Clinical Study Protocol

Clinical Study Protocol Number	MS100070-0035
Title	A Phase I/Ib Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Chinese Subjects with Locally Advanced Unresectable or Metastatic Solid Tumors with Expansion to Selected Indication(s)
Phase	I/Ib
IND Number	Not applicable
EudraCT Number	Not applicable
Coordinating Investigator	PPD Tel: PPD Fax:
Sponsor	Merck KGaA, Darmstadt, Germany Medical Responsible: PPD Merck Serono (Beijing), Pharmaceutical R&D Co. Ltd. 25F NUO Center Office No.2A, Jiangtai Road， Chaoyang District, Beijing China 100016 People's Republic of China Tel.: PPD Fax:
Clinical Study Protocol Version	17 May 2019 / Version 4.0 including amendment 3.0
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- Confidential -

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List of Abbreviations

λ_z	Terminal elimination rate constant
ADA	Antidrug antibody
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from zero to infinity
AUC_{0-t}	Area under the concentration-time curve from zero to time t
CCI [redacted]	
CI	Confidence interval
C_{last}	Last quantifiable concentration
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CR	Complete response
CRA	Clinical Research Associate
CRF	Case report form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte antigen 4
C_{trough}	The concentration observed immediately before next dosing
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
CCI [redacted]	
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End-of-Treatment

ESCC	Esophageal squamous cell carcinoma
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HAHA	Human antihuman antibody
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous(ly)
IVRS	Interactive voice response system
LFT	Liver function test
Mb	per megabase
MCC	Merkel cell carcinoma
MMR	Mismatch repair
CCI [redacted]	
CCI [redacted]	
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
CCI [redacted]	
PD	Progressive disease/disease progression
CCI [redacted]	

CCI [redacted]

CCI [redacted]

PK	Pharmacokinetic(s)
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SMC	Safety Monitoring Committee
$t_{1/2}$	Elimination half-life
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TIL	Tumor infiltrating lymphocyte
TLS	Tumor lysis syndrome
t_{max}	Time to maximum concentration

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CCI [redacted]

TTR	Time to response
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

1 Synopsis

Clinical Study Protocol Number	MS100070-0035
Title	A Phase I/Ib Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Chinese Subjects with Locally Advanced Unresectable or Metastatic Solid Tumors with Expansion to Selected Indication(s)
Study Phase	I/Ib
IND Number	Not applicable
FDA covered study	No
EudraCT Number	Not applicable
Coordinating Investigator	PPD
Sponsor	Merck KGaA, Darmstadt, Germany
Sponsor Legal Representative in the European Union	Merck KGaA, Darmstadt, Germany
Study centers/countries	The study will be conducted at approximately 3 sites in mainland China.
Planned study period (first subject in-last subject out)	First subject in: Q1 2018 Last subject out: Q4 2019
Trial Registry	Clinicaltrials.gov Chinadrugtrials.org.cn

Objectives:

Primary Objectives:

- To evaluate the maximum tolerated dose (MTD) of avelumab (MSB0010718C) monotherapy in Chinese subjects.
- To characterize the pharmacokinetics (PK) of avelumab in Chinese subjects.

Secondary Objectives:

- To determine the safety and tolerability of avelumab by assessing treatment-emergent adverse events (TEAEs) and treatment-related adverse events (AEs) for all dose groups according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) Version (v) 4.03 in Chinese subjects.
- To characterize immunogenicity of avelumab in Chinese subjects.

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[redacted]

Methodology:

This is a Phase I/Ib, open-label, dose-escalation study.

Dose escalation will be performed at the following 3 dose levels, subjects will receive avelumab by intravenous (IV) infusion over 1 hour once every 2 weeks:

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

The dose escalation uses a modified "3 + 3" design. Thus, 3 or 6 subjects will be enrolled at each dose level. The decision to escalate to the next dose level will be based on safety assessments after all subjects of a cohort have reached Day 21 (dose-limiting toxicity [DLT] observation period). In order to assess the safety of avelumab, a Safety Monitoring Committee (SMC), responsible for dose escalation decisions, will be established. Safety and tolerability of avelumab at a given dose level in Chinese subjects will be confirmed if no DLT observed in the first 3 subjects or less than 2 out of 6 subjects in the corresponding dose cohort.

Once the safety of avelumab at 20 mg/kg once every 2 weeks have been established and can be regarded as safe (ie, no DLT observed in the first 3 subjects or less than 2 out of 6 subjects experience a DLT), a new cohort of 10 mg/kg administered once weekly can be immediately initiated in 6 evaluable subjects to assess safety of a more frequent dosing. Subjects in this cohort of 6 evaluable subjects will receive avelumab once weekly at a dose of 10 mg/kg for 12 consecutive weeks (10 mg/kg once weekly cohort) and then starting at Week 13, once every 2 weeks thereafter (this cohort will not be subjected to DLT evaluation as a primary endpoint).

Planned number of subjects:

Approximately 21 subjects (up to approximately 24 subjects).

Primary endpoints:

- Occurrence of DLTs during the DLT observation period (first 21 days of treatment; excluding 10 mg/kg once weekly cohort).
- PK profiles in Chinese subjects.

Secondary endpoints:

- Occurrence of TEAEs for all dose groups according to NCI-CTCAE v4.03.
- Occurrence of treatment-related AEs for all dose groups according to NCI-CTCAE v4.03.
- Serum titers of antidrug antibodies (ADA) against avelumab.

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Pharmacokinetics:

- AUC_{0-t}: area under the concentration-time curve from time zero to time t (calculated by linear trapezoidal summation).
- AUC_{0-tau}: area under the concentration-time curve from time zero to tau, the respective dosing interval, ie, one- or two-week (calculated by linear trapezoidal summation).
- $AUC_{0-\infty}$: area under the concentration-time curve from time zero to infinity (calculated by linear trapezoidal summation and extrapolated to infinity using the last quantifiable concentration/terminal elimination rate constant [C_{last}/λ_z]).
- λ_z: terminal elimination rate constant. The value of λ_z is determined from the slope of the regression line of log (concentration) versus time.
- C_{max}: maximum serum concentration.
- C_{trough}: serum concentration observed immediately before next dosing.
- C_{last}: last quantifiable concentration.
- t_{max}: time to maximum concentration.
- $t_{1/2}$: elimination half-life determined as $0.693/\lambda_z$.

Diagnosis and key inclusion and exclusion criteria:

Key inclusion criteria

- Signed written informed consent prior to any study-related procedures are undertaken that are not part of standard patient management.
- Chinese men or women aged ≥ 18 years.
- Histologically or cytologically proven locally advanced unresectable or metastatic solid tumors, for which no standard therapy exists, or standard therapy has failed.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at study entry.
- Availability of a recently obtained formalin-fixed, paraffin-embedded block containing tumor tissue (biopsy from a non-irradiated area within 6 months) or 12 or more unstained tumor slides suitable for biomarker detection.

Key exclusion criteria

- Prior therapy with any antibody/drug targeting T cell coregulatory proteins (immune checkpoints) such as programmed death 1 (PD-1), PD-L1, cytotoxic T-lymphocyte antigen-4 (CTLA-4), 4-1BB, LAG-3, TIM-3 or anti-CD127.
- Persisting toxicity related to prior therapy (Grade ≥ 2 NCI-CTCAE v4.03, except Grade < 3 neuropathy and alopecia of any grade).
- Concurrent anticancer treatment (eg, cytoreductive therapy, radiotherapy [with the exception of limited palliative bone-directed radiotherapy], immune therapy, or cytokine therapy except for erythropoietin).
- Concurrent immunosuppressive agents (except for corticosteroids at physiologic replacement dose, equivalent to ≤ 10 mg prednisone daily).
- Severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v4.03).
- Active brain metastases (except those treated locally and have not been progressing for at least 2 weeks after the completion of therapy, with no steroid maintenance therapy required, and no ongoing neurological symptoms related to brain localization of the disease).
- Any history of anaphylaxis*, or uncontrolled asthma (ie, 3 or more features of partially controlled asthma).

  *Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. It is characterized by rapidly developing, life-threatening problems (CTCAE Grading 3-5).

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

Avelumab will be administered from a starting dose of 3 mg/kg up to a maximum dose of 20 mg/kg by IV infusion over 1 hour with the regimen of once every week or every 2 weeks until disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or from avelumab occurs. For the every week regimen (6 subjects in the 10 mg/kg once weekly cohort), subjects will receive avelumab every week for 12 consecutive weeks and then starting at Week 13, once every 2 weeks thereafter.

To mitigate infusion-related reactions, a premedication regimen of 25 to 50 mg diphenhydramine and 500 to 650 mg acetaminophen (IV or oral equivalent) is mandatory approximately 30 to 60 minutes prior to the first 4 doses of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate. However, the prophylactic use of systemic corticosteroids is not permitted.

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

Not applicable.

Planned study and treatment duration per subject:

Subjects will complete the following study phases/visits:

- Clinical Screening, to be completed within 14 days prior to the first administration of avelumab.
- Treatment Phase.
- End-of-Treatment (EOT) Visit to be completed within 7 days after the decision to discontinue avelumab.
- Safety Follow-up, comprising a Safety Follow-up Visit to be performed 30 days after the last dose of avelumab and a phone call 90 days after the last dose of avelumab.
- Long-term Follow-up, with visits to be performed every 12 weeks until 2 years after the last subject receives the last dose of avelumab or the last subject dies, whichever comes first.

Each subject will continue to receive avelumab according to the protocol until:

- disease progression according to RECIST 1.1 assessed by Investigator,
- significant clinical deterioration (clinical progression),
- unacceptable toxicity, or
- any criterion for withdrawal from the study or avelumab, is met.

Subjects may continue avelumab beyond RECIST 1.1-defined disease progression if their ECOG performance status has remained stable, there are no new symptoms or worsening of existing symptoms, and if, in the opinion of the Investigator, the subject will benefit from continued treatment with avelumab.

Subjects receiving avelumab who have experienced a complete response (CR) should be treated for a minimum of 12 months and/or until disease progression or unacceptable toxicity, after confirmation of response.

If a subject with confirmed CR relapses after stopping treatment, but prior to the end of the study, 1 re-initiation of treatment is allowed at the discretion of the Investigator and with the agreement of the Sponsor Medical Monitor. Subjects who re-initiate treatment (retreated subjects) will stay on the study and be treated and monitored according to the protocol.

Statistical methods:

The sample size estimated for the study is not based on any statistical assumptions. Rather, it follows the "3 + 3" rule, a well-established methodology for the design of dose-finding studies in oncology.

For the primary endpoints, the number and proportion of subjects experiencing DLTs will be reported by dose level (excluding 10 mg/kg once weekly cohort). Pharmacokinetic parameters will be summarized using descriptive statistics. The point estimate of ORR/median DOR and 95% CIs will be calculated.

The primary analysis, including all endpoints analyses, for study data will be conducted at the time when all subjects complete PK sample collection (including all samples collected if the

treatment discontinued earlier than Week 13). The data cutoff time point for primary analysis is set at Week 13 (Day 85) of the last subject.

The data from primary analysis will be summarized in the Clinical Study Report (CSR).

The final analysis of study data will be conducted after End of Study, which is defined as the last patient complete 90-day Safety Follow-up Phone Call or last patient died, whichever comes first. Additional data from primary analysis up to this cutoff date will be analyzed and presented as an addendum of CSR.

Table 1-1 Schedule of Assessments for Subjects Receiving Avelumab Once Every 2 Weeks

Assessment	Clinical Screening /Baseline Assessments	Treatment Phase[1]								EOT Visit[2]	Safety Follow-up[2]		Long-term Follow-up[2]
	≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	Until progression	Within 7 days after decision to discontinue IMP[3,4]	30 days (± 5 days) after last IMP	Phone Call 90 days (± 5 days) after last IMP	Every 12 weeks (± 7 days)[5]
		W1	W3	W5	W7	W9	W11	W13					
		D1	D15	D29	D43	D57	D71	D85					
CCI [redacted]													
Written informed consent	X												
Inclusion/exclusion criteria	X												
Medical history[7]	X												
Demographic data	X												
Hepatitis B, hepatitis C, and HIV tests	X												
Full physical examination[8]	X									X	X		

Assessment	Clinical Screening /Baseline Assessments	Treatment Phase[1]								EOT Visit[2]	Safety Follow-up[2]		Long-term Follow-up[2]
	≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	Until progression	Within 7 days after decision to discontinue IMP[3,4]	30 days (± 5 days) after last IMP	Phone Call 90 days (± 5 days) after last IMP	Every 12 weeks (± 7 days)[5]
		W1	W3	W5	W7	W9	W11	W13					
		D1	D15	D29	D43	D57	D71	D85					
Symptom-directed physical exam[8]		As indicated throughout the Treatment Phase											
Height	X												
Vital signs	X	X	X	X	X	X	X	X	2-weekly	X	X		
Weight	X	X	X	X	X	X	X	X	2-weekly	X	X		
ECOG PS[9]	X	X[9]	X	X	X	X	X	X	2-weekly	X	X		
Enrolment (if eligible)[10]	X												
DLT assessment[11]		X	X[11]										
12-lead ECG	X	X	X	X	As indicated and decided by Investigator					X			
Hematology and hemostaseology	X		X	X	X	X	X	X	2-weekly	X	X		
Core serum chemistry[12]			X	X		X	X		2-weekly		X		
Full serum chemistry[13]	X				X			X	6-weekly	X			

Assessment	Clinical Screening /Baseline Assessments	Treatment Phase[1]								EOT Visit[2]	Safety Follow-up[2]		Long-term Follow-up[2]
	≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	Until progression	Within 7 days after decision to discontinue IMP[3,4]	30 days (± 5 days) after last IMP	Phone Call 90 days (± 5 days) after last IMP	Every 12 weeks (± 7 days)[5]
		W1	W3	W5	W7	W9	W11	W13					
		D1	D15	D29	D43	D57	D71	D85					
Full urinalysis[14]	X									X			
Basic urinalysis[14]					X			X	6-weekly				
Serum beta-hCG pregnancy test (if applicable)[15]	X												
Urine pregnancy test (if applicable)[15]		X		X		X		X	4-weekly	X			
CCI [redacted]													
Premedication[21]		X	X	X	X								
Avelumab administration		X	X	X	X	X	X	X	2-weekly				
Concomitant medication and procedures[22]	Collected at each study visit through the 30-day Safety Follow-up Visit												

Assessment	Clinical Screening /Baseline Assessments	Treatment Phase[1]								EOT Visit[2]	Safety Follow-up[2]		Long-term Follow-up[2]
	≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	Until progression	Within 7 days after decision to discontinue IMP[3,4]	30 days (± 5 days) after last IMP	Phone Call 90 days (± 5 days) after last IMP	Every 12 weeks (± 7 days)[5]
		W1	W3	W5	W7	W9	W11	W13					
		D1	D15	D29	D43	D57	D71	D85					
AE collection[23]	AEs are collected through the 30-day Safety Follow-up Visit Treatment-related nonserious AEs are collected until the 90-day Safety Follow-up Phone Call												
SAE collection[24]	All SAEs are documented until the 90-day Safety Follow-up Phone Call Ongoing SAEs at the 30-day Safety Follow-up Visit will be followed up												
Free T4 and TSH	X				X			X	6-weekly	X	X		
PK sampling[25]	See Table 1-3												
ADA sampling[25]	See Table 1-3												
Survival[26]		X	X	X	X	X	X	X	Every visit	X	X	X	X
Further anticancer therapy[26]											X	X	X

ADA: antidrug antibody; AE: adverse event; CR: complete response; CT: computed tomography; D: Day; DLT: dose-limiting toxicity; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group performance status; EOT: End-of-Treatment; hCG: human chorionic gonadotropin; HIV: Human immunodeficiency virus; ICF: Informed consent form; IMP: investigational medicinal product; MRI: magnetic resonance imaging; PD: progressive disease; CCI PK: pharmacokinetics; PR: partial response; RECIST: response evaluation criteria in solid tumors; SAE: serious adverse event; T4: thyroxine; TSH: thyroid-stimulating hormone; V: Visit; W: Week.

1. A time window of up to 3 days before or 1 day after the scheduled visit day (- 3/+ 1 days) is permitted for all study procedures (except for PK sampling visits on Day 2 and 3, see Table 1-3). The calculation of the dose of avelumab will be based on the weight of the subject determined within 72 hours prior to the day of drug administration.
2. All subjects will have an EOT Visit within 7 days after the decision to discontinue avelumab. In addition, subjects will be followed every 12 weeks (± 7 days) for survival (including assessment of any further anticancer therapy).

CCI [redacted]

4. If another anticancer therapy is administered before the end of this 7-day period, the EOT Visit should be conducted prior to the start of this new therapy, if possible. The EOT Visit may be performed on the day of the decision to discontinue avelumab.

CCI [redacted]

7. Medical history should include history of cancer, previous and ongoing medications, previous surgeries, radiotherapies, baseline medical conditions, smoking and alcohol history, and family cancer history.
8. A full physical examination will be conducted at Clinical Screening, at the EOT Visit and at the 30-day Safety Follow-up Visit. During the Treatment Phase, the physical examination will be symptom-directed.
9. If the Clinical Screening ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1/Cycle 1 Day 1.
10. Enrolment will be done after confirmation that the subject meets all screening inclusion criteria (Section 5.3.1) without matching any exclusion criterion (Section 5.3.2).
11. The observation period for DLTs is the 21-day period after the first administration of avelumab for subjects with data used for implementing the dose-escalation algorithm for dose determination (the DLT assessment is not applicable for the 6 subjects in 10 mg/kg once weekly cohort).
12. Core serum chemistry includes liver function panel (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, bilirubin), acute chemistry panel (sodium, potassium, chloride, blood urea nitrogen/total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). If full and core chemistry are scheduled at the same visit, the full chemistry will be performed.
13. Full chemistry panel and other laboratory studies are detailed in Section 7.4.3. Follicle-stimulating hormone at Clinical Screening, if applicable.
14. Full urinalysis (protein content required, and optional parameters albumin and immunoglobulin G to be tested depending on study site capability) at Clinical Screening/baseline, and EOT; basic urinalysis (protein content only) on Days 43 and 85, and then every 6 weeks thereafter prior to administration of avelumab. If urinalysis (full or basic) is positive for protein, sediment will be evaluated.
15. In serum at Clinical Screening; in urine thereafter. Results of the most recent pregnancy test should be available prior to next administration of avelumab.

CCI [redacted]

CCI [redacted]

21. Premedication is mandatory approximately 30 to 60 minutes prior to the first 4 doses of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate. However, the prophylactic use of systemic corticosteroids is not permitted.
22. Concomitant medications and procedures will be documented at each study visit until the 30-day Safety Follow-up Visit.
23. All AEs will be documented at each study visit until the 30-day Safety Follow-up Visit. After this visit, only treatment-related nonserious AEs have to be documented until the 90-day Safety Follow-up Phone Call.
24. All SAEs will be documented at each study visit until the 90-day Safety Follow-up Phone Call. After this, all ongoing SAEs must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as lost to follow-up. Any SAE assessed as related to study drug must be reported whenever it occurs, irrespective of the time elapsed since the last administration of avelumab. At 90 days (± 5 days) after the last dose of avelumab, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related nonserious AEs.
25. Blood samples for PK and ADA will be collected as detailed in Table 1-3.
26. Subjects will be followed every 12 weeks (± 7 days) for survival (including assessment of any further anticancer therapy).

