount of blood to be drawn from a single subject must not exceed 60 mL/day and 300 mL in an 8-week period for safety laboratory testing, pregnancy testing, PK analyses, CCI and antibody evaluation.

7.2 Demographic and Other Baseline Characteristics

The assessments and procedures described in this section must be performed during the Screening period.

7.2.1 Demographic Data

The following demographic data will be recoded:

- Subject identifier
- Date of birth
- Sex
- Ethnicity
- Race.

7.2.2 Diagnosis of Tumor

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

- Detailed history of the tumor, including histopathological diagnosis, grading and staging in accordance with the Union Internationale Contre le Cancer Tumor Node Metastasis Classification at diagnosis.
- All therapy used for prior treatment of the tumor (including surgery, radiotherapy and chemotherapy, immunotherapy, etc).
- Any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy.
- Current cancer signs and symptoms and side effects from current and/or previous anticancer treatments.
- Current cancer disease status.

7.2.3 Medical History

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

- Past and concomitant non-malignant diseases and treatments.
- All medications taken and procedures carried out within 30 days prior to Screening.

For the trial entry, all the subjects must fulfill all inclusion criteria described in Section 5.3.1, and none of the subjects should have any exclusion criterion from the list described in Section 5.3.2.

7.2.4 Vital Signs and Physical Examination

Vital signs including body temperature, respiratory rate, heart rate (after 5-minute rest), and arterial blood pressure (after 5-minute rest), body weight and height will be recorded at study entry.

A complete physical examination will be performed. Oxygen saturation will be measured. An ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be conducted.

The ECOG PS will be documented during the Screening period.

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

A CT scan or MRI (if MRI is used, CT of chest is mandatory) of the chest, abdomen, and pelvis (at a minimum and other established assessments of tumor burden if CT/MRI imaging is not sufficient for the individual subject; other regions as specifically required for specific tumor indications) will be performed within 28 days prior to trial treatment start in order to document the baseline status of the tumor disease using RECIST 1.1 target and nontarget lesions and secondarily using mRECIST for subjects in the HCC cohort (see vendor manual). However, if the results of a CT scan or MRI performed within 4 weeks prior to first treatment are available, the Screening CT/MRI does not need to be performed.

A brain CT/MRI scan (either, contrast preferred) is required at Screening if not performed within the previous 6 weeks. Thereafter, brain CT/MRI scan should be done if clinically indicated by development of new specific symptoms.

A bone scan should be done at Screening as clinically indicated.

7.2.6 Cardiac Assessments

A 12-lead ECG will be recorded at Screening. The ECG will be recorded under institution's guidance after the subject has been in a supine position breathing quietly for 5 minutes. The ECG results will be used to evaluate the heart rate, atrial-ventricular conduction, QR, QT, RR duration and corrected QT intervals, and possible arrhythmias.

The ECGs will be documented by recording date and time of collection. All ECG results must be reviewed at the site by the Investigator or a medically qualified designee for clinical management of the subject.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided if the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF. Abnormal values will not be recorded as AEs unless they are the reason for discontinuation of the trial IMP due to AEs or are SAEs.

7.2.7 Clinical Laboratory Tests

Blood samples will be collected at Screening for clinical laboratory parameter evaluations. These clinical laboratory test results will serve not only as the baseline values for subsequent safety clinical laboratory evaluations during the trial, but also help to make sure that each enrolled subject fulfills all the trial entry criteria as listed in Section 5.3.1 and does not meet any of the trial exclusion criteria for laboratory parameters as listed in Section 5.3.2. Detailed description of laboratory assessments is provided in Section 7.4.3.

7.3 Efficacy Assessments

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

A brain CT/MRI scan (either, with contrast preferred) is required at Screening if not performed within the previous 6 weeks. Thereafter brain CT/MRI scan should be performed, if clinically indicated by development of new specific symptoms. A bone scan should be performed at Screening and beyond as clinically indicated. Skin metastasis can be used as target lesions according to RECIST 1.1 using measurements by caliper, if they fulfill RECIST 1.1 for target lesions as described below. The presence of new cutaneous lesions will be considered diagnostic of progression for RECIST 1.1, even if not imaged. For each subject, 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 trial period will be considered. The most appropriate measures to evaluate the tumor status of a subject should be used. The measure(s) to be chosen for sequential evaluation during the trial have to correspond to the measures used to document the progressive tumor status that qualifies the subject for enrollment. The tumor response assessment will be assessed and listed according to the Schedule of Assessments (refer to Table 1 and Table 2).

The foreseen treatment duration is until disease progression verified by a scan subsequent to the initial documentation of PD, unacceptable toxicity, or any criterion for withdrawal from the trial

or IMP occurs (see Section 5.5). Before stopping the treatment, PD should be confirmed by imaging 4 to 6 weeks (preferably 6 weeks, but not later) after progression has been diagnosed according to RECIST 1.1. If progression is based on the occurrence of a new lesion in an area not scanned at Baseline, a further on-study scan 6 weeks later should be considered before performing the End-of-Treatment visit. Treatment may be continued despite progression according to RECIST 1.1 at any time if:

- There are no new symptoms or worsening of existing symptoms.
- There is no decrease in ECOG PS.
- The Investigator does not consider it necessary to administer a salvage therapy.

The treatment should be stopped immediately, if the subject does not tolerate MSB0011359C anymore or if therapeutic failure occurs, which requires urgent treatment with an additional drug or results in clinically significant progression/deterioration.

Tumor responses to treatment will be assigned based on the evaluation of the response of target, nontarget, and new lesions according to RECIST 1.1 (all measurements should be recorded in metric notation) and secondarily using mRECIST for subjects in the HCC cohort.

- To assess objective response, the tumor burden at baseline will be estimated and used for comparison with subsequent measurements. At baseline, tumor lesions will be categorized in target and nontarget lesions according to RECIST 1.1 and secondarily using mRECIST for subjects in the HCC cohort.

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

Any CR or PR should be confirmed according to RECIST 1.1. In the case of a PR or CR, a confirmatory CT or MRI scan must be done no sooner than 4 weeks (preferably at the scheduled 6-week interval).

The Investigator may perform scans in addition to a scheduled trial scan for medical reasons or if the Investigator suspects PD.

As outlined in Section 5.1, treatment should continue with the investigational drug and the subject may remain on study according to the Investigator's decision and in agreement with the subject in case of PD according to RECIST 1.1. Following PD on RECIST 1.1, modified "immune-related response criteria" (irRC; see below and Nishino 2013) should be used as guidance for further clinical care.

Subjects who have experienced a CR, PR or SD should continue treatment through the end of 12 months after confirmation, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after

discussion with the Medical Monitor. Subjects re-initiating treatment should be assessed according to the Schedule of Assessments (Table 1 and Table 2).

7.3.1 Modified Immune-related Response Criteria, Derived from RECIST 1.1

This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. For this trial, the concepts of the irRC (Nishino 2013) are combined with RECIST 1.1 to come up with the modified irRC, which uses unidimensional measurements.

For modified irRC, only target and measurable lesions are taken into account. In contrast to the RECIST 1.1, the modified irRC criteria

a) require confirmation of both progression and response by imaging at 4 to 6 weeks (preferably 6 weeks) after initial imaging, and

b) do not necessarily score the appearance of new lesions as PD if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥ 20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at Baseline, during the trial, and at the End-of-Treatment visit. All measurements should be recorded in metric notation. The modified irRC based on RECIST 1.1 are displayed below.

Modified irRC are defined as follows:

- New measurable lesions: Incorporated into tumor burden.
- New non-measurable lesions: Do not define progression but precludes immune-related complete response (irCR).

Overall irCR: Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to 10 mm or less.

Overall immune-related partial response (irPR): Sum of the longest diameters of target and new measurable lesions decreases ≥ 30%.

Overall immune-related stable disease (irSD): Sum of the longest diameters of target and new measurable lesions neither irCR, irPR, (compared to baseline) or immune-related progressive disease (irPD; compared to nadir).

Overall immune-related progressive disease (irPD): Sum of the longest diameters of target and new measurable lesions increases ≥ 20% (compared to nadir), confirmed by a repeat, consecutive observations at least 4 weeks (normally it should be done at 6 weeks) from the date first documented.

Documentation of irPD (based on modified irRC) does not mandate discontinuation of the trial treatment, even after irPD is confirmed with CT scan 6 weeks after the initial observation of irPD. Please refer to Section 5.5.1 (Withdrawal from the Trial Treatment) to determine when it is appropriate to discontinue treatment with the study drug.

Overall responses derived from changes in index, non-index, and new lesions are shown in Table 6.

Table 6 Overall Responses Derived from Changes in Index, Non-Index, and New Lesions

Measurable Response	Non-Measurable Response		Overall Response Using Modified irRC
Index and New, Measurable Lesions (Tumor Burden)	**Non-Index Lesions**	**New, Non-Measurable Lesions**	
Decrease 100%	Absent	Absent	irCR[a]
Decrease 100%	Stable	Any	irPR[a]
Decrease 100%	Unequivocal progression	Any	irPR[a]
Decrease ≥ 30%	Absent/Stable	Any	irPR[a]
Decrease ≥ 30%	Unequivocal progression	Any	irPR[a]
Decrease < 30% increase < 20%	Absent/Stable	Any	irSD
Decrease < 30% to increase < 20%	Unequivocal progression	Any	irSD
Increase ≥ 20%	Any	Any	irPD

irCR=immune-related complete response; irPD=immune-related progressive disease; irPR=immune-related partial response; irSD=immune-related stable disease.

a Assuming that the response (irCR and irPR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart (normally it should be done 6 weeks apart).

7.3.2 Modified Response Evaluation Criteria in Solid Tumors for Hepatocellular Carcinoma

The text below was obtained from Lencioni 2010.

SUMMARY OF THE mRECIST ASSESSMENT OF RESPONSE: STANDARDIZING RESPONSE ASSESSMENT

1. Image Acquisition

The administration of intravenous contrast is recommended for all CT or MRI studies if not medically contraindicated. In contrast-enhanced studies, it is mandatory to obtain a dual-phase imaging of the liver. Every effort should be made to time the contrast administration so that high-quality arterial-phase imaging is obtained throughout the liver on the first run, and high quality portal venous-phase imaging is obtained throughout the liver on the second run.

2. Image Interpretation

To properly use the proposed mRECIST for HCC to assess response rates and time to progression in HCC clinical trials and to ensure comparability across studies, uniform image acquisition parameters, rigorous quality control, and independent blinded multireader assessments are mandatory.

3. Assessment of Tumor Lesion at Baseline

To be selected as a target lesion using mRECIST, a HCC lesion should meet all the following criteria:

- The lesion can be classified as a RECIST measurable lesion (that is, the lesion can be accurately measured in at least one dimension as 1 cm or more).
- The lesion is suitable for repeat measurement.
- The lesion shows intratumoral arterial enhancement on contrast-enhanced CT or MRI.

It is important to point out that only well-delineated, arterially enhancing lesions can be selected as target lesions for mRECIST.

DEFINING TREATMENT RESPONSE AND TUMOR PROGRESSION

1. Target Lesion Response

The mRECIST for HCC has introduced the following amendments to RECIST in the determination of tumor response for target lesions, which are summarized in Table 7.

Table 7 Assessment of Target Lesion Response: Conventional RECIST and mRECIST Assessment for Hepatocellular Carcinoma Following the American Association for the Study of Liver Disease-Journal of the National Cancer Institute Guideline

Assessment	RECIST	mRECIST for HCC
Complete response	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial response	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as

Assessment	RECIST	mRECIST for HCC
	of target lesions	reference the baseline sum of the diameters of target lesions
Stable disease	Any cases that do not qualify for either partial response or progressive disease	Any cases that do not qualify for either partial response or progressive disease
Progressive disease	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

HCC=hepatocellular carcinoma; mRECIST=modified Response Evaluation Criteria in Solid Tumors.

2. Nontarget Lesion Response

According to mRECIST for HCC, tumor necrosis should be taken into account when assessing the response of nontarget lesions. The disappearance of intratumoral arterial enhancement in nontarget lesions should be considered equivalent to the disappearance of nontarget lesions, and therefore, should declare complete response of nontarget lesions. The persistence of intratumoral arterial enhancement in one or more nontarget lesions should be considered equivalent to persistence of one or more nontarget lesions, and therefore, should declare incomplete response/stable disease. The appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions should declare progressive disease.

Special recommendations for the assessment of tumor response in nontarget lesions in patients with HCC and cirrhosis can be made regarding the following points:

- Portal vein thrombosis: Malignant portal vein thrombosis should be considered a non-measurable lesion due to the difficulty in performing consistent measurements of the malignant thrombus during the course of the treatment.
- Porta hepatis lymph node: Lymph nodes detected at the porta hepatis can be considered as malignant if the lymph node short axis is at least 20 mm.
- Pleural effusion and ascites: The mRECIST for HCC emphasizes that cytopathologic confirmation of the neoplastic nature of any effusion (particularly ascites) that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease.

3. New Lesions

In the assessment of tumor progression, these concepts have been adopted by the mRECIST assessment proposal, considering some specificities for the frame of progression mode:

- A newly detected hepatic nodule will be classified as HCC – and therefore will be declared as evidence of progression – when its longest diameter is at least 1 cm and the nodule shows the typical vascular pattern of HCC on dynamic imaging, that is, hypervascularization in the arterial phase with washout in the portal venous or late venous phase.
- Liver lesions larger than 1 cm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least 1-cm-interval growth in subsequent scans.
- An individual radiologic event will be adjudicated in retrospect as progression at the time it was first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiologic testing.

OVERALL RESPONSE ASSESSMENT

Any newly detected focal liver lesion that does not meet the criteria reported above should be considered equivocal and not conclusive for disease progression.

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analyzing of baseline medical conditions, AEs, physical examination findings including vital signs and eyes signs and symptoms, and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2). Given the intended MoA, particular attention will be given to AEs that may follow the enhanced T-cell activation such as persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, uveitis and other inflammatory eye conditions, or other immune-related reactions. Ophthalmologic examinations should be considered, when clinically indicated, for signs or symptoms of uveitis. Furthermore, due to the anti-TGFβ activity, particular attention will also be given to events associated with, anemia, and rash with hyperkeratosis/keratoacanthoma and squamous cell carcinoma of the skin.

The reporting period for AEs is described in Section 7.4.1.3.

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

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

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

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

In case of a fatality, the cause of death is considered as an AE, and the death is considered as its OUTCOME.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the NCI-CTCAE v4.03 (publication date: 14 June 2010), a descriptive terminology that can be used for AE reporting.

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

If a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

Grade 1: Mild

Grade 2: Moderate

Grade 3: Severe

Grade 4: Life-threatening or disabling

Grade 5: Death related to AE*

According to the Sponsor's convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE as per Section 7.4.1.4; however, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

*Note: Death (Grade 5 as defined by NCI-CTCAE Version 4.0) is mainly regarded as an outcome, to be documented as described below.

If death occurs, the primary cause of death or the event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (eg, sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to the IMP using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the MSB0011359C include, but may not be limited to, temporal relationship between the AE and the MSB0011359C, the known safety profile of MSB0011359C, medical history, concomitant medication, course of the underlying disease, trial procedures.

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

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

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

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

7.4.1.1.1 Adverse Drug Reaction

An ADR is defined in this trial as any AE assessed as related to MSB0011359C by the Investigator and/or Sponsor.