Table 1-2 Schedule of Assessments for Subjects Receiving Avelumab Once a Week for the First 12 Weeks Followed by Once Every 2 Weeks (10 mg/kg Once Weekly Cohort)

Assessment[2]	Clinical Screening /Baseline Assessments	Treatment Phase[1]													
	≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	Until progression
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13 (Roll-over into Once every-2-weeks dosing)	
		D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85	
CCI [redacted]															
Written informed consent	X														
Inclusion/exclusion criteria	X														
Medical history[4]	X														
Demographic data	X														
Hepatitis B, hepatitis C and HIV tests	X														
Full physical examination[5]	X														
Symptom-directed physical exam[5]		As indicated throughout the Treatment Phase													
Height	X														

Assessment[2]	Clinical Screening /Baseline Assessments	Treatment Phase[1]													
	≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	Until progression
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13 (Roll-over into Once every-2-weeks dosing)	
		D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly
ECOG PS[6]	X	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly
Enrolment (if eligible)[7]	X														
12-lead ECG	X	X	X	X	As indicated and decided by Investigator										
Hematology and hemostaseology	X		X	X	X	X	X	X	X	X	X	X	X	X	2-weekly
Core serum chemistry[8]			X	X	X	X	X		X	X	X	X	X		2-weekly
Full serum chemistry[9]	X							X						X	6-weekly
Full urinalysis[10]	X														
Basic urinalysis[10]								X						X	6-weekly
Serum beta-hCG pregnancy test (if applicable)[11]	X														
Urine pregnancy test (if applicable)[11]		X				X				X				X	4-weekly

Assessment[2]	Clinical Screening /Baseline Assessments	Treatment Phase[1]													
	≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	Until progression
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13 (Roll-over into Once every-2-weeks dosing)	
		D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85	
CCI [redacted]															
Premedication[17]		X	X	X	X										
Avelumab administration		X	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly
Concomitant medication and procedures	Collected at each study visit until the 30-day Safety Follow-up Visit														
AE collection[18]	AEs are collected through the 30-day Safety Follow-up Visit Treatment-related nonserious AEs are collected until the 90-day Safety Follow-up Phone Call														
SAE collection[19]	All SAEs are documented until the 90-day Safety Follow-up Phone Call Ongoing SAEs at the 30-day Safety Follow-up Visit will be followed up														
Free T4 and TSH	X							X						X	6-weekly
PK sampling[20]	See Table 1-4														
ADA sampling[20]	See Table 1-4														
Survival[21]		X	X	X	X	X	X	X	X	X	X	X	X	X	Every visit

	Clinical Screening /Baseline Assessments	Treatment Phase[1]													
	≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	Until progression
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13 (Roll-over into Once every-2-weeks dosing)	
Assessment[2]		D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85	
Further anticancer therapy[21]	Collected through Safety Follow-up and Long-term Follow-up														

ADA: antidrug antibody; AE: adverse event; CR: complete response; CT: computed tomography; D: Day; DLT: dose-limiting toxicity; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group performance status; EOT: End-of-Treatment; hCG: human chorionic gonadotropin; HIV: Human immunodeficiency virus; ICF: Informed consent form; IMP: investigational medicinal product; MRI: magnetic resonance imaging; PD; progressive disease; CCI [redacted]; PK: pharmacokinetics; PR: partial response; RECIST: response evaluation criteria in solid tumors; SAE: serious adverse event; T4: thyroxine; TSH: thyroid-stimulating hormone; V: Visit; W: Week.

1. A time window of 1 day before or 1 day after the scheduled visit day (- 1/+ 1 days) is permitted for all study procedures while subjects receiving avelumab once weekly (12 consecutive weeks). A time window of up to 3 days before or 1 day after the scheduled visit day (- 3/+ 1 days) is permitted for all study procedures while subjects receiving avelumab once every 2 weeks (Week 13 and thereafter). The calculation of the dose of avelumab will be based on the weight of subject determined within 72 hours prior to the day of drug administration.
2. Columns of EOT Visit, Safety Follow-up, and the Long-term Follow-up Visits are omitted due to layout readability. The procedures at EOT Visit, Safety Follow-up, and the Long-term Follow-up are identical to the procedures planned for subjects receiving avelumab once every 2 weeks (as shown in Table 1-1).

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4. Medical history should include history of cancer, previous and ongoing medications, previous surgeries, radiotherapies, baseline medical conditions, smoking and alcohol history, and family cancer history.
5. A full physical examination will be conducted at Clinical Screening, at the EOT Visit and at the 30-day Safety Follow-up Visit. During the Treatment Phase, the physical examination will be symptom-directed.
6. If the Clinical Screening ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1/Cycle 1 Day 1.
7. Enrolment will be done after confirmation that the subject meets all screening inclusion criteria (Section 5.3.1) without matching any exclusion criterion (Section 5.3.2).

8. Core serum chemistry includes liver function panel (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, bilirubin), acute chemistry panel (sodium, potassium, chloride, blood urea nitrogen/total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). If full and core chemistry are scheduled at the same visit, the full chemistry will be performed.
9. Full chemistry panel and other laboratory studies are detailed in Section 7.4.3. Follicle-stimulating hormone at Clinical Screening, if applicable.
10. Full urinalysis (protein content required, and optional parameters albumin and immunoglobulin G to be tested depending on study site capability) at Clinical Screening/baseline, and EOT; basic urinalysis (protein content only) on Days 43 and 85, and then every 6 weeks thereafter prior to administration of avelumab. If urinalysis (full or basic) is positive for protein, sediment will be evaluated.
11. In serum at Clinical Screening; in urine thereafter. Results of the most recent pregnancy test should be available prior to next administration of avelumab.

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17. Premedication is mandatory approximately 30 to 60 minutes prior to the first 4 doses of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate. However, the prophylactic use of systemic corticosteroids is not permitted.
18. All AEs will be documented at each study visit until the 30-day Safety Follow-up Visit. After this visit, only treatment-related nonserious AEs have to be documented until the 90-day Safety Follow-up Phone Call.
19. All SAEs will be documented at each study visit until the 90-day Safety Follow-up Phone Call. After this, all ongoing SAEs must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as lost to follow-up. Any SAE assessed as related to study drug must be reported whenever it occurs, irrespective of the time elapsed since the last administration of avelumab. At 90 days (± 5 days) after the last dose of avelumab, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related nonserious AEs.
20. Blood samples for PK and ADA will be collected as detailed in Table 1-4.
21. Subjects will be followed every 12 weeks (± 7 days) for survival (including assessment of any further anticancer therapy).

Table 1-3 Schedule of Assessments – Pharmacokinetic and Antidrug Antibody Sampling for Subjects Receiving Avelumab Once Every 2 Weeks

Assessment	Treatment Phase														EOT Visit	Safety Follow-up
	V1					V2		V3		V4		V7		Until Progression	Within 7 days after decision to discontinue IMP	30 days (±5 days) after last IMP
	W1 D1		W1 D2	W1 D3	W2 D8	W3 D15		W5 D29		W7 D43		W13 D85				
	Prior to infusion	End of infusion				Prior to infusion	End of infusion	Prior to infusion	End of infusion	Prior to infusion	End of infusion	Prior to infusion	End of infusion			
PK sampling[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	6-weekly up to W25 (D169), then 12-weekly	X	X
ADA sampling[2]	X					X		X		X		X		6-weekly up to W25 (D169), then 12 weekly to EOT		X

ADA: antidrug antibody; D: Day; EOT: End-of-Treatment; IMP: investigational medicinal product; PK: pharmacokinetics; V: Visit; W: Week.

1. For subjects receiving avelumab once every 2 weeks, PK serum samples will be collected at the following time points:
   - Day 1: within 2 hours prior to and at the end of the 1-hour infusion, and at 0.5, 1, 2, 4, 6, and 12 hours after the end of the infusion.
   - Day 2: 2 samples will be collected 24 and 36 hours after the end of the infusion.
   - Day 3: a single sample will be collected 48 hours after the end of the infusion.
   - Day 8: a single sample will be collected 168 hours after the end of the infusion.
   - Days 15, 29, 43, 85, 127, and 169 (Week 25): samples will be collected within 2 hours prior to infusion (trough value) and immediately after the infusion is completed (peak value).
   - Every 12 weeks beyond Week 25: a single sample will be collected within 2 hours prior to infusion (trough value).
   - EOT Visit.
   - 30-day Safety Follow-up Visit.

*The time window for PK sampling time points are: + 10 minutes for the end of infusion sample collection on Day 1; ± 10 minutes for 0.5 and 1 hour after the end of infusion; ± 20 minutes for 2, 4, and 6 hours after the end of infusion; ± 2 hours for 12, 24, 36, 48, and 168 hours after the end of infusion. The time window for PK sampling time points is applicable for all scheduled PK sample collection for all subjects.

2. For subjects receiving avelumab once every 2 weeks, ADA serum samples will be collected at the following time points:
   - Day 1 (baseline): the baseline sample should be collected within 2 hours prior to the first administration of avelumab, ie, either during Clinical Screening or predose on Day 1.
   - Days 15, 29, 43, 85, 127 and 169: samples will be collected within 2 hours prior to infusion.
   - After Day 169, 1 sample (within 2 hours prior to infusion) every 12 weeks until the EOT Visit.
   - 30-day Safety Follow-up Visit.

Table 1-4 Schedule of Assessments - Pharmacokinetic and Antidrug Antibody Sampling for Subjects Receiving Avelumab Once a Week for the First 12 Weeks Followed by Once Every 2 Weeks (10 mg/kg Once Weekly Cohort)

Assessment	Treatment Phase														EOT Visit	Safety Follow-up
	V1		V2	V3	V5	V7		V13		V14	V16	V19		Until Progression	Within 7 days after decision to discontinue IMP	30 days (± 5 days) after last IMP
	W1 D1		W2 D8	W3 D15	W5 D29	W7 D43		W13 D85		W15 Day99	W19 Day127	W25 D169				
	Prior to infusion	End of infusion	Prior to infusion	Prior to infusion	Prior to infusion	Prior to infusion	End of infusion	Prior to infusion	End of infusion	Prior to infusion	Prior to infusion	Prior to infusion	End of infusion			
PK sampling[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	Every 12 weeks, same as Week 5	X	X
ADA sampling[2]	X			X	X	X		X			X	X		Every 12 weeks, same as Week 5		X

ADA: antidrug antibody; D: Day; EOT: End-of-Treatment; IMP: investigational medicinal product; PK: pharmacokinetics; V: Visit; W: Week.

1. For 6 subjects receiving avelumab once a week, PK serum samples will be collected within 2 hours prior to each infusion at Weeks 1, 2, 3, 5, and 7, at Weeks 13, 15, 19, and 25, and then at 12-week intervals while on treatment. A sample at the end of infusion (within 15 minutes) will be collected at Weeks 1, 7, 13, and 25. Samples will be collected at the EOT visit and the 30-day Safety Follow-up Visit.
2. For 6 subjects receiving avelumab once a week, blood samples for ADA (immunogenicity) analysis will be collected within 2 hours prior to each infusion at Weeks 1, 3, 5, 7 (every 2 weeks), at Weeks 13, 19, and 25 (every 6 weeks), and then every 12 weeks while on treatment, and at the 30-day Safety Follow-up Visit.

Table 1-5 Schedule of Assessments-Pharmacokinetic and Antidrug Antibody Sampling for Retreated Subjects

Assessment for retreated subjects[1]	Treatment Phase			EOT Visit
	V1	V1	V1 or V2	Within 7 days after decision to discontinue IMP
	W1	W1	W2	
	D1	D3	D8	
PK sampling[2]	X			X
ADA sampling[3]	X			X

ADA: antidrug antibody; CR: complete response; D: Day; ECG: electrocardiogram; EOT: End-of-Treatment; hCG: human chorionic gonadotropin; IMP: investigational medicinal product; PD: progressive disease; PK: pharmacokinetics; T4: thyroxine; TSH: thyroid-stimulating hormone; V: Visit; W: Week.

1. For subjects who achieve a CR on avelumab therapy and subsequently develop PD after stopping therapy prior to the end of the study, one re-initiation of treatment at the same dose and schedule is allowed at the discretion of the Investigator and with the agreement of the Sponsor Medical Monitor. To be eligible for retreatment, the subject must not have experienced any toxicity that led to discontinuation of the initial avelumab therapy. Prior to retreatment, malignant disease must 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 retreatment. The following procedures will be repeated prior to the re-initiation of treatment: full physical examination, 12-lead ECG, hematology and hemostaseology, full serum chemistry, full urinalysis, serum beta-hCG pregnancy test (if applicable), free T4 and TSH. For other assessments for retreated subjects, please see Table 1-1 or Table 1-2.
2. PK samples will be collected within 2 hours prior to the first retreatment infusion (predose) on Day 1 and at the EOT Visit.
3. ADA samples will be collected within 2 hours prior to the first retreatment infusion (predose) on Day 1 and at the EOT Visit.

2 Sponsor, Investigators and Study Administrative Structure

The Sponsor of this clinical study with avelumab (MSB0010718C) is Merck KGaA, Darmstadt, Germany.

This study requires a significant logistic and administrative structure for its efficient execution. Details of such structures and associated procedures will be defined in a separate Manual of Operations. This will be prepared under the supervision of the Clinical Trial Leader in close collaboration with the responsible units at the Sponsor.

The study will be conducted at approximately 3 enrolling study sites in mainland China.

The Coordinating Investigator represents all Investigators with respect to decisions and discussions regarding this study, consistent with the International Council for Harmonization (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 the study design and execution and is responsible for the review and signoff of the Clinical Study Report.

Signature pages for the Protocol Lead and the Coordinating Investigator, as well as a list of Sponsor responsible persons, are provided in Section 12, Appendix I.

The study will appear in the following clinical study registries: clinicaltrials.gov and chinadrugtrials.org.cn.

The Sponsor will coordinate the study and will enlist the support of Contract Research Organizations (CROs) for some of the study activities. The Sponsor's Global Clinical Operations will perform oversight of the activities performed by the CRO(s).

The Sponsor's Clinical Trial Supplies department will supply the investigational medicinal product (IMP), avelumab, which will be distributed to the study sites by the CRO(s).

The assignment of subject number and allocation of IMP will be managed by an interactive voice response system (IVRS).

Safety laboratory assessments (see Section 7.4.3; except antidrug antibody [ADA] in Table 7-1) will be performed locally by the study sites. Pharmacokinetic (PK), pharmacodynamic, ADA against avelumab, and biomarker assessments will be performed by central laboratories under the responsibility of the Sponsor.

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

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

The statistical analyses will be performed by a CRO and supervised by the Sponsor's Global Biostatistics department.

2.1 Safety Monitoring Committee

To ensure subjects' safety during the study, a Safety Monitoring Committee (SMC) will review the safety data on a regular basis. The SMC consists of permanent members from the Sponsor (eg, but not limited to, early development lead, medical lead, and Global Patient Safety representative), the Coordinating Investigator as well as of ad hoc members (eg, but not limited to, all participating Principal Investigators [as applicable]). During the study, the SMC will evaluate the safety data and will decide on dose-limiting toxicities (DLTs) relevant for the treatment and will advise on dose escalation or suspension of enrolment, with the final adjudication being a Sponsor prerogative. In 10 mg/kg once weekly cohort, the SMC will evaluate overall safety data when all 6 subjects have completed minimum 4-week treatment period, and after 12 weeks of observation has been completed for all subjects enrolled in this cohort. The SMC may modify the frequency of meetings as deemed appropriate by the SMC during the course of the study.

The membership and specific working procedures of the SMC will be described in an SMC Charter, which will be established prior to the start of subject recruitment.

3 Background Information

3.1 Programmed Death Receptor and Ligands

The programmed death 1 (PD-1) receptor and PD-1 ligands 1 and 2 (PD-L1, PD-L2) play major roles in immune regulation. Expressed on activated T cells, PD-1 is activated by PD-L1 and PD-L2 expressed by stromal cells, tumor cells, or both, initiating T cell death and localized immune suppression (Dong et al 1999; Dong et al 2002; Freeman et al 2000; Topalian et al 2012a), potentially providing an immune-tolerant environment for tumor development and growth. Conversely, inhibition of this interaction can enhance local T cell responses and mediate antitumor activity in nonclinical animal models (Dong et al 2002; Iwai et al 2002).

In the clinical setting, treatment with antibodies that block the PD-1–PD-L1 interaction have been reported to produce ORRs of 7% to 38% in patients with advanced or metastatic solid tumors, with tolerable safety profiles (Hamid et al 2013; Brahmer et al 2012; Topalian et al 2012b). Notably, responses appeared prolonged, with durations of 1 year or more for the majority of patients (Topalian et al 2012b).

The use of immune checkpoint blockade, a class of immune therapy, to inhibit the PD-1/PD-L1 axis has demonstrated clinical benefit in subjects with advanced non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma, and several other tumor types, but clinical data from these studies also indicate that the efficacy of PD-1/PD-L1 blockade may not be limited to these specific tumor types.

3.2 Avelumab

The IMP for the present study is avelumab (MSB0010718C). Avelumab is a fully human monoclonal antibody of the immunoglobulin G1 isotype. This anti-PD-L1 therapeutic antibody concept is being developed in oncological settings by Merck KGaA, Darmstadt, Germany, and its subsidiary, EMD Serono R&D, Billerica, MA, United States.

Avelumab selectively binds to PD-L1 and competitively blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This removes the suppressive effects of PD-L1 on antitumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response. Compared with anti-PD-1 antibodies that target T cells, avelumab targets tumor cells and may potentially offer the chance of fewer AEs, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the PD-L2/PD-1 pathway intact to promote peripheral self-tolerance (Latchman et al 2001). CCI [redacted]

In light of recent data demonstrating the clinical efficacy of an anti-PD-L1 antibody in advanced gastric cancer, and given the clinical importance of PD-L1 expression in gastric cancer tumor cells (Oki et al 2014) and the mode of action of avelumab, avelumab has potential as a therapy for patients with various advanced solid tumors.

Avelumab is currently being evaluated in multiple settings, including the following oncology indications: solid tumors, Merkel cell carcinoma (MCC), NSCLC, gastric and gastroesophageal junction cancer, metastatic breast cancer, colorectal cancer, castrate-resistant prostate cancer, melanoma, ovarian cancer, adrenocortical carcinoma, mesothelioma, urothelial carcinoma, bladder and renal cell carcinoma. The ongoing clinical study program for avelumab is described in more detail in the most current IB. Please refer to the IB for the most up-to-date information.