7.4.1.1.2 Serious Adverse Event

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

- Results in death.
- Is life-threatening (NOTE: The term "life-threatening" in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe).

- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is otherwise considered as medically important.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Any type of new (secondary) cancer including squamous cell cancer of the skin should be considered as medically important condition.

For the purposes of reporting, any suspected transmission of an infectious agent via the IMP is also considered an SAE, and all such cases should be reported in an expedited manner as described in Section 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

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

7.4.1.1.3 Events Not to Be Considered as AEs/SAEs

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

AE/SAEs Observed in Association with Disease Progression

Disease progression recorded in the course of efficacy assessments only, but without any adverse signs or symptoms should not be reported as AEs.

However, if adverse signs or symptoms occur in association with disease progression then these should be recorded as AEs or reported as SAEs, if they meet criteria for seriousness.

7.4.1.1.4 Pre-defined AEs of Special Interest (AESI) for Safety Monitoring

Any AE that is suspicious to be a potential irAE (see Section 6.5.4.3), including ophthalmologic findings, has to be reported in an expeditious manner and will be considered an AESI.

Infusion-related reactions/hypersensitivity, regardless of grade, must be reported as AESIs.

In addition, rash with hyperkeratosis/keratoacanthoma/squamous cell cancer of the skin are regarded as AESIs. Please note that squamous cell cancer of the skin should be considered as medically important condition and thus as a serious AESI, which has to be reported in an expedited manner as a SAE.

Anemia suspected by the Investigator to be drug related should also be reported as an AESI.

The reporting of AESI is defined in Section 7.4.1.4.

7.4.1.2 Methods of Recording and Assessing Adverse Events

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

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

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

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

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is included into the trial (date and time of first signature of informed consent) and continues through the trial's End-of-Treatment visit, defined as 28 days (±5 days) after last trial drug administration. After the

End-of-Treatment visit, only AEs that are deemed attributable to trial drug by the Investigator should be documented until the Safety Follow-up visit, defined as 10 weeks (± 2 weeks) after the last trial drug administration.

Any SAE assessed as related to MSB0011359C must be reported whenever it occurs, irrespective of the time elapsed since the last administration of MSB0011359C.

7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest

Serious Adverse Events

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

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

Reporting procedures and timelines are the same for any new information on a previously reported SAE (= follow-up).

Relevant pages from the eCRF may be provided in parallel (eg, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (eg, laboratory results, hospital report, and autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator/reporter must respond to any request for follow-up information (eg, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor may have on the AE within the same timelines as initial reports. This is necessary to ensure a prompt assessment of the event by the Sponsor or designee and, where applicable, to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made by the responsible Medical Monitor. In exceptional cases where a particularly critical event occurs, the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

Adverse Events of Special Interest

In the event of a ***nonserious*** AESI, the Investigator must complete the AESI Report Form and provide it to the Sponsor/designee immediately (within 24 hours) following the specific completion instructions. Serious AESIs have to be reported in an expedited manner as SAEs as outlined above.

Dose-Limiting Toxicities

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

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

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

The Investigator must report SAEs in accordance with applicable site-specific requirements to the IRB that approved the trial.

In accordance with the ICH GCP guidelines and the Japanese ministerial ordinance on GCP, the Sponsor or designee will immediately inform all the trial investigators and the Heads of the trial sites of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IRB's approval/favorable opinion to continue the trial." In particular and in line with respective applicable regulations, the Sponsor/designee will immediately inform all the trial investigators and the Heads of the trial sites of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). In addition, according to applicable regulations, the Sponsor/designee will inform the trial investigators and the Heads of the trial sites of all SAEs which were reported to the health authorities. In accordance with the Japanese regulatory requirements concerning safety reporting, the Investigator should place copies of the safety reports in the Investigator Site File. The Head of the trial site should also maintain copies of safety reports appropriately. National regulations with regard to safety report notifications to investigators will be taken into account.

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

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

7.4.1.6 Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed continuously throughout the trial (see Section 7.4.1.3) and are assessed for final outcome at the End-of-Treatment visit. After the End-of-Treatment visit, only AEs that are deemed attributable to trial drug by the Investigator should be documented until the Safety Follow-up visit.

All SAEs ongoing at the End-of-Treatment visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". In addition, all trial drug related SAEs occurring after End-of-Treatment visit and ongoing at the Safety Follow-up visit must be followed up in the same manner. Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

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

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

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

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

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

7.4.3 Clinical Laboratory Assessments

It is essential that the Sponsor be provided with a list of laboratory normal ranges before shipment of IMP. Any change in laboratory normal ranges during the trial will additionally be forwarded to the CRO and the Sponsor.

All routine laboratory analyses will be performed at a laboratory facility local to the investigational site and relevant results must be drawn and checked before administration of MSB0011359C. The report of the results must be retained as a part of the subject's medical record or source documents. However, an assessment for albumin for the HCC cohort at Screening should be performed centrally. Blood samples for the tests listed in Table 8 will be taken from non-fasted subjects during the Screening period, at the End-of-Treatment visit, and during the treatment period as specified in the Schedules of Assessments (Table 1 and Table 2). Complete blood count and core serum chemistry must be checked within 48 hours prior to each dose administration.

Serum electrophoresis (for dose escalation part only), ACTH, ANA, RF, free T4, TSH, and urinalysis will be assessed at the time points defined in the Schedules of Assessments (Table 1 and Table 2). If confirmation of a subject's postmenopausal status is necessary, an FSH level will also be performed at Screening, see Section 7.1.1.

Table 8 Required Laboratory Panel Tests

Full Chemistry	Hematology
AFP (HCC cohort only)	Absolute lymphocyte count
Albumin	ANC
Alkaline phosphatase*	Hematocrit
ALT*	Hemoglobin
Amylase	Platelet count
AST*	RBC count
GGT	WBC count and differential count
BUN/total urea*	RBC morphology**
Calcium*	Reticulocytes
Chloride*	MCH
Cholesterol	Mean corpuscular volume
Creatine kinase	MCHC
Creatinine*	
CRP	**Hemostaseology**
Glucose*	aPTT
LDH	Prothrombin time/INR
Lipase	
Phosphorus/phosphates*	**Basic Urinalysis** (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the Screening and End-of-Treatment visits and a basic urinalysis prior to each administration of the IMP.
Magnesium*	
Potassium*	
Sodium*	
Total bilirubin/indirect bilirubin*	
Total protein	Totality of binding ADAs
Uric acid	
Triglycerides	**ACTH, ANA, RF, TSH, and free T4**
Hormone	
FSH (if applicable)	

ACTH=adrenocorticotropic hormone; ADA=anti-drug antibody; AFP=alpha-fetoprotein; ALT=alanine aminotransferase; ANA=antinuclear antibody; ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; FSH=follicle stimulating hormone; GGT=gamma-glutamyltransferase; IMP=Investigational Medicinal Product; INR=international normalized ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; RBC=red blood cell; RF=rheumatoid factor; TSH=thyroid stimulating hormone; T4=thyroxine; WBC=white blood cell.

* Core serum chemistries. ** This test will be conducted in cases that a patient has anemia due to hemolysis or anemia of unknown etiology.

If a subject has a clinically significant abnormal laboratory test value that is not present at Baseline, the test will be repeated weekly and the subject will be followed until the test value has returned to the normal range or the Investigator has determined that the abnormality is chronic or stable. In addition, RBC morphology will be assessed in case of anemia onset caused by hemolysis, or other unknown causes.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

The ECOG PS will be assessed at Screening and at subsequent visits as indicated in the Schedules of Assessments (Table 1 and Table 2) and documented in the eCRF.

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

A physical examination will be conducted and SpO_2 measured at Screening and at subsequent visits as indicated in the Schedules of Assessments (Table 1 and Table 2) and documented in the eCRF (detailed description in Section 7.1). Any abnormalities arising or worsening after the signing of the ICF should be documented in the eCRF Adverse Event section (see Section 7.4.1). Abnormal findings are to be reassessed at subsequent visits.

An ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be conducted at Screening. At subsequent visits, eye signs and symptoms should be checked. If there are any clinically relevant findings, then an appropriate ophthalmology examination including slit lamp evaluation inclusive of the anterior segment and with visual acuity should be obtained within 2 days.

Digital 12-lead ECGs will be recorded at Screening and at trial visits as indicated in the Schedules of Assessments (Table 1 and Table 2) until Week 13 (Visit 10).

All newly diagnosed or worsening conditions, signs and symptoms observed since Screening, whether related to trial treatment or not, are to be reported as AEs.

For female subjects of childbearing potential, serum β-HCG pregnancy test will be carried out during the Screening period. A urine or serum β-HCG test will be performed once a month during the treatment period as indicated in the Schedules of Assessments (Table 1 and Table 2), at the End-of-Treatment visit, and at the Safety Follow-up visit. Results of the most recent pregnancy test should be available prior to the next dosing of IMP. Subjects who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and if needed FSH > 40 mIU/mL [in the postmenopausal range] as outlined in Section 7.1.1), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.

7.5 Pharmacokinetics

7.5.1 Dose Escalation Part

Pharmacokinetics parameters include area under the concentration-time curve (AUC), maximum serum concentration observed postdose (C_{max}), minimum serum concentration observed postdose (C_{min}), and terminal half-life ($t_{1/2}$) (for definitions, see Section 8.5.3.2). Blood samples for the analysis of serum concentrations of MSB0011359C will be drawn in all subjects according to the Schedule of Assessments (Table 3).

7.5.2 Expansion Part

Pharmacokinetics parameters will include C_{max} and C_{min}. Blood samples for the analysis of serum concentrations of MSB0011359C will be drawn in all subjects according to the Schedule of Assessments (Table 3).

7.5.3 Body Fluid

Whole blood (2.5 mL per sample) will be collected for PK assessments. Post-infusion samples should be drawn from a site other than the infusion site (ie, the contralateral arm) on the days of infusion. If the infusion is interrupted, the reason for interruption and the exact infusion times will be documented on the eCRF.

The total amount of blood taken during the first 8 weeks of the trial will not exceed the total of 300 mL and during the first 85 days will not exceed the total of 350 mL.

Further details will be summarized in the Laboratory Manual.

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7.7 Other Assessments

7.7.1 Anti-drug antibody Analysis

The blood sample for Baseline ADA analysis will be collected before trial treatment start. Further serum samples for ADA analysis will be collected as indicated in the Schedule of Assessments (Table 3). Whole blood (3.5 mL per sample) will be collected for ADA analysis at each sampling point.

Samples positive for ADAs will be re-analyzed to determine the titer.

The detection of antibodies to M7824 will be performed using a validated assay method with tiered testing of Screening, confirmatory, and titration. Confirmed positive antibodies may be tested for the presence of neutralizing antibodies and may be further characterized.

Further details will be summarized in the Laboratory Manual.

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7.7.3 Health-related Quality of Life

For subjects in the GC, ESCC, and BTC expansion cohorts, symptom severity will be assessed using a generic question to assess severity of symptoms (PGIS) and using instruments for the assessment of cancer-specific symptoms (Table 2). Each of the instruments and the selected items for administration are described below.

PGIS: The PGIS is an in-house questionnaire to assess how the subject rates their overall symptom severity (How would you rate the overall severity of your symptoms over the past 7 days – none, mild, moderate, severe, very severe?). The PGIS will be administered in the GC, ESCC, and BTC expansion cohorts.

EORTC QLQ-C30: The EORTC QLQ-C30 is a 30-item patient-reported outcome questionnaire created to measure broad functioning, symptoms, and health-related quality of life issues across all types of cancers (Aaronson 1991). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much). A subset of the EORTC QLQ-C30 items have been selected for administration to reduce patient burden while allowing for key tumor-related and metastasis-related symptoms to be assessed, as follows:

- GC: Fatigue (3 items)
- ESCC: Fatigue (3 items) and general pain (2 items)
- BTC: Fatigue (3 items)

EORTC QLQ-STO22: The EORTC QLQ-STO22 is a 22-item patient-reported outcome questionnaire created to measure functioning, symptoms, and health-related quality of life issues specific to stomach cancer (Vickery 2001). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much).

- GC: Dysphagia (3 items), stomach pain (3 items), and early satiety (1 item)

EORTC QLQ-OES18: The EORTC QLQ-OES18 is an 18-item patient-reported outcome questionnaire created to measure functioning, symptoms, and health-related quality of life issues specific to esophageal cancer (Blazeby 2003). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much).

- ESCC: Dysphagia (3 items) and reflux pain (2 items)
- **EORTC QLQ-BIL21**: The EORTC QLQ-BIL21 is a 21-item patient-reported outcome questionnaire created to measure functioning, symptoms, and health-related quality of life issues specific to cholangiocarcinoma and gallbladder cancer (Friend 2011). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much).
- BTC: Stomach/back pain (3 items), early satiety (1 item), and itching (1 item)

EORTC QLQ-HCC18: The EORTC QLQ-HCC18 is an 18-item patient-reported outcome questionnaire created to measure functioning, symptoms, and health-related quality of life issues specific to HCC (Blazeby 2004). Each of these items is rated on a 4-point response scale (1 = not at all; 4 = very much). While not specifically designed for BTC, the EORTC QLQ-HCC18 includes two items that are a key symptom associated with BTC:

- BTC: Fevers (2 items)

8 Statistics

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8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Primary Endpoints

The primary endpoints for the dose escalation part of the trial are:

- Occurrence of DLTs during the first 3 weeks (21 days) of treatment in the dose escalation part.
- Number, severity, and duration of treatment-emergent AEs (TEAEs) according to the NCI-CTCAE v4.03.
- Number, severity and duration of treatment-related AEs for all dose groups/indications according to CTCAE v4.03.

8.3.2 Secondary Endpoints

The secondary endpoints for the dose escalation part of the trial are:

- MSB0011359C PK profile (for dose escalation), including area under the concentration-time curve (AUC), maximum serum concentration observed postdose (C_{max}), minimum serum concentration observed postdose (C_{min}), and terminal half-life ($t_{1/2}$).
- Serum titers of anti-MSB0011359C antibodies.
- BOR according to RECIST 1.1 per investigator assessments.

The secondary endpoints for the expansion part of the trial are:

- BOR according to RECIST 1.1 as adjudicated by the IRC
- BOR according to RECIST 1.1 per investigator assessments
- Duration of response according to RECIST 1.1 as adjudicated by the IRC
- Disease control rate according to RECIST 1.1 as adjudicated by the IRC
- PFS time according to RECIST 1.1 as adjudicated by the IRC
- OS time.

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8.3.4 Safety Endpoints

Besides the endpoints specified as primary and secondary variables, the following endpoints will be evaluated:

- Laboratory parameters

- Vital signs
- ECG parameters.

8.4 Analysis Sets

The following analysis sets will be defined separately for the dose escalation part and the expansion cohort in this trial, as applicable:

- **DLT analysis set (dose escalation part)**: All subjects with data used for implementing the dose-escalation schedule. These subjects will have received all trial treatment administrations in the DLT evaluation period or should have stopped treatment because of DLTs in the DLT evaluation period.
- **Safety analysis set**: All subjects who receive at least 1 dose of trial treatment.
- **Full analysis set:** All subjects who receive at least 1 dose of trial treatment.
- **PK analysis set:** All subjects who complete at least 1 infusion of IMP, and who provide at least 1 sample with a measurable concentration of MSB0011359C.
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8.5 Description of Statistical Analyses

Full details of the planned analyses will be described in the trial statistical analysis plan (SAP), separately for the dose escalation and the expansion part of the trial.