3.2.1 Safety

As of 05 November 2015, the safety profile of avelumab has been evaluated based on data from more than 1400 subjects in 4 ongoing studies in subjects with various solid tumors: Study EMR100070-001, Study EMR100070-002 (local Japanese study), Study EMR100070-003 in MCC, and Study EMR100070-004 in NSCLC.

Available safety and efficacy data for the avelumab program are discussed in the IB and establish a positive benefit-risk ratio for conducting Phase III studies with 10 mg/kg of avelumab. Highlights of the safety data relevant to the development of this Clinical Study Protocol are provided below.

Study EMR100070-001 is a global Phase I study mainly conducted in a Western population. As of 05 November 2015, 53 subjects had been treated in the dose escalation phase of the study and a total of 1300 subjects had been treated in the treatment expansion phase, comprising the 16 pooled tumor expansion cohorts. All 1353 subjects received at least 1 dose and were followed-up for at least 4 weeks from the first dose.

According to the study protocol, the DLT assessment was performed on 19 out of the 53 subjects who participated in the 3 + 3 dose escalation algorithm (1 mg/kg [n = 4], 3 mg/kg [n = 3], 10 mg/kg [n = 6], and 20 mg/kg [n = 6]). None of the subjects treated with doses up to 10 mg/kg experienced a DLT, and the 10 mg/kg dose of avelumab was thus considered a safe and well-tolerated dose for further investigation in the expansion cohorts. One DLT was observed in the 6 subjects who received 20 mg/kg of avelumab. The event, which occurred 18 days after the subject received the first 20 mg/kg dose of avelumab, was a Grade 3 immune-related disorder with creatine kinase increase, myositis, and myocarditis, considered related to avelumab by the Investigator. Avelumab was permanently discontinued and the subject was placed on steroid therapy. Within 2 weeks, the elevated creatine kinase level had returned to within the normal range, and 23 days after its onset, the event of autoimmune disorder was considered resolved with sequelae (right bundle branch block).

The majority of subjects in the dose expansion cohorts received the proposed treatment dose of 10 mg/kg of avelumab. The safety data from subjects with different tumor types treated with avelumab suggests an acceptable safety profile of the compound. Most of the observed events were either in line with those expected in subjects with advanced solid tumors or were similar to class effects of monoclonal antibodies blocking the PD-1/PD-L1 axis. Infusion-related reactions including hypersensitivity reactions, and immune-mediated adverse reactions (eg, hypothyroidism, pneumonitis, hyperthyroidism, arthritis, adrenal insufficiency, autoimmune hepatitis, colitis, thyroiditis or myositis) have been identified as important risks for avelumab.

Study EMR100070-002 is being conducted in Japan only. As of the cutoff date of 17 December 2015, 17 subjects had been treated in the dose escalation phase with up to 20 mg/kg of avelumab once every 2 weeks, and 35 subjects with gastric cancer had been treated in the treatment expansion phase at 10 mg/kg once every 2 weeks. At 20 mg/kg every 2 weeks, the maximum tolerated dose (MTD) for Japanese subjects has not been exceeded and, to date, no new safety concerns have been observed in the gastric expansion cohort.

Please refer to the most current IB for more details. Based on the available safety data, appropriate risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, and are included in the current study (see Sections 6.4, 6.5.4, and 6.5.5).

3.2.2 Pharmacokinetics

Pharmacokinetic assessments have been performed in the ongoing Studies EMR100070-001 and EMR100070-002. The results presented in Sections 3.2.2.1 and 3.2.2.2 are based on the data available as of 19 May 2015 (EMR100070-001) and 13 October 2014 (EMR100070-002), respectively.

3.2.2.1 Study EMR100070-001

Pharmacokinetics following the first 1-hour infusion and dose proportionality of avelumab have been characterized in 77 mainly Caucasian subjects treated in the dose escalation and expansion cohort of the Phase I Study EMR100070-001 by standard noncompartmental analysis based on

rich serum concentration-time data obtained over a complete dosing interval of 2 weeks (= tau). The exposure parameters maximum concentration (C_{max}) and area under the concentration-time curve (AUC) after first dose generally increased in an approximately dose-proportional manner in the range from 3 to 20 mg/kg. The concentration at the end of dose interval (C_{min}) increased proportionally with dose between 10 to 20 mg/kg, but more than proportionally for doses between 1 to 10 mg/kg. The total systemic clearance was low, 0.37 mL/h/kg ± 0.11 mL/h/kg at the 10 mg/kg dose (n = 40).

The terminal half-life ($t_{1/2}$) increased with dose. However, the average values were 102 hours and 120 hours for 10 mg/kg and 20 mg/kg doses, respectively, with no significant difference between these 2 dose groups. Trough concentrations were obtained for the majority of subjects enrolled in the study. The mean ± standard deviation trough concentration at the end of the first cycle for all cohorts receiving 80%-120% of the planned 10 mg/kg dose was 21 ± 12 µg/mL (n = 283). This median trough concentration increased during subsequent cycles to 25 ± 16 µg/mL (2nd cycle) (n = 269), 27 ± 17 µg/mL (3rd) (n = 202), 27 ± 17 µg/mL (4th) (n = 171), 28 ± 19 µg/mL (5th) (n = 145), 29 ± 18 µg/mL (6th) (n = 122), 34 ± 18 µg/mL (9th) (n = 81), and 36 ± 18 µg/mL (12^{th} cycle) (n = 55).

3.2.2.2 Study EMR100070-002

A preliminary analysis of the PK data from this Japanese Phase I study was performed based on the serum concentration of avelumab obtained from 5 subjects treated with 3 mg/kg, 6 subjects treated with 10 mg/kg, and 6 subjects treated with 20 mg/kg following a 1-hour intravenous (IV) infusion once every 2 weeks.

Although a formal analysis has not been conducted, it is apparent that the preliminary concentrations obtained over time and the clearance during the first dosing interval were similar in Japanese and Caucasian subjects (Table 3-1).

Table 3-1 Main Pharmacokinetic Parameters after First Dose of Avelumab

Pharmacokinetic Parameter mean (StD)	Study EMR100070-001 (Caucasian Subjects)			Study EMR100070-002 (Japanese Subjects)		
	3 mg/kg (n=13)	10 mg/kg (n=40)	20 mg/kg (n=21)	3 mg/kg (n=5)	10 mg/kg (n=6)	20 mg/kg (n=6)
C_{max} (µg/mL)	82 (22)	301 (102)	489 (140)	65 (14)	182 (35)	462 (61)
C_{min} (µg/mL)	3.5 (2.6)	22 (12)	50 (35)	3.4 (2.1)	24 (15)	44 (15)
AUC_{0-t} (µg/mL*h)	6207 (1865)	25785 (7262)	46054 (16153)	5586 (1422)	21447 (8525)	48263 (11237)
$t_{½}$ (h)	85 (21)	102 (28)	120 (42)	92 (26)	127 (34)	115 (14)

AUC_{0-t}: area under the concentration-time curve from 0 to last quantifiable concentration; C_{max}: maximum concentration; C_{min}: minimum (trough) concentration; StD: standard deviation; $t_{1/2}$: terminal half-life.

3.2.3 Clinical Pharmacodynamics

In vitro target occupancy was measured using flow cytometry on peripheral blood CD3+ T cells from 8 healthy volunteers after spiking avelumab over a concentration range of 0.003 to 10 µg/mL. In this assay, free receptors were measured in samples spiked over this range and compared with the amount of free receptors in an unspiked sample. A 50% target occupancy was observed at a mean drug concentration (± standard deviation) of 0.122 µg/mL ± 0.042 µg/mL, and a plateau indicating at least 95% receptor occupancy was reached in all donor blood samples at 1 µg/mL.

These in vitro data combined with PK data were confirmed in ex vivo samples taken at C_{min} after the first dose (Day 15) in a small number of subjects during the initial dose-escalation part of the EMR100070-001 Phase I study (n = 9). For doses of 10 mg/kg, target occupancy was greater than 90% for these 4 subjects, at C_{min} levels ranging between 12.69 and 26.87 µg/mL. Also, at the 3 mg/kg dose, available target occupancy data for 2 subjects with trough levels ranging from 4.56 to 6.99 µg/mL, showed greater than 90% target occupancy at trough exposure levels. At the dose level of 1 mg/kg, 2 out of 3 subjects displayed less than 90% target occupancy at trough serum concentrations and avelumab serum concentrations were below the quantification limit of 0.2 µg/mL in these 2 subjects.

Based on the observed avelumab serum concentrations in the EMR100070-001 Phase I clinical study and the in vitro receptor occupancy data, trough concentrations were sufficient to achieve full target occupancy throughout the entire dosing interval in all of the subjects receiving the 10 mg/kg dose. After the 3 mg/kg dose, C_{min} was insufficient in 3 of the 13 subjects to assure full target occupancy; therefore, in order to achieve target saturation during the whole Treatment Phase in all subjects, the dose of 10 mg/kg once every 2 weeks was selected as the dose for further investigation in the Phase Ib expansion cohorts and for subsequent clinical studies.

3.3 Rationale for the Study

This study is conducted to investigate primarily the tolerability, safety, and PK of avelumab as a single agent in Chinese subjects and will be included in the submission for marketing authorization in China. In addition, the study will also explore the efficacy of avelumab in Chinese patients with locally advanced unresectable or metastatic solid tumor and the correlation between specific biomarker and efficacy of avelumab.

3.3.1 Rationale for 10 mg/kg Once Weekly Dose-Escalation Cohort

Avelumab dosing regimen of 10 mg/kg once weekly for the first 12 weeks followed by once every 2 weeks starting at Week 13 would be evaluated with the following considerations:

- An exposure-efficacy response relationship was observed in second-line NSCLC subjects treated with 10 mg/kg once every 2 weeks. In 184 avelumab-treated subjects, unselected for PD-L1 expression, ORRs were 8.7%, 10.9%, 19.6%, and 17.4% for increasing quartiles of trough concentrations after first dose ($C_{troughfirst\text{-}dose}$ Q1-4). Using ≥ 1%, ≥ 5%, ≥ 50%, and ≥ 80% PD-L1 staining cutoffs, subjects in the upper half of exposure ($C_{troughfirst\text{-}dose}$ Q3-4 [n = 92]), had ORRs of 25% (n = 59), 26% (n = 39), 33% (n = 21), and 43% (n = 14),

respectively (data on file). The trends of longer progression-free survival (PFS) and OS for subjects in the higher exposure quartiles based on steady state trough concentration was also seen in the cohorts of urothelial cancer, gastric cancer, and others.

- Population PK analysis and simulation showed that a 10 mg/kg once every week regimen will increase the exposure, the median steady state trough concentration is predicted to increase from 22.9 µg/mL (range: 4.2-74.5 µg/mL) in the once every 2 weeks regimen to 83.3 µg/mL (range: 28.6-204 µg/mL) in the once weekly regimen (data on file), potentially enhancing efficacy as suggested by the exposure-efficacy analyses described above.
- In the above second-line NSCLC cohort, higher avelumab exposure was associated with a modest increase in immune-related AEs (irAEs). For all other AEs analyzed, AE incidence appeared to not increase with increasing exposure. And based on population PK modeling, median exposures are not expected to exceed those for previously administered regimens; the steady state maximum concentration is similar to that for 10 mg/kg once every 2 weeks regimen, while steady state AUC is similar to that for 20 mg/kg once every 2 weeks regimen (data on file).

In summary, the dosing regimen of 10 mg/kg once a week for 12 weeks followed by 10 mg/kg once every 2 weeks starting at Week 13 is supported by the exposure-efficacy relationship, time-to-response analyses, and an acceptable benefit-risk profile, as described above.

3.4 Summary of Overall Benefit and Risk

CCI [redacted] For further details regarding the dose selection rationale, please refer to the IB. An SMC is planned for the ongoing assessment of the risk-benefit ratio (see Section 2.1). The study will be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship for avelumab and would render continuation of the study unjustifiable.

The primary known identified risks of exposure to avelumab include:

- Infusion-related reactions.
- Immune-related adverse events (irAEs).

As of 05 November 2015, 3 (0.2%) of the 1300 subjects treated with avelumab in the pooled expansion cohort in Study EMR1000070-001 had experienced a Grade 4 infusion reaction; therefore, already implemented risk mitigation measures for infusion-related reactions/hypersensitivity have been extended by a mandatory premedication with histamine-1 receptor blockers and acetaminophen for all subjects prior to the first 4 infusions of avelumab. Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to the first 4 doses of avelumab is mandatory (eg, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] IV or oral equivalent). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and

guidelines, as appropriate. However, the prophylactic use of systemic corticosteroids is not permitted.

As noted in Section 3.1, studies with antibodies that block the PD-1–PD-L1 interaction have been reported to produce ORRs of 7% to 38% in subjects with advanced or metastatic solid tumors (Hamid et al 2013; Brahmer et al 2012; Topalian et al 2012b), with response durations of 1 year or more for the majority of subjects (Topalian et al 2012b).

This clinical study will be conducted in compliance with the Clinical Study Protocol, ICH GCP, and the applicable national regulatory requirements.

4 Study Objectives

4.1 Primary Objectives

- To evaluate the MTD of avelumab monotherapy in Chinese subjects.
- To characterize the PK of avelumab in Chinese subjects.

4.2 Secondary Objectives

- To determine the safety and tolerability of avelumab by assessing treatment-emergent adverse events (TEAEs) and treatment-related AEs for all dose groups according to the NCI-Common Terminology Criteria for Adverse Events (CTCAE) v4.03 in Chinese subjects.
- To characterize immunogenicity of avelumab in Chinese subjects.

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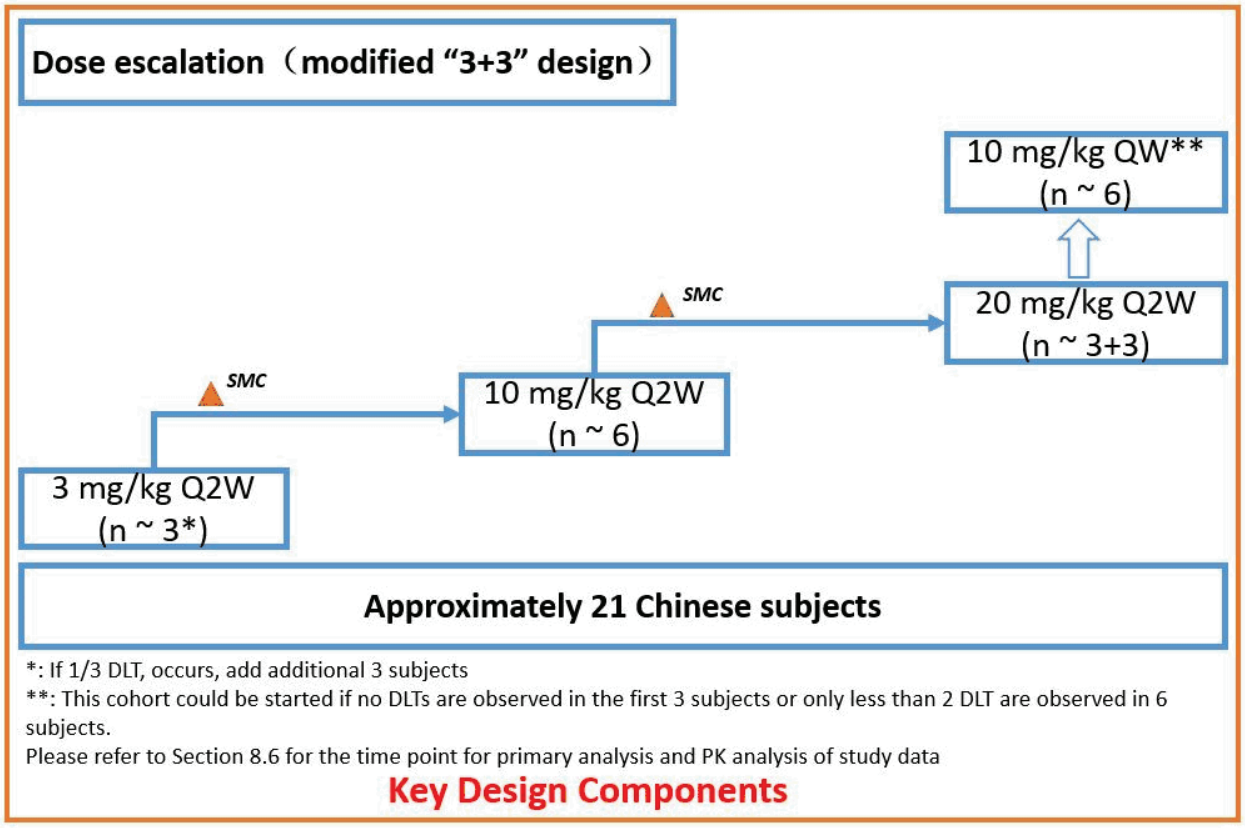
5 Investigational Plan

5.1 Overall Study Design and Plan

5.1.1 Overall Study Design

This is a Phase I/Ib, open-label, dose-escalation study for MTD evaluation. Additional safety and efficacy data may be obtained from the participating patients (Figure 5-1). Results from the current study may facilitate the design of expansion study on tumor types of interest to be conducted in the future.

Figure 5-1 **Schematic of the Study Design for Dose Escalation**



DLT: dose-limiting toxicity; PK: pharmacokinetics; Q2W: every 2 weeks; QW: every week; SMC: Safety Monitoring Committee.

5.1.1.1 Dose Escalation Design

The dose escalation of this study is based on a modified "3 + 3" cohort design. An initial cohort of 3 Chinese subjects with metastatic or locally advanced solid tumors will receive 3 mg/kg of

avelumab (IMP) once every 2 weeks. Each of these first 3 subjects will be observed for 21 days (DLT observation period). The SMC will review the safety data, including DLTs, and advise on further escalation to the next cohort (10 mg/kg of avelumab once every 2 weeks). As this study represents the introduction of avelumab into a new region, the 3 mg/kg dose has been selected as the starting dose, a minus 1 dose level to avelumab 10 mg/kg, as an extra precaution to further mitigate risks in Chinese subjects (Figure 5-3).

The 10 mg/kg once every 2 weeks cohort will enroll 6 Chinese subjects with metastatic or locally advanced solid tumors. Since more than 1400 subjects have been exposed to avelumab at a dose of 10 mg/kg once every 2 weeks and it has been well tolerated, it is unlikely that there are ethnic differences with respect to avelumab safety and PK; therefore staggered enrolment (3 + 3) will not be used for the 10 mg/kg once every 2 weeks cohort and all 6 slots will be opened at the same time for competitive recruitment.

After completion of 10 mg/kg once every 2 weeks cohort, the avelumab dose will be further escalated up to 20 mg/kg once every 2 weeks to characterize the safety and PK of avelumab at a higher dose level. A staggered "3 + 3" enrolment will be used for the 20 mg/kg avelumab cohort.