8.5.1 General Considerations

All data recorded during the trial will be presented in individual data listings performed on the safety analysis set. All data will be evaluated as observed, and no imputation method for missing values will be used. All data will be presented in a descriptive manner. Each cohort will be analyzed separately and no multiplicity adjustment across cohorts will be performed. All other analyses are considered as exploratory, even if statistical tests are used.

Descriptive statistics will be used to summarize the trial results, ie, statistics for continuous variables may include means, medians, ranges, and appropriate measures of variability.

Qualitative variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by CIs. Unless otherwise specified, the calculation of proportions will be based on the sample size of the population of interest. Counts of missing observations will be included in the denominator and presented as a separate category if not otherwise specified in the SAP.

The DLT analysis set is the underlying data set for the MTD determination. Safety analyses will be performed on the safety analysis set. Baseline summaries and efficacy analyses will be performed on the full analysis set. Analyses of PK variables will be performed on the PK analysis set.

The estimation of PK parameters will be performed using WinNonlin® Version 5.0 or higher. All other statistical analyses will be performed using SAS® Version 9.1.3 or higher, or R, Version 2.10.1 or higher.

Unless otherwise specified, the endpoint analyses described in the following will be performed separately for both the dose escalation part and the expansion part of the trial.

8.5.2 Analysis of Primary Endpoints

8.5.2.1 Maximum Tolerated Dose Determination

For determination of the MTD, individual subject data from the dose escalation part will be reported.

In addition, for the final statistical analysis, the following will be analyzed for the escalation part:

- At each dose level, the number and proportion of subjects in the DLT analysis set who experience a DLT during the DLT evaluation period.
- At each dose level, the number and proportion of TEAEs experienced by subjects by overall and the worst severity in the safety analysis set and duration of TEAEs.
- At each dose level, the number and proportion of treatment related TEAEs experienced by subjects by overall and the worst severity in the safety analysis se and duration of treatment related TEAEs.

The MTD will be determined according to the dose escalation plan described in Section 5.1.3.2. The MTD is defined as the highest dose level at which no more than 1 subject out of 6 subjects treated in a cohort and evaluable for DLT determination experiences a DLT.

8.5.3 Analysis of Secondary Endpoints

8.5.3.1 Efficacy Parameters

Clinical efficacy parameters will be analyzed descriptively in the full analysis set.

Does escalation

For the dose escalation part of the trial, the secondary efficacy endpoint is BOR according to RECIST 1.1 per investigator assessment. For a BOR of PR or CR, confirmation of the response according to RECIST 1.1 (Eisenhauer 2009) will be required. The response at each scheduled tumor assessment and the BOR will be listed for each subject. The ORR, defined as the proportion of subjects with BOR of PR or CR, will be tabulated by dose level.

Dose expansion

For the dose expansion part of the trial, the primary secondary efficacy endpoint is confirmed BOR according to RECIST 1.1 as adjudicated by the IRC (Section 2.2.2) for the GC, ESCC and BTC cohorts.

For a BOR of PR or CR, confirmation of the response according to RECIST 1.1 (Eisenhauer 2009) will be required for the final analysis for both escalation and expansion parts. The response at each scheduled tumor assessment and the BOR will be listed for each subject. The ORR and associated 95% CIs will be tabulated for each cohort.

The following secondary endpoints will also be reported:

- Duration of response according to RECIST 1.1 as adjudicated by the IRC will be defined as the time from first confirmed response until the first documented disease progression that is subsequently confirmed. It will be analyzed using Kaplan-Meier method. Subjects without an event at the analysis cut-off date will be censored on the date of the last tumor assessment.
    - Disease control rate, defined as the proportion of subjects with BOR of CR, PR, or SD with minimum duration of 12 weeks according to RECIST 1.1 as adjudicated by the IRC, will be tabulated within each expansion cohort.
    - PFS time according to RECIST 1.1 as adjudicated by the IRC
        - The PFS time is defined as the time (months) from first administration of trial drug to the first observation of radiological PD (as assessed by the IRC) or occurrence of death due to any cause. PFS will be presented in listings and analyzed using the Kaplan-Meier method in GC, ESCC and BTC cohorts separately if the cohort enrolls the full planned number of subjects. The detailed censoring rules will be provided in the SAP.
        - OS, defined as the time between the first dose date and death. If a patient has not died, the patient will be censored at the time of last contact (last known alive date). OS will be presented in listings and analyzed using the Kaplan-Meier method in GC, ESCC and BTC cohorts separately if the cohort enrolls the full planned number of subjects.
- OS time.

8.5.3.2 Pharmacokinetics Profile

Serum concentrations of MSB0011359C will be determined by a validated method at the times listed in the Schedule of Assessments (refer to Table 3).

The following PK parameters will be estimated and reported:

- AUC_{0-t} (dose escalation part only): Area under the concentration-time curve from the time of dosing to the time of the last observation (calculated by linear trapezoidal summation).
- $AUC_{0-\infty}$ (dose escalation part only): Area under the concentration-time curve from the time of dosing extrapolated to infinity (calculated by the linear trapezoidal summation and extrapolated to infinity using $C_{last}/\lambda z$ [terminal elimination rate constant]).
- C_{max} : Maximum serum concentration observed postdose (for the expansion phase, 2 postdose samples in 3 cycles).
- C_{min} : Minimum serum concentration observed postdose.
- $t_{½}$ (dose escalation part only): Elimination half-life, determined as $0.693/\lambda_z$ (terminal elimination rate constant).

The PK parameters will be summarized using descriptive statistics. Individual as well as mean concentration-time plots will be depicted.

Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation.

8.5.3.3 Serum Titers of Anti-MSB0011359C Antibodies (ADA)

Immunogenicity testing strategy will be implemented and conducted in line with:

- Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (April 2008. EMEA/CHMP/BMWP/14327/2006).
- Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (24 May 2012. EMA/CHMP/BMWP/86289/2010).
- Food and Drug Administration (December 2009, draft) Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins.

A qualified method that uses an acid dissociation step to detect ADAs in the presence of excess drug in human serum will be applied. Removal of drug after acid treatment is not required. The ADA titers of positive samples will be determined.

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8.5.5 Analysis of Safety

The extent of exposure to MSB0011359C will be characterized by duration (weeks), number of administrations, cumulative dose (mg/kg), dose intensity (mg/kg/2 weeks), relative dose intensity (actual dose given/planned dose), and number of dose delays.

Safety analyses will be performed on the Safety analysis set. The safety endpoints will be tabulated by dose-level or cohort, using descriptive statistics.

Safety assessments will be based on review of the incidence of AEs, including AEs of special interest, ADRs, and changes in vital signs, ECGs, body weight, and laboratory values (hematology and serum chemistry).

8.5.5.1 Adverse Events

Adverse events will be coded according to the most current version of MedDRA. Severity of AEs will be graded using the NCI-CTCAE v4.03 toxicity grading scale.

The incidence TEAEs regardless of attribution and AEs defined as related to MSB0011359C will be summarized by Preferred Term and System Organ Class, and described in terms of intensity and relationship to MSB0011359C. Adverse events (serious and nonserious) will be considered TEAEs when emerging in the on-treatment period defined as the time from the first trial drug administration to the last drug administration date + 30 days or the earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurs first, unless otherwise stated. AEs occurring after the last trial drug administration will always be classified as TEAE if it is considered trial drug-related by the Investigator. All premature terminations will be summarized by primary reason for treatment withdrawal.