Once the safety of avelumab at 20 mg/kg once every 2 weeks have been established and can be regarded as safe (ie, no DLT observed in the first 3 subjects or less than 2 out of the 6 subjects experience a DLT), a new cohort of 10 mg/kg administered once weekly can be immediately initiated to assess safety of already established dose strength with a more frequent dose administration. Six (6) evaluable subjects are planned to be included in this cohort. The DLT assessment is not applicable for the 6 subjects in the 10 mg/kg once weekly cohort. Subjects in this cohort will receive avelumab at 10 mg/kg once weekly for the first 12 weeks. Starting from Week 13, dose frequency will be changed to once every 2 weeks. All 6 slots will be opened at the same time for competitive recruitment.

In 10 mg/kg once weekly cohort, the SMC will evaluate overall safety data when all 6 evaluable subjects have completed a minimum 4-week treatment period, and after 12 weeks of observation has been completed for all subjects enrolled in this cohort (see Section 2.1).

See Section 5.1.2.1.2 and Figure 5-3 for further details of the dose escalation algorithm, and Section 5.2.2 for a discussion of the rationale for dose selection.

Subjects will not be replaced unless the subject does not fulfill the requirement for dose determination. Dose determination is achieved when the subject receives 2 doses of avelumab at the scheduled regimen and completes the minimal 21-day safety observation period (DLT observation period) unless they discontinue due to a DLT. For the definition of a DLT, see Section 7.4.1.1.

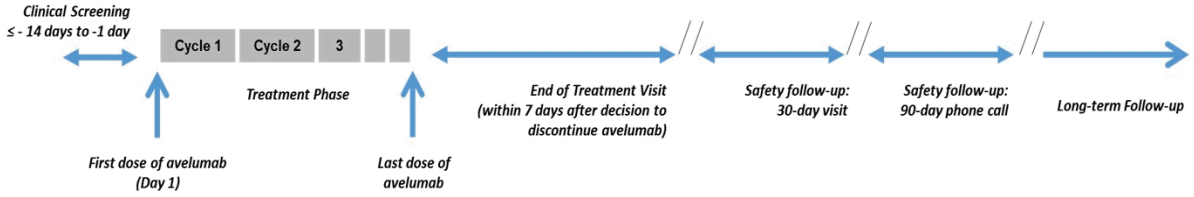
The design of the dose escalation is based on Studies EMR100070-001 and EMR100070-002 and therefore allows for the ethnic sensitivity of avelumab to be evaluated across studies.

The overall study design is shown in Figure 5-1.

5.1.1.2 Study Phases for Each Subject

Each subject enrolled in this study will undergo the following study phases/visits: Clinical Screening, Treatment Phase, End-of-Treatment (EOT) Visit, Safety Follow-up (30-day Safety Follow-up Visit and 90-day Phone Call), and Long-term Follow-up. Further details are provided in Figure 5-2 and Section 7.1.

Figure 5-2 Study Phases per Subject



5.1.2 Investigational Medicinal Product Administration and Schedule

The Schedule of Assessment for the study, including the treatment schedule, is provided in Table 1-1 (for all subjects receiving avelumab once every 2 weeks); Table 1-2 (for 6 subjects receiving avelumab once a week for the first 12 weeks followed by once every 2 weeks).

5.1.2.1 Avelumab

Subjects will receive an IV infusion of avelumab (over 1 hour [- 10 minutes/+ 20 minutes, ie, 50 to 80 minutes]) once every 2 weeks or every week (10 mg/kg once weekly cohort) for the first 12 weeks, then starting with Week 13, once every 2 weeks thereafter. The dose of avelumab will be calculated based on the weight of the subject determined within 72 hours prior to the day of drug administration. The dose of avelumab used for the previous administration can be repeated if the change in subject's weight is < 10% than the weight used for the last dose calculation. If the weight change is ≥10%, the intended dose should be recalculated.

In order to mitigate infusion-related reactions, a premedication regimen of 25 to 50 mg diphenhydramine and 500 to 650 mg acetaminophen (IV or oral equivalent) is mandatory approximately 30 to 60 minutes prior to the first 4 doses of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines, as appropriate. However, the prophylactic use of systemic corticosteroids is not permitted. (See Section 6.4).

Formulation and packaging information for avelumab are provided in Sections 6.1 and 6.6, respectively.

5.1.2.1.1 Avelumab Starting Dose

The starting dose of avelumab in Chinese subjects, ie, subjects in the first dose escalation cohort, will be 3 mg/kg.

5.1.2.1.2 Dose Escalation Scheme

Subjects will receive avelumab by IV infusion over 1 hour once every 2 weeks. Dose escalation of avelumab will be performed according to the following dose levels, representing a 3.3 or 2 times increase at each escalation. Each subject will receive a fixed dose of avelumab according to their allocated dose level:

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

The dose escalation criteria are as follows:

For each dose level, DLTs (as defined in Section 7.4.1.1) will be assessed during the 21 days after administration of avelumab. The criteria for moving from 3 mg/kg to 10 mg/kg of avelumab is if no subject experiences a DLT in the first 3 subjects. No additional 3 subjects will be enrolled. If 1 out of the first 3 subjects in the 3 mg/kg cohort experiences a DLT, this cohort will be expanded to 6 subjects. If ≥ 2 out of 3 or 6 subjects in the 3 mg/kg cohort experience a DLT, the study will be placed on hold. See also Section 2.1.

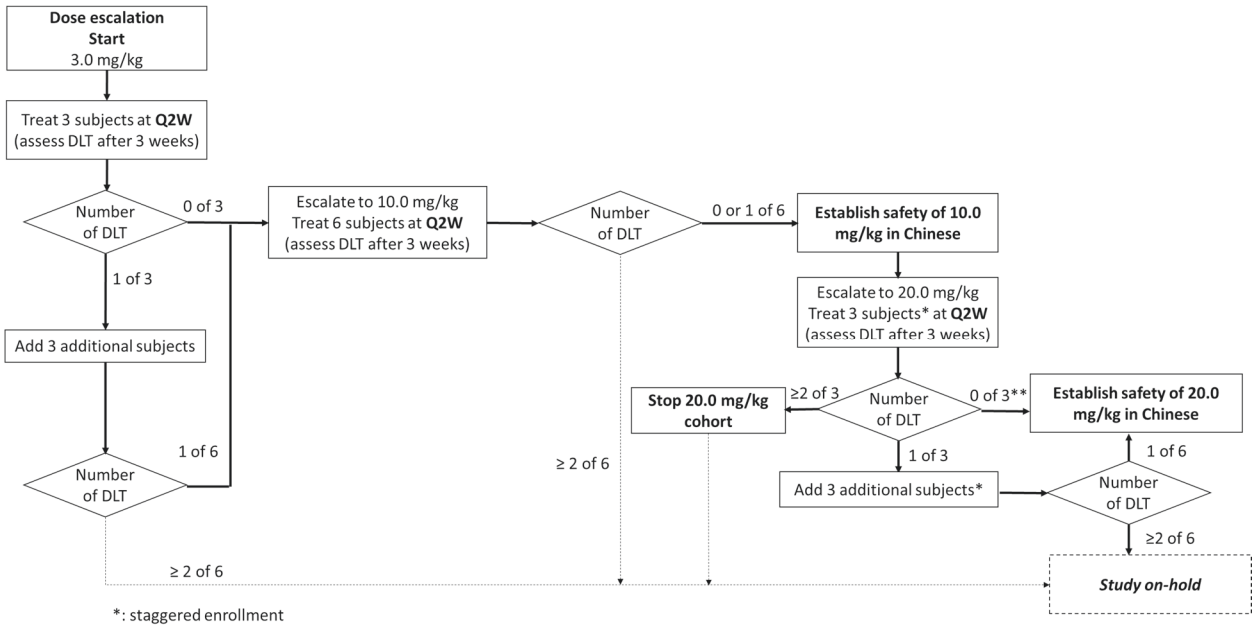
In the 10 mg/kg once every 2 weeks cohort, 6 slots will be opened at the same time for competitive enrolment of 6 subjects. If less than 2 out of the 6 subjects in this cohort experience a DLT, the dose of 10 mg/kg will be considered safe in Chinese subjects. If 2 or more subjects experience a DLT, the study will be placed on hold.

After completion of the 10 mg/kg once every 2 weeks cohort, the dose of avelumab will be escalated to 20 mg/kg once every 2 weeks in order to characterize the safety and PK of avelumab at a higher dose level. The criteria for moving from 10 mg/kg to 20 mg/kg of avelumab is if less than 2 out of 6 subjects experience a DLT at the 10 mg/kg dose level (once every 2 weeks cohort). Staggered "3 + 3" enrolment will be used for the 20 mg/kg cohort. If no subject experiences a DLT in the first 3 subjects, the avelumab dose level at 20 mg/kg once every 2 weeks will be regarded as safe in Chinese subjects; the additional 3 subjects will be enrolled to fill up the cohort for PK evaluation, but they will not be subjected to further DLT evaluation.

If 1 subject in the first 3 subjects experiences a DLT (confirmed by SMC only), an additional 3 subjects will be enrolled. If less than 2 out of the 6 subjects experience a DLT, the dose of 20 mg/kg will be considered safe in Chinese subjects. If ≥ 2 out of 3 or 6 subjects experience a DLT, the 20 mg/kg cohort will be put on hold (the decision will be made by SMC).

A schematic of the dose escalation algorithm is presented in Figure 5-3.

Figure 5-3 Dose Escalation Algorithm for Doses up to 20 mg/kg of Avelumab



DLT: dose-limiting toxicity; Q2W: every 2 weeks; QW: every week.

At the conclusion of the 21-day DLT observation period for each cohort (excluding 10 mg/kg once weekly cohort), a data review will be conducted. The SMC (including Principal Investigators), is responsible for making dose escalation decisions. The SMC will decide whether or not to escalate the dose of avelumab to the next level, or whether an interim dose level will be added by reviewing the safety data after all subjects of a cohort have completed the DLT observation period (see Section 2.1 and SMC Charter).

5.1.3 Dose Modification and Adverse Drug Reactions Requiring Treatment Discontinuation

Dose Modification for Avelumab

Each subject will stay on the avelumab dose level assigned in the study unless the treatment needs to be stopped. Dosing modifications (changes in infusion rate) and dose delays are described in Sections 6.5.4 and 6.5.5. There will be no dose reductions.

Treatment with avelumab can be skipped for a delay of up to 4 weeks from the previous dose for any non-related AEs, laboratory abnormalities, or intercurrent illness, which in the judgment of the Investigator warrants delaying the dose of study medication. If dosing is delayed more than 4 weeks, treatment may be resumed only after consultation with the study Medical Monitor. Any delay in dosing in excess of 12 weeks is not permitted.

5.1.3.1 Adverse Drug Reactions Requiring Treatment Discontinuation or Modifications

The following adverse drug reactions (ADRs) require permanent discontinuation or treatment modification of avelumab treatment:

- Any Grade 4 ADRs: permanently discontinue avelumab except for laboratory values out of normal range that do not have any clinical correlation.
- Any Grade 3 ADRs:
  - Withhold avelumab except for laboratory values out of normal range that do not have any clinical correlate.
  - Permanently discontinue avelumab if toxicity does not resolve to Grade ≤ 1 or baseline within 12 weeks of last administration or if the same Grade 3 toxicity recurs (consider consult with the medical monitor before permanently discontinuing the treatment).
- Infusion should not be given if ECOG performance status is ≥ 3 on the day of study treatment administration. Treatment should be discontinued if ECOG performance status has not improved to ≤ 2 by the next scheduled treatment administration.
- Any Grade 2 ADRs should be managed as follows:
  - Infusion should not be given in case of ongoing Grade 2 ADR on the day of study treatment administration.
  - Treatment can be resumed according to original schedule* once ADR resolved to Grade ≤1. Up to 2 subsequent study drug doses may be omitted. If more than 2 doses are skipped, treatment may be resumed after consultation with the Medical Monitor.

*Original schedule is defined as "the dosing schedule calculated according to first dose".

If dosing is delayed more than 4 weeks, treatment may be resumed after consultation with the study Medical Monitor. Any delay in dosing in excess of 12 weeks is not permitted.

Infusion-related reactions and irAEs should be handled according to the guidelines provided in Sections 6.5.5.1 and 6.5.5.2, respectively.

5.2 Discussion of Study Design

Although the MTD of avelumab as a single agent has been evaluated in 2 other Phase I studies (the global EMR100070-001 study and the Japanese EMR100070-002 study), the Health Authority in China requires that a dedicated study be performed to assess the safety, tolerability, and PK of avelumab in Chinese subjects. Thus, this Phase I/Ib, open-label, dose-escalation study is designed to assess the PK, safety, tolerability, and also exploring efficacy of avelumab in Chinese adults with locally advanced unresectable or metastatic solid tumors who have failed standard of care or for whom no standard of care exists.

5.2.1 Study Population

The target population comprises subjects with metastatic or locally advanced unresectable solid tumors who fail standard therapy or subjects for whom no standard therapy exists. Candidate tumor types in the study may include tumors with known reports of PD-L1 overexpression, such as MCC, NSCLC, gastric/gastroesophageal junction cancer, esophageal cancer, urothelial cancer, melanoma, castration-resistance prostate cancer, ovarian cancer, head and neck squamous cell carcinoma, renal cell carcinoma, adenoid cystic carcinoma, mesothelioma, liver cancer (hepatocellular carcinoma and biliary), nasopharyngeal cancer, or other tumor types that are considered appropriate by Investigators.

5.2.2 Avelumab Dose Selection

Two Phase I studies (the global EMR100070-001 study and the Japanese EMR100070-002 study) have already evaluated the MTD of avelumab and established the recommended Phase II dose (RP2D) of avelumab as a single agent as 10 mg/kg every 2 weeks. The 3 dose levels selected for this study (3, 10, and 20 mg/kg of avelumab) are the same as those studied in the EMR1000070-001, and -002 studies. At the dose level of 10 mg/kg, avelumab will be evaluated in 2 dose regimens: 10 mg/kg once every 2 weeks, and 10 mg/kg every week for 12 weeks, followed by transition to once every 2 weeks at Week 13 for the remainder of the treatment period. The rationale for the regimen of 10 mg/kg once weekly is described in Section 3.3.1. This will allow the safety, tolerability and PK of all 3 dose levels (2 regimens at the level of 10 mg/kg) of avelumab to be compared across studies, including with respect to ethnic sensitivity.

Furthermore, within the dose range of 1 mg/kg to 20 mg/kg, avelumab was shown to be well tolerated and is deemed to have an acceptable safety profile. In this first study in Chinese subjects with solid tumor there is added value in evaluating 20 mg/kg of avelumab with respect to safety and tolerability, and hence to provide a margin for the likely RP2D at 10 mg/kg in future development. In addition, with 3 dose levels ranging from 3 mg/kg to 20 mg/kg, a more informative assessment of the dose-exposure-response relationship may be obtained.

5.2.3 Rationale for the Primary Endpoints

The occurrence of DLTs is considered to be an appropriate endpoint to assess safety and tolerability in this dose escalation Phase I study.

Pharmacokinetic data from approximately 30 Chinese subjects is deemed necessary to meet regulatory requirements and will be used for ethnic sensitivity assessment. The PK of avelumab, a monoclonal antibody binding to a tumor surface target, may present important features, eg, target mediated disposition and nonlinearity. A number of factors, including the dose levels and tumor target expression, may also play a role in the PK and CCI behavior. Pharmacokinetic data will be collected to explore these PK and CCI characteristics.

5.2.4 Rationale for the Secondary Endpoints

Secondary safety and immunogenicity endpoints will be assessed and used to support evaluation of the primary endpoints.

CCI

[redacted]

5.2.6 Inclusion of Special Populations

Not applicable.

5.3 Selection of Study Population

Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled in this study. Prior to performing any study assessments that are 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.

5.3.1 Inclusion Criteria

1. Signed written informed consent.
2. Chinese men or women ≥ 18 years of age.
3. Availability of a recently obtained FFPE block containing tumor tissue (biopsy from a non-irradiated area within 6 months) or 12 or more unstained tumor slides suitable for biomarker detection (see Section 7.6).
4. Histologically or cytologically proven locally advanced unresectable or metastatic solid tumor, for which no standard therapy exists or standard therapy has failed.
5. ECOG performance status of 0 or 1 at study entry.
6. Estimated life expectancy of at least 3 months.
7. Adequate hematological function as defined below:

- White blood cell count ≥ 3×10^9/L
- Absolute neutrophil count ≥ 1.5×10^9/L
- Lymphocyte count ≥ 0.5×10^9/L
- Platelet count ≥ 100×10^9/L
- Hemoglobin ≥ 90 g/L (may have been transfused).

8. Adequate liver function as defined below:
   - Total bilirubin ≤ 1.5 × upper limit of normal (ULN)
   - Aspartate aminotransferase (AST) ≤ 2.5 × ULN
   - Alanine aminotransferase (ALT) ≤ 2.5 × ULN.
9. Adequate renal function as defined below:
   - Estimated creatinine clearance ≥ 50 mL/min according to Cockcroft-Gault formula.
10. Negative blood pregnancy test at Clinical Screening for women of childbearing potential. For the purposes of this study, women of childbearing potential are defined as: All female subjects after puberty unless they have age-related natural (spontaneous) amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone (FSH) > 40 mIU/mL, are surgically sterile, or are sexually inactive.
11. Highly effective contraception (ie, methods with a failure rate of less than 1% per year) for both men and women if the risk of conception exists. See Section 12, Appendix III for further guidance on methods of contraception that are considered highly effective.

Note: The effects of avelumab on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use effective contraception, as defined in Section 12, Appendix III, or as stipulated in national or local guidelines. Highly effective contraception must be used from Clinical Screening, for the duration of the study treatment, and until at least 60 days after stopping avelumab. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, the treating physician should be informed immediately.

5.3.2 Exclusion Criteria

1. Prior therapy with any antibody/drug targeting T cell coregulatory proteins (immune checkpoints) such as PD-1, PD-L1, cytotoxic T-lymphocyte antigen-4 (CTLA-4), 4-1BB, LAG-3, TIM-3 or anti-CD127. Prior therapy with a cancer vaccine is acceptable.
2. Concurrent anticancer treatment(s) (eg, cytoreductive therapy, radiotherapy [with the exception of *palliative bone-directed radiotherapy and radiotherapy administered to superficial lesions], immune therapy, or cytokine therapy except for erythropoietin). Radiation to more than 30% of the bone marrow or with a wide field of radiation should not be used within 28 days prior to the first administration of avelumab and is prohibited throughout the study.

*Palliative bone-directed radiotherapy should be within a limited field of radiation and for palliation only. It should be a short course, according to local institutional recommendation, and should be completed at least 7 days prior to the first administration of avelumab.

3. Major surgery for any reason, except diagnostic biopsy, within 28 days of the first administration of avelumab and/or if the subject has not fully recovered from the surgery within 28 days of the first administration of avelumab.
4. Concurrent use of nonpermitted drug(s) (see Section 6.5.2).
5. Rapidly progressive disease (eg, tumor lysis syndrome).
6. All subjects with active brain metastases, except those meeting the following criteria:
    - Brain metastases that have been treated locally, and have not been progressing for at least 2 weeks after the completion of therapy, and no steroid maintenance therapy is required, AND
    - No ongoing neurological symptoms that are related to brain localization of the disease (sequelae that are a consequence of the treatment of brain metastases are acceptable).