8.5.5.2 Laboratory Variables

Laboratory results will be classified by grade according to NCI-CTCAE v4.03. The worst on-trial grades after the first trial treatment will be summarized. Shifts in toxicity grading from first treatment to highest grade will be displayed. Results for variables that are not part of NCI-CTCAE will be presented as within or above normal limits. Only subjects with post-Baseline laboratory values will be included in these analyses.

8.5.5.3 Physical Examination, Including Vital Signs and 12-lead Electrocardiogram

Clinically significant, abnormal findings from the physical examination are to be reported as AEs. Separate summaries of the physical examination will therefore not be provided.

Vital signs (including body temperature, respiratory rate, heart rate, and blood pressure), and 12-lead ECG recorded according to the Schedules of Assessments (refer to Table 1 and Table 2) will be descriptively presented.

Further details on the safety analyses will be provided in the SAP.

8.6 Interim Analyses

Enrollment of expansion cohorts will not be stopped for the purpose of conducting their respective interim analyses but will stop if futility is met as specified.

Dose Escalation Part

In the dose escalation part, the trial data will be evaluated before decision is made to go to the next dose level or to start with treatment in the expansion part.

BTC Cohort

One interim analysis is planned for this cohort 12 weeks after the 20th subject in the cohort started treatment. The endpoint in this interim analysis is BOR (confirmation is not required). No multiplicity adjusted is applied to the interim analysis.

Additional Interim Analyses

In general, interim analyses at time points that are not specified in the protocol may be performed for internal planning purposes.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at his/her site. Throughout this clinical trial protocol, Investigator refers to both the principal investigator and any subinvestigators. He/she will ensure that the trial is performed in accordance with the clinical trial protocol, the ethical principles that have their origin in the Declaration of Helsinki, and with the standards stipulated in Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law; and "Ministerial Ordinance on Standards for the Implementation of Clinical Studies on Pharmaceutical Product (GCP). In particular, the Investigator must ensure that only subjects who have given their informed consent are included in the trial.

In 1998, the United States' FDA introduced a regulation (21 CFR, Part 54) entitled "Financial Disclosure by Clinical Investigators". For studies conducted in any country that could result in a product submission to the FDA for marketing approval and could contribute significantly to the demonstration of efficacy and safety of the IMP(s) (named "covered studies" by the FDA), the Investigator and all sub-Investigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the trial and for 12 months following completion of the trial.

9.2 Subject Information and Informed Consent

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

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). With the cooperation of the Sponsor, and in accordance with the Note for Guidance on GCP (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP, and the ethical principles that have their origin in the Declaration of Helsinki, the Investigator or designee will prepare the ICF and other written information to be used in obtaining informed consent from the trial subjects. The Sponsor should provide the Investigator or designee with documents/information necessary for preparing the aforementioned written information and cooperate with the Investigator to prepare it. In addition to providing this written information to a potential subject, the Investigator or his/her designate will inform the subject of all pertinent aspects of the trial orally as well as in writing. The language used in the aforementioned oral and written information about the trial must be fully and readily understandable to lay persons.

Before consent may be obtained, the Investigator should provide the prospective subject (the prospective subject's legally acceptable representative in the case of obtaining the consent of the legally acceptable representative) with ample time and opportunity to inquire about details of the

clinical trial and to decide whether or not to participate in the trial. In such cases, the Investigator or the trial collaborator giving supplementary explanation should answer all questions about the trial to the satisfaction of the prospective subject (or of the prospective subject's legally acceptable representative in the case of obtaining the consent of the legally acceptable representative).

Depending on national regulations, a person other than the Investigator may inform the subject about the trial and sign the ICF, as above.

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

For subjects who wish to continue participation following the completion of their DLT period, another written consent is required.

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

Whenever important new information becomes available that may be relevant to the subject's consent, the Investigator will revise the subject information sheet and any other written information provided to the subjects and submit them to the IRB for review and opinion. Using the approved revised subject information sheet and other written information, the Investigator will explain the changes to the previous version to each trial subject and obtain his/her written consent for continued participation in the trial.

9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion by the interactive web response system. Subject number will be assigned immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database.

The subject's data collected in the trial will be stored under this number. Only the Investigator will be able to link the subject's trial data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the Monitor, audits, and regulatory inspections will be kept strictly confidential.

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

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9.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the Sponsor. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial.

Clinical trial investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical trial investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, s/he will answer any questions. Any subsequent action (eg, unblinding) will follow the standard processes established for the Investigators.

In cases where the Investigator is not available, Merck Biopharma/EMD Serono or designee will provide the appropriate means to contact a Sponsor physician. This includes the provision of a 24- hour contact number at a call centre, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency and to provide support for the potential unblinding of the subject concerned.

9.5 Clinical Trial Insurance and Compensation to Subjects

The Sponsor is entirely responsible for AEs that are associated with this trial and impair the health of the subjects, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the trial site, and/or the subject. The Sponsor will provide insurance to fulfill the responsibility.

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

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, the clinical trial protocol will be submitted, through the Head of the trial site, together with its associated documents (such as the ICF) to the responsible IEC/IRB for its favorable opinion/approval. The written favorable opinion/approval of the IEC/IRB will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File at the CRO.

The Sponsor will initiate the trial at a site after obtaining written approval from the Head of the trial site based on favorable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, its membership list, and names of members who were present and voted at the meeting. Written favorable opinion/approval should clearly identify the trial, the clinical trial protocol version and the Subject Information and ICF version that were reviewed at the meeting. Where possible, copies of the meeting minutes should also be obtained.

Plans for any substantial amendments to the clinical trial will also be submitted to the concerned IEC/IRB before they are implemented (see Section 10.5). Relevant safety information will be submitted to the IEC/IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (eg, IMP Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with the regulations of the country involved in the trial.

10 Trial Management

10.1 Case Report Form Handling

Refer to the Manual of Operations for eCRF handling guidelines.

The Investigator or designee will be responsible for entering trial data in the eCRF provided by the CRO and follow the data standards of the Sponsor. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs.

The data will be entered into a validated database. The CRO will be responsible for data review and processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. All PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Subject Files

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and medical information for the subject, and should be as complete as possible. In particular, the following data should be available in this file: (adapt to trial as necessary)

- Subject's full name
- Date of birth
- Sex
- Height
- Weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification (MS200647-0008)
- Date of subject's inclusion into the trial (ie, date of giving informed consent)
- Subject number in the trial
- Dates of the subject's visits to the site
- Any medical examinations and clinical findings predefined in the clinical trial protocol
- All AEs observed in the subject
- Date of subject's end of trial
- Date of and reason for early withdrawal of the subject from the trial or from the IMP, if applicable.

It must be possible to identify each subject by using this subject file.

Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, photographic negatives, X-rays, CT or MRI scan images, ECG recordings, laboratory value listings, etc. Such documents must bear at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

10.3 Investigator Site File and Archiving

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Monitor, and must be ready for Sponsor audit as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or in accordance with the requirements of Japan GCP or as otherwise notified by the Sponsor) after the end of the trial. The documents to be thus archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor.

The Head of the trial site must retain all records, including documents and data, which relate to the clinical trial in accordance with GCP. The Head of the trial site must retain the records for the longest possible time permitted by Japan GCP, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Head of the trial site should ensure that no destruction of medical records is performed without the written approval of the Sponsor. The principal investigator must retain records, including documents and data, which relate to the clinical trial in accordance with the instructions from the Head of the trial site.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH Note for Guidance on GCP (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP, and any other applicable regulations. The site Monitor will perform visits to the trial site at regular intervals.

Representatives of the Sponsor's Quality Assurance unit or a designated organization, as well as Health Authorities, must be permitted to access all trial-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs, the IMP, IMP accountability records, and the subjects' original medical records/files.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and to the relevant IRB through the Head of the trial site for approval or favorable opinion. In such cases, the amendment will be implemented only after written approval from the Head of the trial site based on favorable opinion/approval from the relevant IRB has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IRB or to Health Authorities only where requested by pertinent regulations.

Any amendment that could have an impact on the subject's agreement to participate in the trial requires the subject's informed consent prior to implementation (see Section 9.2).

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, or completion of a particular cohort or cohorts if applicable, a clinical trial report according to ICH Topic E3 will be written by the Sponsor or the designated CRO in consultation with the Coordinating Investigator.

10.6.2 Publication

The first publication may be a publication of the results of the analysis of the primary endpoint(s) that will include data from all trial sites that participated in the dose escalation part of the trial.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require pre-submission review by the Sponsor.

The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

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12 Appendices

Appendix 1 Eastern Cooperative Oncology Group Performance Status

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

Appendix 2 Guidance on Contraception

Birth control methods considered as highly effective

Aligned with the Clinical Trials Facilitation Group (CTFG 2014) "Recommendations related to contraception and pregnancy testing in clinical trials" methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods, such as:

- combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[1] (oral, intravaginal, transdermal)
- progesterone-only hormonal contraception associated with inhibition of ovulation[1] (oral, injectable, implantable[2*])
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomized partner[2,3]
- sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method

[2] Contraception methods in the context of this guidance are considered to have low user dependency

[3] Vasectomised partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Abstinence needs to be in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

*not approved in Japan

Appendix 3 Protocol Amendments History

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

Changes from Version 5.0 to Version 6.0 Included in the Amendment

Section # and Name	Description of Change	Brief Rationale
Synopsis, Planned Trial Period; 5.1.6 Planned Treatment Duration	Updated last subject out	CCI [redacted]
CCI [redacted]	[redacted]	[redacted] document irRC per Investigator
Table 2 Schedule of Assessments: Expansion Part, Table 3 Schedule of Assessments – Pharmacokinetics Sampling, CCI [redacted]	Footnote cc added in Table 2 and footnote h added in Table 3	To clarify visits and procedures which are not applicable for re-initiated subjects
1 Synopsis, Table 3 Schedule of Assessments – Pharmacokinetics Sampling, CCI [redacted]	Footnote g and m added	To clarify timing for ADA sample and to clarify there will be no re-initiated HCC subjects
3.4 Summary of Overall Benefit and Risk	Added important risk of mild to moderate mucosal bleeding events	To include new important risk
3.4.4 Alterations in Wound Healing or Repair of Tissue Damage	Added text	To include guidance for treatment following minor and major surgery
3.4.7 Mild to Moderate Mucosal Bleeding Events	Section added	To include details of new potential risk
5.1.6 Planned Treatment Duration	Updated last subject out Amended follow up of adverse drug reactions	To extend planned trial period for dose escalation and expansion cohorts To include adverse drug reactions could be followed up until start of new therapy
5.6 Premature Discontinuation of the Trial	Added allowance for subjects to enter a rollover study	To add rollover study for subjects to continue to receive study drug following study termination
7.1.2.2 Expansion Part Treatment Period	Deleted reference to cytology form for cytology data collection	Cytology data to be captured in the EDC
7.1.3 Rechallenge	Added section	To provide details of re-initiated subjects

Section # and Name	Description of Change	Brief Rationale
7.1.5.2 Long-term Follow-up/Trial Termination	Amended follow up of serious adverse events	To include serious adverse events could be followed up until start of new therapy

Changes from Version 4.0 to Version 5.0 Included in the Amendment

Section # and Name	Description of Change	Brief Rationale
Cover page, synopsis, and Appendix 4 Signature pages	Removed "M7824" from the title	To align title with other studies in this program for consistency.
Synopsis and Section 5.1.8 Analysis Cut-Off Dates	Changed the analysis cut-off dates for dose escalation part	To align the analysis cut-off dates for dose escalation part.
Synopsis and Sections 5.1.5 Planned Number of Subjects and 8.1.2 Expansion Cohorts	Updated number of subjects to be enrolled in expansion part of the study	To account for the additional subjects in the BTC cohort.
Synopsis – Key inclusion criteria for the dose escalation 5.3.1.1 Inclusion Criteria for Dose Escalation	Added statement that subjects with liver involvement could have AST ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and bilirubin ≤ 3.0 is acceptable	To not exclude subjects who could benefit from treatment
Synopsis-Key inclusion criteria expansion cohort Section 5.3.1.2 Inclusion criteria for expansion cohort	Added statement regarding biopsies of target lesions for subjects in the [redacted] cohort	To provide additional guidance to Investigators.
Synopsis- Planned trial and treatment duration per subject	Added subjects with PR or SD as those to be treated through the end of 12 months	To provide treatment for subjects who may benefit
Synopsis- statistical methods	Added language for BTC analysis	Provide clarification for analysis of BTC cohort and update total sample size to account for this cohort.
Schedule of Assessments – Table 1 – Footnote "f" and Table 2 – Footnote "f"	Revised footnote "f" on guidance on ECG assessment	Provide clarification for ECG assessment.
Schedule of Assessments – Table 1 – Footnote "i" and Table 2 – Footnote "i"	Added to footnote "i" stipulating guidance from the Medical Monitor	For additional guidance for Investigators and additional oversight.
Schedule of Assessments – Table 1 – Footnote "j" and Table 2 – Footnote "j"	Added statement that subjects with signs of anemia should be monitored on a weekly basis	To provide additional guidance for Investigators and ensure proper safety monitoring
Table 2	Added Patient reported Outcomes assessment for discontinuation visit	To clarify that PROs should be assessed at discontinuation or EOT.
3.1 Investigational Medicinal Product	Added "M7824" as additional designation for MSB0011359C and deleted "proposed" from the INN of avelumab as the name is now accepted	Deleted "proposed", as avelumab is now the accepted non-proprietary name and to align with other documents in the program.

Section # and Name	Description of Change	Brief Rationale
3.1 Investigational Medicinal Product	Updated to state that MSB0011359C binds all TGFβ isoforms	Updated due to new information
5.1.1.1- Dose Escalation 7.1.2 Treatment Period	Added subjects with PR or SD as those to be treated through the end of 12 months	To provide treatment for subjects who may benefit
5.1.1.2 Expansion Cohorts 5.1.6 Planned Treatment Duration 6.2 Dosage and Administration 7.3 Efficacy Assessments	Added subjects with PR or SD as those to be treated through the end of 12 months	To provide treatment for subjects who may benefit
5.1.7.2 Adverse Drug Reactions Requiring Treatment Discontinuation	Modified ADR text	To provide greater clarity and guidance to Investigators.
5.1.7.2 Adverse Drug Reactions Requiring Treatment Discontinuation	Added guidelines for continuing treatment after Grade 3 or 4 dermatological and symptomatic endocrinopathies resolve	To provide greater clarity and guidance to Investigators.
5.3.1.1 Inclusion Criteria for Dose Escalation #9 & 10 and Section 5.3.1.2 Inclusion Criteria for Expansion Cohorts #11 & 12	Modified language for inclusion criteria for contraception	To correct inclusion criteria regarding contraception.
5.3.2 Exclusion criteria #10	Modified language for exclusion criteria for CNS metastases	To clarify exclusion criteria for CNS metastases
5.5.1 Withdrawal from the Trial	Modified language to clarify withdrawal criteria	To clarify that the Medical Monitor should be consulted for missing doses
6.1 Description of the Investigational Medicinal Product	Updated the investigational product information to include a liquid formulation	To provide information on the liquid formulation
6.5.4.3 Immune-Related Adverse Events – Table 5	Added guidance for cardiac irAEs	To provide extra guidance to Investigators.
6.6 Packaging and Labeling of the Investigational Medicinal Product	Updated the investigational product information to include a liquid formulation	To provide information on the liquid formulation
CCI [redacted]	[redacted]	[redacted]
Section 7.1.1 -Screening and Baseline Procedures and Assessments	Updated language for definition of postmenopausal	To clarify definition of postmenopausal.
7.1.1 Screening and Baseline Procedures and Assessments	Added statement that ADA is HAHA in the CRF	To provide greater clarity and guidance to Investigators.