Note: Subjects with mild residual neurologic deficit that is permanent as a result of prior brain metastases after local treatment are eligible provided the residual lesion is stable for at least 4 weeks and without evidence of enlarging, and the subject is not on steroid therapy.

7. Previous malignant disease other than the target malignancies to be investigated in this study, with the exception of in situ carcinoma of the cervix, or adequately treated non-melanomatous cancers of the skin, or other malignancy treated at least 5 years previously with surgery and/or radiotherapy, and there is no evidence of recurrence since that time.
8. Subjects who have received any investigational product within a period of time that is less than the cycle length used for that treatment or equal to 28 days (whichever is shorter) prior to the first administration of avelumab.
9. Prior solid organ or bone marrow transplant.
10. Significant acute or chronic infections including, for example:
    - Uncontrolled acute infection.
    - Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome. Subjects who do not know their HIV status are required to undergo HIV testing, subject to the provision of informed consent. Subjects who do not know their HIV status who are unwilling to undergo HIV testing are not eligible for the study (see Section 7.1.1).
    - Positive test for hepatitis B virus surface antigen and/or confirmatory hepatitis C virus ribonucleic acid (if antihepatitis C virus antibody tested positive); tests to be performed at Clinical Screening.
11. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:

- Subjects with Type I diabetes, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
- Subjects receiving immunosuppressive agents (such as steroids) for any reason should be tapered off these drugs before initiation of avelumab (with the exception of subjects with adrenal insufficiency, who may continue corticosteroids at physiologic replacement doses, equivalent to ≤ 10 mg prednisone daily). Subjects who are not allowed to taper off immunosuppressive agents should be excluded. Administration of steroids for other conditions through a route known to result in a minimal systemic exposure (topical, intranasal, intra-ocular, or inhalation) are acceptable.

12. Previous or ongoing administration of systemic steroids for the management of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the daily dose after 14 days will be ≤ 10 mg/day of prednisone or equivalent.
13. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥3 NCI-CTCAE v4.03), any history of anaphylaxis*, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma).

*Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. It is characterized by rapidly developing, life-threatening problems (CTCAE Grading 3-5).

14. Persisting toxicity related to prior therapy (including any prior investigational therapy) of Grade ≥ 2 NCI-CTCAE v4.03 (except < Grade 3 neuropathy and alopecia of any grade).
15. Pregnancy or lactation.
16. Known alcohol or drug abuse.
17. History of uncontrolled intercurrent illness including but not limited to:
    - Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower), or
    - Uncontrolled active infection, or
    - Uncontrolled diabetes (eg, hemoglobin A1c ≥ 8%).
18. Clinically significant (that is, active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrolment), myocardial infarction (< 6 months prior to enrolment), unstable angina pectoris, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious cardiac arrhythmia requiring medication (including corrected QT interval prolongation of > 470 msec calculated according to Fridericia and/or pacemaker or prior diagnosis of congenital long QT syndrome).
19. All other significant diseases (eg, inflammatory bowel disease, colitis, pneumonitis, and fibrosis), which, in the opinion of the Investigator, might impair the subject's tolerance of avelumab.
20. Any psychiatric condition that would prohibit the understanding or rendering of informed consent or that would limit compliance with study requirements.

21. Vaccination within 28 days of the first administration of avelumab and throughout the study is prohibited, except for administration of inactivated vaccines (eg, inactivated influenza vaccines).
22. Legal incapacity or limited legal capacity.

5.4 Criteria for Initiation of Study Treatment

The inclusion and exclusion criteria will be checked during Clinical Screening. Eligible subjects will be enrolled prior to the initiation of avelumab and after verification that the subject fulfils all inclusion criteria without meeting any of the exclusion criteria.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from the Study

Subjects are free to discontinue the study at any time without giving their reason(s). Withdrawal of consent will be considered withdrawal from the study. In case of withdrawal from the study, the assessments scheduled for the last visit (EOT Visit) should be performed, if possible, with focus on the most relevant assessments (see Section 7.1.3). In any case, the appropriate EOT electronic case report form (eCRF) page must be completed. In case of withdrawal from the treatment, subjects will be asked to continue safety and Long-term Follow-up, which includes the collection of data on survival and subsequent anticancer therapy.

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

- Withdrawal of the subject's consent. If the subject withdraws consent, it must be clearly stated if the subject is also withdrawing their consent from the posttreatment follow-up assessments.
- Participation in any other study during the Treatment Phase of this study; however, subjects will continue to be followed for survival.
- Lost to follow-up.

If a subject will have no further study data collected because he/she withdraws from the study completely or fails to return for visits, the Investigator must determine the primary reason for the subject's withdrawal as completely and accurately as possible and record this information in the eCRF page. For a subject who is "lost to follow-up", the Investigator should show "due diligence" by documenting in the source documents the steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc. Public records may be assessed to determine vital status information (alive/dead) for a subject who is lost to follow-up, as permitted by local laws.

5.5.2 Withdrawal from the Investigational Medicinal Product

The subject must be withdrawn from avelumab administration in the event of any of the following:

- Progressive disease (PD) per RECIST 1.1 assessed by Investigator (**Note**: Subjects receiving avelumab may continue past the initial determination of PD if the subject's ECOG performance

status has remained stable, and if, in the opinion of the Investigator, the subject will benefit from continued treatment [see Section 6.2]).

- Significant clinical deterioration (clinical progression) is defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms.
- 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 drug (if applicable).
- Unacceptable toxicity:
  - Occurrence of any Grade ≥ 4 ADRs (see Section 5.1.3.1).
  - Occurrence of AEs, resulting in the discontinuation of avelumab being desired or considered necessary by the Investigator and/or the subject (if applicable).
- Occurrence of pregnancy.
- Use of a nonpermitted concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from avelumab.
- Withdrawal of the subject's consent to continue avelumab (if a subject withdraws consent, the subject will be asked to continue tumor assessments if RECIST 1.1-defined PD by Investigator does not occur).
- Noncompliance (as defined in Section 6.9).

5.6 Premature Termination of the Study

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

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

*Evidence of inefficacy may arise from this study or from other studies; unfavorable safety findings may arise from clinical or nonclinical examinations, eg, toxicology.

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

Should premature termination of the study occur, the subject should be seen as soon as possible and the same assessments as required for a prematurely withdrawn subject should be performed, as described in Section 7.1.3. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interest.

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

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

5.7 Definition of End of Study

If the study is not terminated for a reason given in Section 5.6, the End of Study is defined as the last subject complete 90-day Safety Follow-up Phone Call or the last subject died, whichever comes first.

6 Investigational Medicinal Product and Other Drugs Used in the Study

The term IMP refers to the investigational drug undergoing a clinical study, as well as to any comparator drug or placebo (as applicable). In this study, the IMP is avelumab and no comparator drug or placebo is involved.

6.1 Description of the Investigational Medicinal Product

Avelumab is a sterile, clear, and colorless solution intended for IV administration. It is presented at a concentration of 20 mg/mL in CCI [redacted] and sealed with an CCI [redacted].

6.2 Dosage and Administration

Subjects will receive an IV infusion of avelumab over 1 hour (- 10 minutes/+ 20 minutes, ie, over 50 to 80 minutes) once every 2 weeks or every week for the first 12 weeks, then starting with Week 13, once every 2 weeks thereafter.

In order to mitigate infusion-related reactions, a premedication regimen of 25 to 50 mg diphenhydramine and 500 to 650 mg acetaminophen (IV or oral equivalent) is mandatory approximately 30 to 60 minutes prior to the first 4 doses of avelumab (see Section 6.4). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines, as appropriate. However, the prophylactic use of systemic corticosteroids is not permitted. Modifications of the infusion rate to be made in the event of infusion-related reactions are described in Section 6.5.5.1.

The starting dose of avelumab is 3 mg/kg (dose escalation according to modified 3 + 3 design up to 20 mg/kg is intended).

The dose of avelumab will be calculated based on the weight of the subject determined within 72 hours prior to the day of drug administration. The dose of avelumab used for the previous administration can be repeated if the change in the subject's weight is < 10% than the weight used for the last dose calculation. Every subject will receive avelumab at the protocol-scheduled dose until confirmed progression by Investigator, significant clinical deterioration (clinical progression), unacceptable toxicity, or until they meet any of the protocol-defined criteria for withdrawal from the study or from avelumab (see Sections 5.5.1and 5.5.2), or any of the criteria in Section 5.6 are met. Dose modification of avelumab (change in infusion rate) is discussed in Section 5.1.3.

Treatment with avelumab may be continued despite RECIST 1.1-defined progression at any time, if the Investigator considers the subject will continue to receive clinical benefit by continuing treatment with avelumab and if the "Criteria for Continuation of Treatment Beyond Progression" are met.

Criteria for Continuation of Treatment Beyond Progression

- No new symptoms or worsening of existing symptoms.
- Tolerance to avelumab.
- No decrease in ECOG performance status.
- The Investigator does not consider it necessary to administer a salvage therapy.

If disease progression is due to brain metastasis, subjects may continue avelumab treatment after the local treatment of the brain lesions provided that the above criteria are met in addition to the following and in consultation with the Medical Monitor:

- Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to re-initiation of treatment with avelumab
- There are no ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable)
- Subjects must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).

In addition, if disease progression is mainly due to a metastatic lesion (nodal or visceral) which in the opinion of the Investigator may be surgically removed or treated with palliative radiation therapy, subjects may continue avelumab treatment after the local treatment of such a lesion provided that:

- It has been at least 2 weeks (post minor surgery) or 4 weeks (post major surgery) and the subject has fully recovered from the surgery.

- It has been at least 2 weeks since the subject's last dose of radiation therapy and any toxicity related to the radiation therapy is recovered to < Grade 2.

The decision to continue treatment should be discussed with the Medical Monitor and documented in the study records. For subjects who continue avelumab beyond RECIST 1.1-defined progression. If discontinuation occurs due to progression and a definitive diagnosis/radiographic confirmation is not made at the time of discontinuation, a second imaging scan may be allowed for confirmation of PD (Confirmed Discontinuation) (see Sections 7.3.3). If PD is not confirmed and the subject wishes to continue study treatment, this will be allowed provided they meet the Criteria for Continuation of Treatment Beyond Progression. Monitoring should continue according to the Schedule of Assessment (Table 1-1 and Table 1-2). Treatment with avelumab should be stopped immediately if the subject does not tolerate avelumab anymore, or if therapeutic failure occurs.

Subjects receiving avelumab who have experienced a CR should be treated for a minimum of 12 months and/or until disease progression or unacceptable toxicity, after confirmation of response.

For subjects who achieve a confirmed CR on avelumab and subsequently develop PD after stopping therapy, but prior to the End of Study (defined in Section 5.7), 1 re-initiation of treatment at the same dose and schedule is allowed at the discretion of the Investigator and with the agreement of the Sponsor Medical Monitor (retreated subjects). To be eligible for retreatment, the subject must not have experienced any toxicity that led to discontinuation of the initial avelumab therapy (see Section 5.5.2). Prior to retreatment, malignant disease must 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 also be available and verified prior to retreatment. Retreated subjects will stay on the study and be treated and monitored according to the Clinical Study Protocol.

6.3 Assignment to Treatment Groups

Once the subject has provided the signed ICF(s) and has been determined to meet inclusion and exclusion criteria, the Investigator or their delegate will assign a unique Subject Identifier Number and request the study treatment assignment by using the IVRS. Subject Identifiers will comprise 17 digits, the first 10 digits representing the Study Number, the next 3 digits representing the Site Number, and the last 4 digits representing the Subject Number, which will be allocated sequentially starting with 0001. Once the Subject Number is assigned, it must not be reused for any other subject and the Subject Number for that individual must not be changed, even if the subject undergoes re-testing of laboratory parameters that do not meet the inclusion criteria during the 14-day Clinical Screening window (see Section 7.1.1).

If the subject fails to be started on treatment for any reason, the reason and the subject's demographic information should be collected. Other information, such as the reason for not starting treatment, the corresponding eCRF sections should be completed (see Section 7.1.1.1).

The following IMP allocation will be managed manually by Investigator, who assesses how many vials needed for a subject and pick up themselves. The vial number is linked via the GMP qualified system to the corresponding treatment as well as to the subject.

6.4 Noninvestigational Medicinal Products to be Used

In order to mitigate infusion-related reactions, a **premedication regimen** of 25 to 50 mg diphenhydramine and 500 to 650 mg acetaminophen (IV or oral equivalent) is mandatory approximately 30 to 60 minutes prior to the first 4 doses of avelumab. This regimen may be modified based on local treatment standards and guidelines, as appropriate. However, the prophylactic use of systemic corticosteroids is not permitted.

Infusion of avelumab will be stopped in case of Grade ≥ 2 infusion-related, allergic, or anaphylactic reactions. Following avelumab infusion, subjects must be observed for 2 hours after the infusion for potential infusion-related reactions.

If an allergic reaction occurs, the subject must be treated according to the best available medical practice. Guidelines for the management of infusion-related reactions are provided in Section 6.5.5.1. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

6.5 Concomitant Medications and Therapies

6.5.1 Permitted Medicines and Therapies

Any medications (other than those excluded by the Clinical Study Protocol) considered necessary for the subjects' welfare and which will not interfere with avelumab may be given at the Investigator's discretion.

The Investigator will record all concomitant medications taken by the subject during the study, from the date of signature of informed consent, in the appropriate section of the eCRF.

Medications other than those specifically excluded in this study (see Section 6.5.2) may be administered for the management of symptoms associated with the administration of avelumab as required. These might include analgesics, antinausea medications, antihistamines, diuretics, antianxiety medications, and medications for pain management, including narcotic agents.

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

Palliative bone-directed radiotherapy (eg, local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture) may be administered during the study. The assessment of PD will be made according to RECIST 1.1 (Section 12, Appendix II) and not based on the necessity for palliative bone-directed radiotherapy. Bone-directed radiotherapy should be within a limited field

of radiation and for palliation only; the course should be short, according to local institutional recommendation.

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

6.5.2 Prohibited Medicines

As stated in the exclusion criteria (Section 5.3.2), subjects must not have had prior therapy with any antibody or drug targeting T cell coregulatory proteins (immune checkpoints) such as PD-1, PD-L1, CTLA-4, 4-1BB, LAG 3, TIM 3 or anti-CD127, or concurrent anticancer treatment (eg, cytoreductive therapy, radiotherapy [with the exception of palliative bone-directed radiotherapy, and radiotherapy administered to superficial lesions], immune therapy, or cytokine therapy except for erythropoietin), major surgery (excluding prior diagnostic biopsy), concurrent systemic therapy with steroids or other immunosuppressive agents, or use of any investigational drug within 28 days before the start of study treatment.

In addition, the following treatments must not be administered during the study:

- Immunotherapy, immunosuppressive drugs, ie, chemotherapy or systemic corticosteroids except:
    - When required for the treatment of irAEs or infusion-related reactions / hypersensitivity.
    - Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent.
    - Systemic corticosteroids for management of patients with allergy to CT Intravenous Radiographic Contrast Media.
- Any vaccine therapies for the prevention of infectious disease (eg, seasonal influenza vaccine, human papilloma virus vaccine) except administration of the inactive vaccine.
- Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor). Exception: erythropoietin and darbepoetin alpha may be prescribed at the Investigator's discretion.

If the administration of a nonpermitted concomitant drug becomes necessary during the study, the subject will be withdrawn from treatment with avelumab (see Section 5.5.2). The Sponsor may be contacted to discuss whether avelumab must be discontinued.

6.5.2.1 Clarification of Corticosteroid Use

Data indicate that corticosteroids may inhibit and interfere with T cell function (Schleimer et al 1984; Khan 2008). Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressive agents such as corticosteroids will counteract the intended benefit. However, studies with anticytotoxic T-lymphocyte antigen-4 compounds indicate that short-term use of steroids can be employed without compromising

clinical outcomes (Weber et al 2012). Therefore, the use of corticosteroids during this study is restricted as follows:

- Therapeutic use: limited to the treatment of infusion-related reactions and short-term treatment of irAEs. The course of corticosteroid treatment should be completed as soon as clinically feasible and before resuming the next cycle of avelumab provided the event has resolved to a Grade 1 or less.
- Physiologic use: replacement for adrenal insufficiency at doses equivalent to ≤ 10 mg prednisone daily are acceptable.
- Prophylactic use: prophylactic use, eg, for the prevention of acute infusion-related reactions, constitutes concomitant use and is prohibited.

6.5.3 Other Nonpermitted Interventions

The following nondrug therapies must not be administered during the study:

- Radiotherapy (except for palliative bone-directed radiotherapy [see Sections 5.3.2 and 6.5.1] or radiotherapy administered to superficial lesions).
- Herbal remedies with immunostimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin).
- Traditional Chinese medicine that has an approved indication in treating cancer from the China Food and Drug Administration.

6.5.4 Special Precautions

As a routine precaution, subjects enrolled in this study must be observed for 2 hours after the infusion of avelumab in an area with resuscitation equipment and emergency agents. At all times during study 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. Please also refer to Section 6.4.

Infusion of avelumab will be stopped in case of ≥ Grade 2 hypersensitivity, inflammatory response, or anaphylactic reaction. The treatment recommendations for infusion-related reactions, according to the NCI are outlined in Section 6.5.5.1. All infusion-related reactions occurring during the infusion of avelumab or within 2 hours after completion of the administration of avelumab should be reported as irAEs.

Investigators should also monitor subjects closely for potential irAEs, which may manifest at the earliest after weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

6.5.5.1 Infusion-related Reactions

In order to mitigate infusion-related reactions, patients have to be premedicated with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions.

Management of infusion-related reactions should follow guidelines set forth in Table 6-1.

Table 6-1 Management of Hypersensitivity and Infusion-related Reactions Caused by Avelumab

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1: Mild Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Decrease avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2: Moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal antiinflammatory drug, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours	• Temporarily discontinue avelumab 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 avelumab infusion immediately and disconnect infusion tubing from the subject • Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events.

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for the next scheduled infusion. If no infusion-related reaction is observed in the next scheduled infusion the infusion rate may be returned to baseline at the all subsequent infusions. If an infusion reaction occurs, all details about drug preparation and infusion must be recorded.

Subjects should be instructed to report any delayed reactions to the Investigator immediately.

Additional Modification 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 6-1 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids and the infusion should be stopped for that day. At the next cycle, the Investigator may consider the addition of H_2-blocker antihistamines (eg, famotidine or ranitidine), meperidine or ibuprofen in addition to the mandatory premedication, for selected subjects. However, prophylactic steroids are **NOT** permitted (please refer to Section 6.5.2.1).

6.5.5.2 Immune-related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (ie, 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 the guidelines provided in Table 6-2.

Table 6-2 Management of Immune-related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (eg, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: treat as Grade 2, 3, or 4
Grade 2 Diarrhea: 4 to 6 stools per day over baseline; iv fluids indicated < 24 hours; not interfering with activities of daily living Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: resume avelumab therapy If persists > 5 to 7 days or recurs: treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over baseline; incontinence; iv fluids ≥ 24 hours; interfering with activities of daily living Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3 Permanently discontinue avelumab for Grade 4 or recurrent Grade 3 1.0 to 2.0 mg/kg/day prednisone 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, resume avelumab therapy following steroids taper (for initial Grade 3) If worsens, persists > 3 to 5 days or recurs after improvement: add infliximab 5 mg/kg (if no contraindication) **Note**: infliximab should not be used in cases of perforation or sepsis
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (eg, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5 to 1.0 mg/kg/day prednisone or equivalent Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper If worsens: treat as Grade 3 to 4

Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life-threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3 Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3)
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: treat as Grade 3 to 4
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: life-threatening	Permanently discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: taper steroids over at least 1 month If not improving after 48 hours or worsening: add additional immunosuppression (eg, infliximab, cyclophosphamide, iv immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: treat as Grade 2 or 3 to 4

Grade 2 AST or ALT > 3.0 to ≤ 5 × ULN and/or total bilirubin > 1.5 to ≤ 3 × ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4
Grade 3 to 4 AST or ALT > 5 × ULN and /or total bilirubin > 3 × ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: add mycophenolate mofetil 1 g twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 × ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 × ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤ 1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 × ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤ 1: Taper steroids over at least 1 month
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and/or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy Hospitalize In the presence of life-threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis

	Cardiology consult to establish etiology and rule out immune-mediated myocarditis Guideline based supportive treatment as per cardiology consult[a] Consider myocardial biopsy if recommended per cardiology consult	
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult[a] 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	Once improving, taper steroids over at least 1 month 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	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), antithyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate Rule out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), antithyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency), or insulin (for type I diabetes mellitus) as appropriate Rule out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression) Continue hormone replacement/ suppression and monitoring of endocrine function as appropriate

Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/ suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe symptoms or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month • Add prophylactic antibiotics for opportunistic infections	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/ suppression therapy as appropriate.
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent	If improves to Grade ≤ 1: Taper steroids over at least 1 month

	Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab therapy Specialty consult	

ACTH: adrenocorticotropic hormone; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BNP: B-type natriuretic peptide; CK-MB: creatine kinase MB; CT: computerized tomography; FSH: follicle-stimulating hormone; FT4: free thyroxine; GH: growth hormone; IGF-1: insulin-like growth factor 1; irAE: immune-related adverse event; iv: intravenous; LH: luteinizing hormone; MRI: magnetic resonance imaging; NCI-CTCAE v4.03: National Cancer Institute-Common Terminology Criteria for Adverse Events, Version 4.03; PRL: prolactin; TSH: thyroid-stimulating hormone; ULN: upper limit of normal.

6.6 Packaging and Labeling of the Investigational Medicinal Product

Avelumab is formulated as a 20 mg/mL solution in CCI [redacted]. The Sponsor's Clinical Trial Supplies department will supply the IMP, avelumab, which will be distributed to the study sites by the CRO(s).

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

Avelumab will be shipped in transport cool containers CCI [redacted], according to the storage and shipping conditions. Shipments will be monitored with temperature control devices.

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

For use in this study, avelumab drug product must be diluted with CCI [redacted] can be used if needed. It is recommended

that the diluted avelumab solution is used immediately. If not used immediately, the diluted drug product can be stored up to CCI or up to 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.

Avelumab must be stored at CCI until use, with a temperature log maintained daily. All medication boxes supplied to each study site must be stored carefully, safely, and separately from other drugs.

Avelumab stored at room temperature CCI or at elevated temperatures CCI for extended periods is subject to degradation. Avelumab must not be frozen. Rough shaking of avelumab must be avoided. Further information will be provided in the Manual of Preparation.

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

The contents of the avelumab vials are sterile and nonpyrogenic, 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.

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

6.8 Investigational Medicinal Product Accountability

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

- Upon receipt of IMP, the Investigator (or designee) will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided by the Sponsor and returning it to the Sponsor. A copy will be retained for the Investigator Site File.
- Dispensing of avelumab 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 Clinical Research Associate (CRA) (or equivalent) at each monitoring visit.
- IMP accountability records will include:

  1. Confirmation of IMP delivery to the study site.
  2. The inventory at the site of IMP provided by the Sponsor and prepared at the site.
  3. The use of each dose by each subject.

4. Destruction of unused treatment product (unused product will not be returned to the Sponsor).

5. Dates, quantities, batch numbers, expiry dates and (for IMP prepared at the site) formulation, as well as the subjects' Study Identifier Numbers.

- The Investigator should maintain records that adequately document:

1. That the subjects were provided the doses specified by the Clinical Study Protocol/amendment(s).

2. That all IMP provided by the Sponsor was fully reconciled.

Unused avelumab must not be discarded or used for any purpose other than this study. Any avelumab that has been dispensed to a subject must not be re-dispensed to a different subject.

The CRA will periodically collect the IMP accountability forms and will check all returns (both unused and used containers) before authorizing their destruction by the Sponsor or Sponsor delagate whenever applicable. However, it is also acceptable that IMP destruction is managed per site individual SOP regarding clinical study IMP destruction if applicable, and further document by CRA.

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

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

In addition, it must be ensured at each study site that the IMP is not used:

- After the expiry date.
- After the retest date, unless the IMP is re-analyzed and its retest date extended.

This is to be closely monitored by the CRA.

6.9 Assessment of Investigational Medicinal Product Compliance

In this study, subjects will receive the IMP (avelumab by IV infusion) at the study site. Well trained medical staff will monitor and perform administration of avelumab. Details of each administration of avelumab including the date, time, and dose will be recorded on the eCRF. The Investigator will make sure that the information entered onto the eCRF regarding administration is accurate for each subject. Any reason for noncompliance should be documented.

Noncompliance is defined as a subject missing > 1 cycle of avelumab for nonmedical reasons. If 1 cycle is missed and the interval between the subsequent treatment cycle and the last administered treatment cycle is longer than 4 weeks for nonmedical reasons, the criteria for insufficient compliance are met. Should these situations occur, the subject should be withdrawn from avelumab treatment (see Section 5.5.2).

6.10 Blinding

Not applicable.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose 20% greater than the highest daily dose (20 mg/kg) included in the Clinical Study Protocol. Any overdose must be recorded in the IMP 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 Patient Safety department in an expedited manner using the Serious Adverse Event Report Form (see Section 7.4.1.4).

There are no known symptoms of avelumab overdose to date. The Investigator should use his or her clinical judgment when treating an overdose.

6.13 Medical Care of Subjects After End of Study

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

Upon withdrawal from avelumab administration, subjects may receive whatever care they and their physicians agree upon. Subjects will be followed for survival and AEs (as described in Section 7.1.5).

7 Study Procedures and Assessments

7.1 Schedule of Assessments

The Schedule of Assessment is provided in Table 1-1 for subjects receiving avelumab once every 2 weeks; in Table 1-2 for subjects receiving avelumab once a week for the first 12 weeks followed by once every 2 weeks (10 mg/kg once weekly cohort).

Prior to performing any study assessments that are 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(s) (see Section 9.2).

7.1.1 Clinical Screening

There is a 28-day washout/recovery period for prior anticancer treatment (eg, cytoreductive therapy, radiotherapy [with the exception of a short course of palliative bone-directed radiotherapy to a limited field of radiation, and radiotherapy administered to superficial lesions], which must be completed at least 7 days prior to the first administration of avelumab [see Section 5.3.2], immune therapy, or cytokine therapy except for erythropoietin) and major surgery before the start of study treatment. Radiation to more than 30% of the bone marrow or with a wide field of radiation should be completed at least 28 days prior to the first administration of avelumab.

The Clinical Screening procedures and baseline assessments will be completed within 14 days prior to the first administration of avelumab.

The subject information to be documented during Clinical Screening includes demographic information (birth date, sex, and race) and a complete medical history including the history of the tumor disease, previous and concomitant medications, previous surgeries and radiotherapies, and baseline medical conditions; information on concomitant medications and AEs will be monitored throughout the Treatment Phase. In addition, the subject will be given an Emergency Medical Support card at the baseline assessments visit.

During Clinical Screening, subjects will undergo a full physical examination including recording body height, vital signs including body weight, 12-lead electrocardiogram (ECG), and a determination of the ECOG performance status (Table 1-1).

The screening laboratory examination includes hematology, hemostaseology, full serum chemistry, and full urinalysis (protein content required, and optional parameters albumin and immunoglobulin G to be tested depending on study site capability). Free thyroxine (T4) and thyroid-stimulating hormone (TSH) will also be assessed at Clinical Screening (baseline) (Table 7-1).

Blood testing for hepatitis B virus and hepatitis C virus will be performed during Clinical Screening for all subjects, In addition, the subject's HIV status must be known as a condition of study entry (see Section 5.3.2, Exclusion Criterion 10). If necessary to determine HIV status, a blood sample for HIV testing should be collected at Clinical Screening, subject to the provision of

informed consent for HIV testing as per local and national-specific regulations. Where consent is required, subjects who do not know their HIV status and who do not consent to HIV testing will not be allowed to enroll in the study.

During Clinical Screening, a serum β-human chorionic gonadotropin pregnancy test will be performed for all women of childbearing potential. Women are to be considered to be of childbearing potential unless they have age-related natural (spontaneous) amenorrhea ≥ 12 consecutive months and increased FSH > 40 mIU/mL, are surgically sterile, or are sexually inactive. Women who are not of childbearing potential are exempt from pregnancy testing. If necessary to confirm childbearing potential, a blood sample for FSH analysis will be collected at Clinical Screening.

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Following completion of the above Clinical Screening assessments, baseline samples for ADA against avelumab should be collected prior to the first administration of avelumab, ie, either during Clinical Screening or predose on Day 1.

Failure to establish subject eligibility within a 14-day period constitutes Clinical Screening failure and the subject should be excluded from the study. Section 7.1.1.1 details the information to be collected for any subject who fails Clinical Screening. Rescreening of subjects is not allowed, however, laboratory parameters that do not meet the inclusion criteria may be re-tested within the 14-day Clinical Screening window following consultation with the Medical Monitor.

7.1.1.1 Information to be Collected on Clinical Screening Failures

Subjects who sign the ICF but do not start study treatment for any reason will be considered Clinical Screening failures. The following eCRF pages must be completed for all Clinical Screening failures:

- Clinical Screening Disposition page (including reason for the subject not starting study treatment).
- Informed consent.
- Demography.
- Adverse events (only if an SAE occurs).
- Inclusion/exclusion criteria.

7.1.2 Treatment Phase

The Treatment Phase begins on Cycle 1 Day 1 with the first administration of avelumab and will continue until progression (see Sections 6.2 and 7.3.3), significant clinical deterioration (clinical progression), unacceptable toxicity, or any criterion for withdrawal from the study or IMP occurs

(see Sections 5.5.1 and 5.5.2). However, a subject may remain on avelumab beyond RECIST 1.1-defined disease progression if their ECOG performance status has remained stable, there are no new symptoms or worsening of existing symptoms, and, if in the opinion of the Investigator, the subject will benefit from continued treatment with avelumab (see Section 6.2). For subjects who continue avelumab beyond progression, treatment should be stopped immediately if the subject no longer tolerates avelumab or if therapeutic failure occurs. See Section 6.2.

Re-initiation of avelumab may be allowed in a subject who discontinues administration of avelumab but subsequently fails to confirm and verify original PD and meets the Criteria for Continuation of Treatment Beyond Progression (See Section 6.2 and 7.3.3).

Subjects receiving avelumab who have experienced a CR should be treated for a minimum of 12 months, and/or until disease progression or unacceptable toxicity, after confirmation of response.

For subjects receiving avelumab once every 2 weeks, subjects will be asked to visit the study site every 2 weeks during the Treatment Phase. 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 study procedures (except PK sampling visits on Days 2 and 3).

For subjects receiving avelumab once weekly, subjects will be asked to visit the study site once weekly for the first 12 weeks, and then once every 2 weeks starting at Week 13 during the Treatment Phase. A time window of 1 day before or 1 day after the scheduled visit day (- 1/+ 1 days) is permitted for all study procedures while subjects receiving avelumab once weekly (12 consecutive weeks). 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 study procedures while subjects receiving avelumab once every 2 weeks (Week 13 and thereafter).

The assessments to be performed during the Treatment Phase are detailed in Table 1-1 for subjects receiving avelumab once every 2 weeks; in Table 1-2 for subjects receiving avelumab once a week for the first 12 weeks followed by once every 2 weeks (10 mg/kg once weekly cohort).

7.1.3 End-of-Treatment Visit

Subjects must undergo an EOT Visit after discontinuation of avelumab for any reason. The EOT Visit should be performed within 7 days after the decision to discontinue treatment, but before any new anticancer therapy is started (if possible), whichever occurs earlier. The EOT Visit may be performed on the day of the decision to discontinue avelumab.

Any subject who experiences an AE that mandates discontinuation of avelumab should have an EOT Visit as soon as possible after the decision to discontinue avelumab (within 7 days).

The EOT Visit eCRF page should be completed with a visit date reflecting the date the discontinuation decision was made, with the last known date the subject received avelumab, and 1 of the following reasons:

- Adverse event(s).
- Abnormal laboratory value(s).
- Abnormal test procedure result(s).
- Protocol violation.
- Subject withdrew consent.
- Lost to follow-up.
- Death (must state if death is due to "Study Indication" or "Other" reason).

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- Treatment duration completed as per protocol (for subjects who experience a confirmed CR; see Section 6.2).
- Other reasons, including clinical deteriorations, administrative problems.

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Please refer to Table 1-1, Table 1-3, Table 1-4, and Table 1-5 for the specific assessments to be performed at the EOT Visit.

7.1.4 Safety Follow-up

The safety parameters to be assessed during the Safety Follow-up (30-day Safety Follow-up Visit and 90-day Phone Call) are detailed in Table 1-1, Table 1-3, and Table 1-4.

7.1.4.1 30-day Safety Follow-up Visit

All subjects will have a Safety Follow-up Visit scheduled 30 days (± 5 days) after the last administration of avelumab.

After the EOT Visit, all AEs have to be documented until the 30-day Safety Follow-up Visit. After this visit, all SAEs and all treatment-related nonserious AEs must be documented until the 90-day Safety Follow-up Phone Call. Subjects with an ongoing SAE at the 30-day Safety Follow-up Visit

must be monitored and followed up by the Investigator until stabilization or until the outcome is known.

7.1.4.2 90-Day Phone Call

At 90 days (± 5 days) after the last dose of avelumab, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related nonserious AEs. Any SAE assessed as related to study treatment must be reported whenever it occurs, irrespective of the time elapsed since the last administration of avelumab. Subjects will also be asked about any anticancer therapy.

7.1.5 Long-term Follow-up

Subjects with an SAE ongoing after the Safety Follow-up Phone Call 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".

After the EOT Visit, subjects will be followed every 12 weeks (± 7 days) for survival (including the assessment of any further anticancer therapy). Survival follow-up will continue until 2 years after the last subject receives the last dose of avelumab, or the last subject dies, whichever occurs first. Additional survival follow-up data may be collected at the time of primary and final analyses if the last follow-up data were collected more than 30 days earlier. Under some circumstances, subjects may not be followed for survival for 2 years in this study, eg, subjects may be given the opportunity to participate in a rollover study, or the Sponsor may terminate the study early.

Each subject will be followed for survival until death, lost to follow-up, or the cutoff date of the End of Study (Section 5.7).

The assessments to be performed at the Long-term Follow-up Visits are detailed in Table 1-1.

7.2 Demographic and Other Baseline Characteristics

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

7.2.1 Demographic Data

At screening, the following data will be collected:

- Date of birth
- Sex
- Race
- Ethnicity.

7.2.2 Diagnosis of Tumor

The tumor disease information to be documented and verified at the Clinical Screening Visit for each subject includes:

- Detailed history of the tumor including histopathological diagnosis, grading and staging in accordance with the International Union Against Cancer Tumor Node Metastasis Classification of malignant tumors at diagnosis.
- All therapy used for prior treatment of the tumor (including surgery, radiotherapy, chemotherapy, and immunotherapy).
- Any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy.
- Current cancer signs and symptoms, and AEs 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 participate in the study, a complete medical history will be collected and documented during Clinical Screening. This will include, but may not be limited to, the following:

- Past and concomitant nonmalignant diseases and treatments.
- Past and concomitant malignant diseases and treatments.
- All medications (including herbal medications) taken and procedures carried out within 30 days prior to screening.
- Smoking and alcohol history.
- Family cancer history.

7.2.4 Other Baseline Assessments

All other baseline measurements, such as tumor evaluation, vital signs, complete physical examination, ECOG performance status (see Section 12, Appendix IV), clinical laboratory parameters, 12-lead ECG, and biomarker will be assessed as detailed in Table 1-1 and Table 1-2.

Please refer to Sections 7.3.1 and 7.3.2 for details of baseline tumor evaluations, Section 7.4 for baseline safety evaluations, CCI .

For study entry, all subjects must fulfill all the inclusion criteria described in Section 5.3.1 and not meet any of the exclusion criterion described in Section 5.3.2.

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

CCI

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Document No. CCI
Object No. CCI

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7.4 Safety Assessments

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

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

subject (see Section 7.4.1.2). Given the intended mechanism of action of avelumab, particular attention will be given to AEs that may follow the enhanced T cell activation such as dermatitis, colitis, hepatitis, uveitis, or other immune-related reactions. Ophthalmologic examinations should be considered, when clinically indicated, for signs or symptoms of uveitis.

The reporting period for AEs is described in Section 7.4.1.3. The safety assessments will be performed according to Table 1-1 and Table 1-2.

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, which does not necessarily have a 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.

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

The Investigator is required to grade the severity/intensity of each AE.

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

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

If the severity/intensity of a particular AE is not specifically graded by the guidance document, the Investigator is to revert to the general definitions of Grade 1 through Grade 5 and use his or her best medical judgment.

The 5 general grades are:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening or disabling
- Grade 5: Death.

According to the Sponsor's convention, if a severity/intensity of Grade 4 or Grade 5 is applied to an AE, then the Investigator must also report the event as an SAE. However, a laboratory abnormality with a severity/intensity of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

In the case of death, the primary cause of death (the event leading to death) should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this respective event; 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 be reported as an SAE.

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

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

Related: Suspected to be reasonably related to the study treatment. The AE could medically (pharmacologically/clinically) be attributed to the IMP under study in this 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 an abnormality fulfils these criteria, the identified medical condition (eg, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Adverse Drug Reaction

An ADR is defined in this study as any AE suspected to be related to avelumab by the Investigator and/or Sponsor.

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 1 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.

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered a serious adverse reaction 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 a Serious Adverse Event

Elective hospitalizations to administer, or to simplify study treatment or study procedures (eg, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered as 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.