Section # and Name	Description of Change	Brief Rationale
7.1.2.1 Dose Escalation Part Treatment Period 7.1.2.2Expansion Part Treatment Period	Updated HAHA to ADA added statement that ADA is HAHA in the CRF	To provide greater clarity and guidance to Investigators.
7.1.2.2 Expansion Part Treatment Period	Added statement directing Investigators to complete cytology form	To provide guidance to Investigators
7.1.2.2 Expansion Part Treatment Period	Added language for anemia	To provide additional guidance for Investigators and ensure proper safety monitoring
7.2.6 Cardiac Assessments	Added ECG criterion to be evaluated	Correction to match study design
7.4.1.1.4 Pre-defined AEs of Special Interest (AESI) for Safety Monitoring	Added suspected drug-related anemia to list of AESIs	To accelerate reporting of suspected drug-related anemia
7.4.4 Vital Signs, Physical Examinations, and Other Assessments	Modified definition of postmenopausal	Clarified definition of postmenopausal
CCI [redacted]	[redacted]	[redacted]
8.6 Interim Analyses	Added text for additional analyses	Added text for additional planned analyses
11 References	Added a reference regarding contraception	Added reference cited in new Appendix 2
Appendix 2 Guidance on Contraception	Added appendix for guidance on contraception	Added appendix for guidance on contraception to comply with updated template.
(formerly Appendix 2) Appendix 4 Further Sponsor Responsible Persons	Updated contacts for further sponsor responsible persons	Updated contacts for persons responsible

Changes from Version 3.0 to Version 4.0 Included in the Amendment

Section	Change	Brief Rationale
Synopsis	Addition of patient-reported outcome measures	To add health-related Quality-of-Life assessments for the GC, ESCC, and BTC expansion cohorts
Synopsis	Modified the premedication procedures	To clarify the use of premedications
Synopsis	Clarified that a flat dose will be used in the expansion part.	To reflect a flat dose of 1200 mg MSB0011359C administered during the expansion cohort

Section	Change	Brief Rationale
Synopsis	Revised the definition for the BTC target population Clarified the quality of tumor samples	To redefine the target population for Biliary Tract Cancer (BTC) To clarify the quality of tumor samples needed
Synopsis	Clarified that a flat dose will be used in the expansion part. Modified the premedication procedures	To reflect a flat dose of 1200 mg MSB0011359C administered during the expansion cohort To clarify the use of premedications
Synopsis	Addition of patient-reported outcome measures	To add health-related Quality-of-Life assessments for the GC, ESCC, and BTC expansion cohorts
Section 3.3.2 (NEW)	Added rationale for the establishment of a flat dose in the expansion part.	To reflect a flat dose of 1200 mg MSB0011359C administered during the expansion cohort
Section 3.4.1	Modified the premedication procedures	To clarify the use of premedications
Section 4.3	Addition of patient-reported outcome measures	To add health-related Quality-of-Life assessments for the GC, ESCC, and BTC expansion cohorts
Section 5.1.1.2	Addition of patient-reported outcome measures	To add health-related Quality-of-Life assessments for the GC, ESCC, and BTC expansion cohorts
Section 5.1.2	Modified the premedication procedures	To clarify the use of premedications
Section 5.1.4	Clarified the flat dose to be used in the expansion part.	To reflect a flat dose of 1200 mg MSB0011359C administered during the expansion cohort
Section 5.1.7.2	To present guidance for dose interruptions in response to a nonrelated AE	To clarify the dose interruption criteria for AEs not related to study drug
Section 5.3.1.2	Revised the definition for the BTC target population Clarified the quality of tumor samples	To redefine the target population for Biliary Tract Cancer (BTC) To clarify the quality of tumor samples needed
Section 6.2	Modified the premedication procedures Clarified the flat dose to be used in the expansion part.	To clarify the use of premedications To reflect a flat dose of 1200 mg MSB0011359C administered during the expansion cohort

Section	Change	Brief Rationale
Section 6.4	Modified the premedication procedures	To clarify the use of premedications
Section 6.5.4.7 (New)	New section added to clarify the dose interruption criteria for AEs not related to study drug	To clarify the dose interruption criteria for AEs not related to study drug
Section 7.1.1	Addition of patient-reported outcome measures	To add health-related Quality-of-Life assessments for the GC, ESCC, and BTC expansion cohorts
Section 7.1.2.2	Addition of patient-reported outcome measures	To add health-related Quality-of-Life assessments for the GC, ESCC, and BTC expansion cohorts
Section 7.1.3.2	Addition of patient-reported outcome measures	To add health-related Quality-of-Life assessments for the GC, ESCC, and BTC expansion cohorts
Section 7.1.4.1	Addition of patient-reported outcome measures	To add health-related Quality-of-Life assessments for the GC, ESCC, and BTC expansion cohorts
Section 7.5.3	Modified the volume of blood collected	To modify the volume of blood collected for PK/HAHA analysis
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]
Section 7.7.1	Modified the volume of blood collected for PK/HAHA analysis	To modify the volume of blood collected for PK/HAHA analysis
Section 7.7.3 (NEW)	Addition of patient-reported outcome measures	To add health-related Quality-of-Life assessments for the GC, ESCC, and BTC expansion cohorts

Section	Change	Brief Rationale
Section 8.1.2	Clarified that a flat dose will be used in the expansion part.	To reflect a flat dose of 1200 mg MSB0011359C administered during the expansion cohort
Section 8.3.3	Addition of patient-reported outcome measures	To add health-related Quality-of-Life assessments for the GC, ESCC, and BTC expansion cohorts
Section 8.5.4	Addition of patient-reported outcome measures	To add health-related Quality-of-Life assessments for the GC, ESCC, and BTC expansion cohorts

Appendix 4 Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of MSB0011359C in subjects with metastatic or locally advanced solid tumors with expansion to selected indications in Asia
Clinical Trial Protocol Date/Version:	03 March 2020/Version 7.0

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial.

PPD

Signature

PPD

Date of Signature

Name, academic degree	PPD
Function	PPD
Institution	Merck Biopharma Co., Ltd
Address	PPD PPD
Telephone number	PP
Fax number	PP
E-mail address	PPD

CCI
Object No. 0900babe813bc745

Signature Page - Coordinating Investigator

Trial Title:	A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of MSB0011359C in subjects with metastatic or locally advanced solid tumors with expansion to selected indications in Asia
Clinical Trial Protocol Date/Version:	03 March 2020/Version 7.0

I agree to conduct the clinical trial in accordance with this clinical trial protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.

PPD	PPD
Signature	Date of Signature
Name, academic degree	PPD
Function	
Institution	
Address	
Telephone number	
Fax number	
E-mail address	

Document No. CCI [redacted]
Object No. CCI [redacted]

Signature Page - Principal Investigator

Trial Title:	A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of MSB0011359C in subjects with metastatic or locally advanced solid tumors with expansion to selected indications in Asia
Clinical Trial Protocol Date/Version:	03 March 2020/Version 7.0
Center Number:	
Principal Investigator:	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

- I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, ICH Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.
- I will not deviate from the clinical trial protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.

I understand that some Health Authorities require the Sponsors of clinical trials to obtain and supply, when required, details about the Investigators' ownership interests in the Sponsor or Investigational Medicinal Product and information regarding any financial ties with the Sponsor. The Sponsor will use any such information that is collected solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children), and to provide updates as necessary.

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

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Further Sponsor Responsible Persons

Sponsor Responsible Persons not Named on the Cover Page

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Fax number	PPD
E-mail address	PPD