Events Not to Be Considered as Adverse Events or Serious Adverse Events

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

Adverse Events/Serious Adverse Events Observed in Association with Disease Progression

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

Predefined AEs of Special Interest for Safety Monitoring

Any AE that is suspected to be a potential irAE and infusion-related reactions will be considered an adverse event of special interest.

Dose-limiting Toxicity

A DLT is defined as a ≥ Grade 3 ADR according to the NCI-CTCAE v4.03, occurring during the DLT observation period of the dose escalation cohorts. An ADR is defined in this study as any AE suspected to be related to avelumab by the Investigator and/or Sponsor. A DLT must be confirmed by the SMC as being related to avelumab.

A DLT is specifically defined as any Grade ≥ 3 toxicity that is possibly, probably, or definitely related to avelumab, occurring during the DLT observation period, except for any of the following:

- Grade 3 infusion-related reaction resolving within 6 hours 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.
- Grade 3 skin toxicity, or Grade 3 LFT (ALT, AST, or gamma-glutamyl transferase) increase that resolves to ≤ Grade 1 in less than 7 days after medical management (eg, immunosuppressant treatment) has been initiated.
- Grade 3 diarrhea unless to be discontinued according to Treatment Guidelines. In this case it would be an DLT again.
- Single laboratory values out of normal range that are unlikely to be related to avelumab according to the Investigator, do not have any clinical correlate, and resolve to ≤ Grade 1 within 7 days with adequate medical management.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.

The ADRs (including DLTs) that require permanent discontinuation of avelumab are described in Section 5.1.3.1.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each study visit, the subject will be queried on changes in his/her condition. During the reporting period of the study, 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 (as defined in Section 7.4.1.3) will be reported on an ongoing basis in the appropriate section of the eCRF. Among these AEs and all SAEs must also be documented and reported using the appropriate SAE eCRF page (SAESIDT) as described in Section 7.4.1.4.

It is important that each AE report includes a description of the event, its duration (onset and resolution dates [/times "/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 relationship with the study drug, 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.

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 in the study (date of first signature of informed consent) and continues through the 30-days (± 5 days) Safety Follow-up Visit. After the Safety Follow-up Visit all SAEs and treatment-related nonserious AEs need to be documented up until the Safety Follow-up Phone Call, which is defined as 90 days (± 5 days) after the last administration of avelumab.

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

7.4.1.4 Procedure for Reporting Serious Adverse Events

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

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

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, or autopsy report).

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

Requests for follow-up will usually be made by the responsible Monitor, although in exceptional circumstances, the Global Patient Safety department may contact the Investigator directly to obtain clarification or to discuss a particularly critical event.

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

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

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her subjects to the IEC/IRB that approved the study.

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

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

7.4.1.6 Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed continuously throughout the study and are assessed for final outcome at the 30-day Safety Follow-up (Section 7.1.4.1). After the 30-day Safety Follow-up Visit, all new and ongoing SAEs and all treatment-related nonserious AEs ongoing at the 90-day Safety Follow-up Phone Call (Section 7.1.4.2) must be monitored and followed-up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator as related to the study drug (eg, resulting from a drug interaction with a contraceptive medication) are considered as 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 paper Pregnancy Report Form, which

must be transmitted according to the same timeline 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, and in case of abnormal outcome, the SAE Report Form (when the subject sustains an event) and the Parent-Child/Fetus Adverse Event Report Form (when the child/fetus sustains an event).

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 study, the subject must be discontinued from avelumab administration immediately. The Sponsor or designee must be notified without delay and the subject must be followed as described above.

7.4.3 Clinical Laboratory Assessments

It is essential that the Sponsor be provided with a list of local laboratory normal ranges before shipment of the IMP. Any change in laboratory normal ranges during the study should also be forwarded to the CRO and the Sponsor.

Blood samples will be taken from subjects and prior to administration of avelumab. All routine laboratory analyses will be performed at a laboratory facility local to the study site and relevant results essential for subject management decisions (hematology, biochemistry, LFTs) must be available and reviewed prior to administration of avelumab. The report of the results must be retained as a part of the subject's medical record or source documents and documented on the eCRF. Blood samples for the tests listed in Table 7-1 will be taken from subjects during Clinical Screening (within 14 days prior to the first administration of avelumab), at the EOT Visit, 30-day Safety Follow-up Visit, and during the Treatment Phase at the time points specified in Table 1-1 and Table 1-2. In case of LFT elevation (AST, ALT, and/or total bilirubin) requiring additional laboratory draws (see Section 6.5.5.2 and Table 6-2), unscheduled laboratory tests will be performed.

Free thyroxine, TSH, and urinalysis will be assessed at the time points specified in the Schedule of Assessments (Table 1-1 and Table 1-2).

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.

Table 7-1 Required Laboratory Panel Tests

Full Chemistry	**Hematology**
Albumin	Absolute lymphocyte count
Alkaline phosphatase[1]	Absolute neutrophil count
Alanine aminotransferase[1]	Hematocrit
Amylase	Hemoglobin
Aspartate aminotransferase[1]	Platelet count
Gamma-glutamyl transferase	Red blood cells
Blood urea nitrogen/total urea[1]	White blood cells and differential count
Calcium[1]	Red blood cell morphology (optional[4])
Chloride[1]	Reticulocytes
Cholesterol	Mean corpuscular hemoglobin
Creatine kinase	Mean corpuscular volume (optional[4])
Creatinine[1]	Mean corpuscular hemoglobin concentration
C-reactive protein	**Hemostaseology**
Glucose[1]	Activated partial thromboplastin time (aPTT)
Lactate dehydrogenase	Prothrombin time/International Normalized Ratio (INR)
Lipase	**Hormone**
Phosphorus/phosphates[1]	Follicle-stimulating hormone (if applicable)
Magnesium[1]	Thyroid-stimulating hormone (TSH)
Potassium[1]	Free thyroxine (T4)
Sodium[1]	**Antibodies**
Total bilirubin[1]	Totality of binding antidrug antibody (ADA) (Section 7.7)
Total protein	**Urinalysis[3]**
Uric acid	**Full:** protein content[2], albumin (optional[4]) and immunoglobulin G (optional[4])
Triglycerides	**Basic (dipstick):** protein content only[2]
Hemoglobin A1c	

[1]Core serum chemistries.
[2]If urinalysis is positive for protein, sediment will also be evaluated.
[3]Urinalysis is not required for subjects with urothelial cancers.
[4]To be assessed depending on study site capability. For urinalysis parameters, study sites not able to assess urine albumin and immunoglobulin will only test for urine protein content.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

The ECOG performance status (see Section 12, Appendix IV) will be assessed at Clinical Screening and at subsequent visits as indicated in the Schedule of Assessments (Table 1-1 and Table 1-2) and documented in the eCRF, even if the IMP is on hold for the subject. More frequent examination may be performed at the Investigator's discretion, if medically indicated.

Body weight (to the nearest 0.1 kilogram [kg]) will be measured at Clinical Screening and at subsequent visits as indicated in the Schedule of Assessments (Table 1-1 and Table 1-2) and

documented in the eCRF. Body height in centimeters (cm) will be measured at Clinical Screening only.

Physical examination will include an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and a basic nervous system evaluation. A full physical examination will be conducted at Clinical Screening, at the EOT Visit, and at the 30-day Safety Follow-up Visit. At visits during the Treatment Phase (see Schedule of Assessments [Table 1-1 and Table 1-2]), the physical examination will be symptom-directed. Results from the physical examination, including any abnormalities, will be documented in the eCRF. Abnormal findings are to be reassessed at subsequent visits. Details of the physical examination must be present in the source documentation at the study site.

A 12-lead ECG will be performed and recorded at Clinical Screening and as indicated in the Schedule of Assessments (Table 1-1 and Table 1-2). All subjects will have ECG assessment at baseline, and at the first 3 times of study drug treatment after avelumab infusion. In following visits, ECG will be arranged if considered necessary by the Investigator. Electrocardiograms will be performed in the supine position after the subject has been breathing quietly for 5 minutes. The ECG results will be used to evaluate heart rate, atrial-ventricular conduction, QR* and QT intervals, and possible arrhythmias. Interpretation of the ECG trace must be made by a qualified physician and documented on the ECG eCRF. Each ECG trace should be labeled with the Study Number, Subject Identifier Number, and date, and kept in the source documents at the site.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History eCRF page. All newly diagnosed or worsening conditions, signs and symptoms observed since screening, whether related to the study drug or not, are to be reported as AEs on the Adverse Event eCRF page.

For women of childbearing potential, a serum β-human chorionic gonatropin pregnancy test will be carried out during Clinical Screening. Thereafter, a urine pregnancy test will be performed every 4 weeks during the Treatment Phase prior to administration of avelumab and at the visits indicated in the Schedule of Assessments (Table 1-1 and Table 1-2). Results of the most recent pregnancy test should be available prior to the next administration of avelumab. Female subjects who are not considered to be of childbearing potential (age-related natural [spontaneous] amenorrhea ≥ 12 consecutive months and increased FSH > 40 mIU/mL), or who are surgically sterile or are sexually inactive, are exempt from pregnancy testing.

*ECG QR value may not be applicable in some study sites according to site routine practice (which does not report QR value).

7.5 Pharmacokinetics

Full PK blood samples will be collected from all subjects according to the following schedules as indicated in Table 1-3 and Table 1-4.

For subjects receiving avelumab once every 2 weeks:

- Day 1: within 2 hours prior to and at the end of the 1-hour infusion and at 0.5, 1, 2, 4, 6, and 12 hours after the end of the infusion.
- Day 2: 2 samples will be collected 24 and 36 hours after the end of the infusion.
- Day 3: a single sample will be collected 48 hours after the end of the infusion.
- Day 8: a single sample will be collected 168 hours after the end of the infusion.
- Days 15, 29, 43, 85, 127, and 169 (Week 25): samples will be collected within 2 hours prior to infusion (trough value) and immediately after the infusion is completed (peak value).
- Every 12 weeks beyond Week 25: a single sample will be collected within 2 hours prior to infusion (trough value).
- EOT Visit.
- 30-day Safety Follow-up Visit.

*The time window for PK sampling time points are: +10 minutes for the end of infusion sample collection on Day 1; ± 10 minutes for 0.5 and 1 hour after the end of infusion; ± 20 minutes for 2, 4, and 6 hours after the end of infusion; ± 2 hours for 12, 24, 36, 48, and 168 hours after the end of infusion. The time window for PK sampling time points is applicable for all scheduled PK sample collection for all subjects.

For the 6 subjects receiving avelumab once a week:

- Within 2 hours prior to each infusion at Weeks 1, 2, 3, 5, and 7, at Weeks 13, 15, 19, and 25, and then at 12-week intervals while on treatment.
- At the end of infusion (within 15 minutes) at Weeks 1, 7, 13, and 25.
- EOT Visit.
- 30-day Safety Follow-up Visit.

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The collection of blood samples with exact date and clock time of avelumab administrations (relative to the previous and next doses of avelumab) and sample collection will be recorded on the corresponding eCRF page. Whole blood sufficient to provide 1.5 mL of serum will be collected for all PK assessments. Postinfusion samples should be collected from a site other than the avelumab infusion site (ie, contralateral arm) on the days of infusion. If the infusion is interrupted, the reason for interruption will be documented on the eCRF.

Further instructions for PK sample collection and handling will be provided in a separate Laboratory Manual.

7.5.1 Pharmacokinetic Parameters

The following PK parameters will be calculated using noncompartmental analysis:

- AUC_{0-t}: area under the concentration-time curve from time zero to time t (calculated by linear trapezoidal summation).
- AUC_{0-tau}: area under the concentration-time curve from time zero to tau, the respective dosing interval, ie, 1-week or 2-week (calculated by linear trapezoidal summation).
- $AUC_{0-\infty}$: area under the concentration-time curve from time zero to infinity (calculated by the linear trapezoidal summation and extrapolated to infinity using C_{last}/λ_z).
- λ_z: terminal elimination rate constant. The value of λ_z is determined from the slope of the regression line of log (concentration) versus time.
- C_{max}: maximum serum concentration.
- C_{trough}: serum concentration observed immediately before next dosing.
- C_{last}: last quantifiable concentration.
- t_{max}: time to maximum concentration.
- $t_{1/2}$: elimination half-life determined as $0.693/\lambda_z$.

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7.7 Antidrug Antibody Response

Full ADA serum samples will be collected from all subjects according to the following schedule as indicated in Table 1-3 and Table 1-4.

For subjects receiving avelumab once every 2 weeks:

- Day 1 (baseline): the baseline sample should be collected within 2 hours prior to the first administration of avelumab, ie, either during Clinical Screening or predose on Day 1.

- Days 15, 29, 43, 85, 127, and 169: samples will be collected within 2 hours prior to infusion.
- After Day 169, 1 sample (within 2 hours prior to infusion) every 12 weeks until the EOT Visit.
- 30-day Safety Follow-up Visit.

For subjects receiving avelumab once a week:

- Within 2 hours prior to each infusion at Weeks 1, 3, 5, 7 (every 2 weeks), at Weeks 13, 19, and 25 (every 6 weeks), and then every 12 weeks while on treatment.
- 30-day Safety Follow-up Visit.

Blood samples for ADA analysis must be collected prior to avelumab administration (Table 1-3 and Table 1-4).

For retreated subjects (ie, those who achieve a CR on avelumab, subsequently develop PD after stopping therapy, and then re-initiate treatment), ADA samples will be collected according to the following schedule as indicated in Table 1-5:

- Day 1 of retreatment infusion: within 2 hours prior to the infusion.
- EOT Visit.

The immunogenicity testing strategy will be implemented and conducted in line with the following guidance documents:

- European Medicines Agency Guidance: Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins, 2007.
- European Medicines Agency Guidance: Immunogenicity Assessment of Monoclonal Antibodies Intended for In Vivo Clinical Use, 2010.
- Food and Drug Administration (FDA) Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins, 2009.

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

In the event of anaphylactic reactions, the ADA samples from affected subjects will be investigated for the presence of drug-specific immunoglobulin E using a novel Phadia® ImmunoCAP® method developed for this purpose.

Further details of the analysis will be provided separately.

8 Statistics

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8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Primary Endpoints

The primary endpoints are:

- Occurrence of DLTs during the DLT observation period (first 21 days of treatment; excluding 10 mg/kg once weekly cohort).
- Pharmacokinetic profiles in Chinese subjects.

8.3.2 Secondary Endpoints

The secondary endpoints of the study include:

- Occurrence of TEAEs for all dose groups according to NCI-CTCAE v4.03.
- Occurrence of treatment-related AEs for all dose groups according to NCI-CTCAE v4.03.
- Serum titers of ADA against avelumab.

8.3.3 Safety Endpoints

In addition to the endpoints specified as primary and secondary endpoints, laboratory parameters will be evaluated.

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8.4 Analysis Sets

- **Screening Analysis Set:** all subjects who signed the ICF(s).
- **DLT Analysis Set**: all subjects with data used for implementing the dose-escalation schedule (excluding 6 subjects in 10 mg/kg once weekly cohort). These subjects should have received all avelumab administrations in the DLT observation period (first 21 days of treatment) or should have stopped treatment because of DLTs in the DLT observation period.
- **Safety Analysis Set**: all subjects who have received at least 1 dose of avelumab. The Safety Analysis Set will be used for all analyses of safety and efficacy.
- **Efficacy Population:** all subjects who have received at least 1 dose of avelumab and have measurable disease at baseline according to Investigator assessment.
- **PK Analysis Set**: all subjects who have completed at least 1 infusion of avelumab, and who have provided valid PK samples.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

All data recorded during the study will be presented in individual data listings for the Safety Analysis Set. Unless otherwise specified, 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.

Descriptive statistics will be used to summarize the study 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.

Full details of the planned analyses will be provided in the SAP.

8.5.2 Analysis of Primary Endpoints

8.5.2.1 DLTs in Dose Escalation Cohorts

DLT is defined in Section 7.4.1.1. The number and proportion of subjects experiencing DLTs will be reported by dose level based on the DLT Analysis Set (excluding 10 mg/kg once weekly cohort).

8.5.2.2 Pharmacokinetics Profile

Serum concentrations of avelumab will be determined by a validated method at the time points described in the Schedule of Assessments (Table 1-3, Table 1-4, and Table 1-5).

The PK parameters to be estimated and reported for the PK Analysis Set are defined in Section 7.5.1.

The PK parameters will be summarized using descriptive statistics. Additional PK analysis/display may be generated at the discretion of the pharmacokineticist.

8.5.3 Analysis of Secondary and Safety Endpoints

8.5.3.1 Analysis of Safety Endpoints

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

Safety analyses will be performed on the Safety Analysis Set. The safety endpoints will be tabulated by dose level and cohort, using descriptive statistics.

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

The on treatment period is defined as the time from the first administration of avelumab to the last administration of avelumab date plus 30 days or the earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurs first.

Adverse Events

All AEs will be coded according to the Medical Dictionary for Regulatory Activities. Severity of AEs will be graded using the NCI-CTCAE v4.03 toxicity grading scale.

Treatment-emergent AEs are those events with an onset date occurring during the on-treatment period or if the worsening of an event is during the on-treatment period.

The incidence of TEAEs, regardless of attribution and AEs, defined as possibly related to study treatment will be summarized by Preferred Term and System Organ Class, and described in terms of intensity and relationship to study treatment. Adverse events (serious and nonserious) will be considered TEAEs, except for AEs which started prior to the first administration of avelumab (unless a worsening of the event is recorded after the first administration of avelumab, in which case the event will be considered a TEAE). All premature terminations will be summarized by the primary reason for study withdrawal.

Descriptive statistics will be examined for indications of dose-related ADRs.

Laboratory Variables

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

Physical Examination (Including Vital Signs and 12-lead Electrocardiograms)

Physical examination data, including vital signs (body temperature, respiratory rate, heart rate, and blood pressure) and 12-lead ECG recorded at the time points indicated in Table 1-1 and Table 1-2 will be presented.

Further details will be provided in the SAP based on the current safety experience.

8.5.3.2 Serum Titers of Antidrug Antibodies

The immunogenicity analysis will include a listing of ADA results as positive or negative, and if applicable, a numeric titer value.

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8.6 Reporting of Planned Analyses

The primary analysis, including all endpoints analyses, for study data will be conducted at the time when all subjects complete PK sample collection at Week 13 (including all samples collected if the treatment discontinued earlier than Week 13). The data cutoff time point for primary analysis is set at Week 13 (Day 85) of the last subject.

The data from primary analysis will be summarized in the Clinical Study Report (CSR).

The final analysis of study data will be conducted after End of Study, which is defined as the last patient complete 90-day Safety Follow-up Phone Call or last patient died, whichever comes first. Additional data from primary analysis up to this cutoff date will be analyzed and presented as an addendum of CSR.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

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

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

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject’s participation in the study is his/her written informed consent. The subject’s written informed consent to participate in the study must be given before

any study-related activities are performed. The information of HIV testing and biomarker will be included in the ICF.

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

Depending on national regulations, a person other than the Investigator may inform the subject 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 who is willing to participate into the trial and the Investigator.

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

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

9.3 Subject Identification and Privacy

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

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

Blood and CCI samples will be stored for up to 10 years after study completion. During this time, samples may be re-analyzed for newly identified CCI or with new or improved technology. After 10 years, the samples will be destroyed or fully anonymized or a new IEC/IRB approval and informed consent will be requested to keep the samples for an additional period. If tumor tissue remains, the site will be notified and the CCI will be returned to the site upon request. If the site does not request the return of the CCI, it will be destroyed.

9.4 Emergency Medical Support and Subject Card

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

The first point of contact for all emergencies will be the Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action will follow the standard process established for Investigators.

In cases where the Investigator is not available, the Sponsor or designee provides the appropriate means to contact a Sponsor or delegate physician. This includes the provision of a 24-hour contact number at a call center, whereby healthcare providers will be given access to the appropriate Sponsor physician to assist with the medical emergency.

9.5 Clinical Study Insurance and Compensation to Subjects

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

9.6 Independent Ethics Committee/Institutional Review Board

Prior to commencement of the study at a given site, the Clinical Study Protocol will be submitted 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 with the CRO.

The study must not start at a site before the Sponsor has obtained written confirmation of 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, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the study, the Clinical Study Protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the study will also be submitted to the concerned IEC/IRB, before implementation in case of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC/IRB during the course of the study in accordance with national regulations and requirements.

9.7 Health Authorities

The Clinical Study Protocol and any applicable documentation (eg, IMP Dossier, Subject Information, and the ICF) will be submitted or notified to the Health Authorities in accordance with the regulations of all local and national regulations for each site.

10 Study Management

10.1 Case Report Form Handling

The main purpose of the eCRF is to document data required by the Clinical Study Protocol in a complete, accurate, legible, and timely manner. The data in the eCRF should be consistent with the relevant source documents.

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

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

Please refer to the Manual of Operations for eCRF handling guidelines.

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

- Subject's full name, date of birth, sex, race, height, weight.
- Medical history and concomitant diseases.

- Prior and concomitant therapies (including changes during the study).
- Tumor disease information.
- Study identification, that is, the Sponsor Study Number for this clinical study (MS100070-0035), and Subject Number.
- Date of subject's inclusion into the study (ie, date the subject gave informed consent).
- Dates of the subject's visits to the site.
- Any medical examinations and clinical findings predefined in the Clinical Study Protocol.
- All AEs observed in the subject.
- Date that the subject left the study, including any reason for early withdrawal from the study or IMP (if applicable).

All documents containing source data must be filed. 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 Identifier 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.

Electronic subject files will be printed, with printouts signed and dated by the Investigator, and kept in a safe place at the site. When the CRA performs source data verification, electronic subject file will be spot checked by CRA as predefined in the monitoring visit plan.

10.3 Investigator Site File and Archiving

Upon initiation of the study, the Investigator will be provided with an Investigator Site File upon initiation of the study. This file will contain all documents necessary for the conduct of the study and will be updated and completed throughout the study. 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 study, and must be safely archived for at least 15 years (or per local requirements or as otherwise notified by the Sponsor) after the end of the study. 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.

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

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This study will be monitored in accordance with the ICH GCP, and any other applicable regulations. The site CRA will perform visits to the study 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 inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed CRFs, the IMP, and the subjects' original medical records/files.

The Clinical Study Protocol, each step of the data capture procedures, and the handling of the data, including the final Clinical Study Report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

10.5 Changes to the Clinical Study Protocol

Changes to the Clinical Study Protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

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

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

10.6 Clinical Study Report and Publication Policy

10.6.1 Clinical Study Report

After completion of the study, or completion of a particular cohort or cohorts if applicable, a Clinical Study 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 will be a publication of the results of the analysis of the primary endpoint(s) that will include data from all study sites that participated the study.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or

newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require presubmission 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.

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

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12 Appendices

Appendix I Signature Pages and Responsible Persons for the Study

Signature Page – Protocol Lead

Study Title:	A Phase I/Ib Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Chinese Subjects with Locally Advanced Unresectable or Metastatic Solid Tumors with Expansion to Selected Indication(s)
Clinical Study Protocol Date / Version:	17 May 2019/ Version 4.0

Protocol Lead

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function / Title:	Medical Responsible
Institution:	Merck Serono (Beijing), Pharmaceutical R&D Co. Ltd.
Address:	25F NUO Center Office No.2A, Jiangtai Road · Chaoyang District, Beijing China 100016
Telephone number: Fax number: E-mail address:	PPD

Signature Page – Protocol Lead

Study Title:	A Phase I/Ib Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Chinese Subjects with Locally Advanced Unresectable or Metastatic Solid Tumors with Expansion to Selected Indication(s)
Clinical Study Protocol Date / Version:	17 May 2019/ Version 4.0

Protocol Lead

I approve the design of the clinical study:

_____ _____

Signature Date of Signature

Name, academic degree: PPD

Function / Title: Medical Responsible

Institution: Merck Serono (Beijing), Pharmaceutical R&D Co. Ltd.

Address: 25F NUO Center Office
No.2A, Jiangtai Road，Chaoyang District,
Beijing China 100016

Telephone number: PPD

Fax number:

E-mail address:

Signature Page – Coordinating Investigator

Study Title	A Phase I/Ib Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Chinese Subjects with Locally Advanced Unresectable or Metastatic Solid Tumors with Expansion to Selected Indication(s)
Clinical Study Protocol Date / Version	17 May 2019/ Version 4.0

I approve the design of the clinical study and I understand and will conduct the study according to the Clinical Study Protocol, any approved protocol amendments, International Council for Harmonization Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national la

PPD PPD PPD PPD

Signature Date of Signature

Name, academic degree: PPD

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Document No. CCI
Object No. CCI

Signature Page – Coordinating Investigator

Study Title	A Phase I/Ib Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Chinese Subjects with Locally Advanced Unresectable or Metastatic Solid Tumors with Expansion to Selected Indication(s)
Clinical Study Protocol Date / Version	17 May 2019/ Version 4.0

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

_____ _____

Signature Date of Signature

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

Signature Page – Principal Investigator

Study Title	A Phase I/Ib Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Chinese Subjects with Locally Advanced Unresectable or Metastatic Solid Tumors with Expansion to Selected Indication(s)
Clinical Study Protocol Date / Version	17 May 2019/ Version 4.0
Center Number	
Principal Investigator	

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

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

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

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Telephone number: E-mail address:	PPD

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

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Document No. CCI
Object No. CCI

CCI

[redacted]

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

Appendix III Guidance on Contraception

Birth control methods considered as highly effective.

According to the Clinical Trials Facilitation Group (CTFG) Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials, 2014, 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[2]
- intrauterine hormone-releasing system[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]Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential study 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. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

Appendix IV Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status[1]	
Grade	**Eastern Cooperative Oncology Group**
0	Fully active, able to carry on all predisease 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	Death

[1]Oken MM, Creech RH, Tormey DC et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-55.

Appendix V Protocol Amendment and List of Changes

Amendment 3.0:

Previous Protocol Amendments

Yes.

Table of Amendments

Amendment Number	Substantial (Y/N)	Date	Region or Country	Included in the Current Document (Y/N)
1.0	Y	10 May 2017	China	N
2.0	Y	23 February 2018	China	N
3.0	N	17 May 2019	China	Y

Rationale for Changes

This non-substantial amendment is executed due to Sponsor's decision to clarify the secondary endpoint and corresponding procedures as well as the correction period of concomitant medications.

Since only the titers of ADA are to be detected and analyzed in the study. Definition of ADA isotype as well as the neutralizing capacity against avelumab will not be evaluated. The secondary endpoint stated in the protocol "Serum titers, isotypes and neutralizing capacity of ADA against avelumab" therefore will be justified as "Serum titers of ADA against avelumab" only. Furthermore, there will not be procedures regarding analysis of isotypes or neutralizing capacity of ADA executed in this study.

The collection period of concomitant medications is revised to be in line with adverse event recording. Additional descriptions regarding explantion/clarification of specific term or procedures previously addressed by note to files are also included. The amendment also includes the correction of administrative, minor editorial changes and inconsistencies throughout the document that have been identified since the finalization of the clinical trial protocol.

Changes Made

The changes of this protocol amendment (Amendment No.3) are:

1. To change medical responsible personnel after replacement.

2. To clarify the secondary endpoint "Serum titers, isotypes and neutralizing capacity of ADA against avelumab". The secondary endpoint stated in the protocol will be justified as "Serum titers of ADA against avelumab" only.

3. To clarify the collection period of concomitant medication to be in line with adverse event recording.

4. Correct the footnotes of Table 1-1 and Table 1-2, unify the wording of CCI [redacted].

5. To add a footnote in Table 1-2 to address that the procedure of EOT, Safety Follow-up, as well as the Long-term Follow-up schedules for subjects in the 10 mg/kg weekly group are identical to Table 1-1.

6. To add the description "The time window for PK sampling time points is applicable for all scheduled PK sample collection for all subjects" to footnote 1 of Table 1-3, following the description of PK sampling time points.

7. To add a note to define anaphylaxis in No.13 exclusion criteria.

8. To add a note to clarify that "ECG QR value may not be applicable for some sites" to Section 7.4.4 Vital Signs, Physical Examinations, and Other Assessments.

9. To add a note to specify the original schedule means "the dosing schedule which is calculated according to first dose" to Section 5.1.3.1 Adverse Drug Reactions Requiring Treatment Discontinuation or Modifications.

The changes to be made to the clinical trial protocol are described below.

List of Changes

All changes with the exception of minor editorial changes to the Clinical Study Protocol text are presented in the table below. Additions and amended text are shown in bold. If the original Clinical Study Protocol text was already bold, changes are shown in bold and underlined, deletions are marked using strike through.

Comparison with Clinical Study Protocol Version 3.0, 23 February 2018 (Amendment No. 3)

Change	Section	Pages (V3.0)	Previous Wording	New Wording
Revised Sponsor medical responsible affiliations	Cover page	1	Jack Chen	~~Jack Chen~~ **Silvia Sun**
Revised and corrected the secondary enpoint	Synopsis Section 8.3.2	14 94	• Occurrence of TEAEs for all dose groups according to NCI-CTCAE v4.03. • Occurrence of treatment-related AEs for all dose groups according to NCI-CTCAE v4.03. • Serum titers, isotypes and neutralizing capacity of antidrug antibodies (ADA) against avelumab.	• Occurrence of TEAEs for all dose groups according to NCI-CTCAE v4.03. • Occurrence of treatment-related AEs for all dose groups according to NCI-CTCAE v4.03. • Serum titers~~, isotypes and neutralizing capacity~~ of antidrug antibodies (ADA) against avelumab.
Revised key exclusion criteria, add footnote to define anaphylaxis	Synopsis Section 5.3.2	16 52	• Any history of anaphylaxis, or uncontrolled asthma (ie, 3 or more features of partially controlled asthma).	• Any history of anaphylaxis*****, or uncontrolled asthma (ie, 3 or more features of partially controlled asthma). ***Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. It is characterized by rapidly developing, life-threatening problems (CTCAE Grading 3-5).**
Revised exclusion criteria 13, add footnote to define anaphylaxis	Section 5.3.2	52	13. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥3 NCI-CTCAE v4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma).	13. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥3 NCI-CTCAE v4.03), any history of anaphylaxis*****, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma). • ***Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. It is characterized by rapidly developing, life-threatening problems (CTCAE Grading 3-5).**
Added definition of "original schedule" to address the actions for managing adverse drug reactions	Section 5.1.3.1	47	• Any Grade 2 ADRs should be managed as follows: o Infusion should not be given in case of ongoing Grade 2 ADR on the day of study treatment administration. o Treatment can be resumed according to original schedule once ADR resolved to Grade ≤1. Up to 2 subsequent study drug doses may be omitted. If more than 2 doses are skipped, treatment may be resumed after consultation with the Medical Monitor.	• Any Grade 2 ADRs should be managed as follows: o Infusion should not be given in case of ongoing Grade 2 ADR on the day of study treatment administration. o Treatment can be resumed according to original schedule***** once ADR resolved to Grade ≤1. Up to 2 subsequent study drug doses may be omitted. If more than 2 doses are skipped, treatment may be resumed after consultation with the Medical Monitor. ***Original schedule is defined as "the dosing schedule calculated according to first dose".**

Change	Section	Pages (V3.0)	Previous Wording	New Wording
Clarified the reporting of ECG results regarding QR value may be different from study site according to routine practices at each site	Section 7.4.4	89	A 12 lead ECG will be performed and recorded at Clinical Screening and as indicated in the Schedule of Assessments (Table 1-1 and Table 1-2). Electrocardiograms will be performed in the supine position after the subject has been breathing quietly for 5 minutes. The ECG results will be used to evaluate heart rate, atrial-ventricular conduction, QR and QT intervals, and possible arrhythmias. Interpretation of the ECG trace must be made by a qualified physician and documented on the ECG eCRF. Each ECG trace should be labeled with the Study Number, Subject Identifier Number, and date, and kept in the source documents at the site. Significant findings that were present prior to the signing of informed consent (for main study) must be included in the Medical History eCRF page. All newly diagnosed or worsening conditions, signs and symptoms observed since screening, whether related to the study drug or not, are to be reported as AEs on the Adverse Event eCRF page. For women of childbearing potential, a serum β-human chorionic gonatropin pregnancy test will be carried out during Clinical Screening. Thereafter, a urine pregnancy test will be performed every 4 weeks during the Treatment Phase prior to administration of avelumab and at the visits indicated in the Schedule of Assessments (Table 1-1 and Table 1-2). Results of the most recent pregnancy test should be available prior to the next administration of avelumab. Female subjects who are not considered to be of childbearing potential (age-related natural [spontaneous] amenorrhea ≥ 12 consecutive months and increased FSH > 40 mIU/mL), or who are surgically sterile or are sexually inactive, are exempt from pregnancy testing.	A 12 lead ECG will be performed and recorded at Clinical Screening and as indicated in the Schedule of Assessments (Table 1-1 and Table 1-2). Electrocardiograms will be performed in the supine position after the subject has been breathing quietly for 5 minutes. The ECG results will be used to evaluate heart rate, atrial-ventricular conduction, QR* and QT intervals, and possible arrhythmias. Interpretation of the ECG trace must be made by a qualified physician and documented on the ECG eCRF. Each ECG trace should be labeled with the Study Number, Subject Identifier Number, and date, and kept in the source documents at the site. Significant findings that were present prior to the signing of informed consent (for main study) must be included in the Medical History eCRF page. All newly diagnosed or worsening conditions, signs and symptoms observed since screening, whether related to the study drug or not, are to be reported as AEs on the Adverse Event eCRF page. For women of childbearing potential, a serum β-human chorionic gonatropin pregnancy test will be carried out during Clinical Screening. Thereafter, a urine pregnancy test will be performed every 4 weeks during the Treatment Phase prior to administration of avelumab and at the visits indicated in the Schedule of Assessments (Table 1-1 and Table 1-2). Results of the most recent pregnancy test should be available prior to the next administration of avelumab. Female subjects who are not considered to be of childbearing potential (age-related natural [spontaneous] amenorrhea ≥ 12 consecutive months and increased FSH > 40 mIU/mL), or who are surgically sterile or are sexually inactive, are exempt from pregnancy testing. ***ECG QR value may not be applicable in some study sites according to site routine practice (which does not report QR value).**
Added clarification regarding PK sampling time window is applicable for all sugjects	Section 7.5	90	*The time window for PK sampling time points are: +10 minutes for the end of infusion sample collection on Day 1; ± 10 minutes for 0.5 and 1 hour after the end of infusion; ± 20 minutes for 2, 4, and 6 hours after the end of infusion; ± 2 hours for 12, 24, 36, 48, and 168 hours after the end of infusion.	*The time window for PK sampling time points are: +10 minutes for the end of infusion sample collection on Day 1; ± 10 minutes for 0.5 and 1 hour after the end of infusion; ± 20 minutes for 2, 4, and 6 hours after the end of infusion; ± 2 hours for 12, 24, 36, 48, and 168 hours after the end of infusion. **The time window for PK sampling time points is**

Change	Section	Pages (V3.0)	Previous Wording	New Wording
				applicable for all subjects scheduled PK sample collection for all subjects.

Changes in tables (Amendment Version 3.0)

Table 1-1 Schedule of Assessments for Subjects Receiving Avelumab Once Every 2 Weeks

Assessment		Clinical Screening /Baseline Assessments	Treatment Phase[1]								EOT Visit[2]	Safety Follow-up[2]		Long-term Follow-up[2]
		≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	Until progre.	Within	30 day	Phone	Every
			W1	W3	W5	W7	W9	W11	W13					
			D1	D15	D29	D43	D57	D71	D85					
CCI														
Written informed consent		X												
Inclusion/exclusion criteria		X												
Medical history[7]		X												
Demographic data		X												
Hepatitis B, hepatitis C, and HIV tests		X												
Full physical examination[8]		X									X	X		
Symptom-directed physical exam[8]			As indicated throughout the Treatment Phase											
Height		X												

Assessment	Clinical Screening /Baseline Assessments	Treatment Phase[1]							EOT Visit[2]	Safety Follow-up[2]		Long-term Follow-up[2]
	≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	Until progr.	Within	30 day	Phone	Every
		W1	W3	W5	W7	W9	W11	W13					
		D1	D15	D29	D43	D57	D71	D85					
Vital signs	X	X	X	X	X	X	X	X	2-weekly	X	X		
Weight	X	X	X	X	X	X	X	X	2-weekly	X	X		
ECOG PS[9]	X	X[9]	X	X	X	X	X	X	2-weekly	X	X		
Enrolment (if eligible)[10]	X												
DLT assessment[11]		X	X[11]										
12-lead ECG	X	X	X	X	As indicated and decided by Investigator					X			
Hematology and hemostaseology	X		X	X	X	X	X	X	2-weekly	X	X		
Core serum chemistry[12]			X	X		X	X		2-weekly		X		
Full serum chemistry[13]	X				X			X	6-weekly	X			
Full urinalysis[14]	X									X			
Basic urinalysis[14]					X			X	6-weekly				
Serum beta-hCG pregnancy test (if applicable)[15]	X												
Urine pregnancy test (if applicable)[15]		X		X		X		X	4-weekly	X			

Assessment		Clinical Screening /Baseline Assessments	Treatment Phase[1]								EOT Visit[2]	Safety Follow-up[2]		Long-term Follow-up[2]
		≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	Until progre.	Within	30 day	Phone	Every
			W1	W3	W5	W7	W9	W11	W13					
			D1	D15	D29	D43	D57	D71	D85					
CCI [redacted]														
Premedication[21]			X	X	X	X								
Avelumab administration			X	X	X	X	X	X	X	2-weekly				
Concomitant medication and procedures[22]		Collected at each study visit until through the 30-day Safety Follow-up Visit												
AE collection[23]		AEs are collected through the 30-day Safety Follow-up Visit Treatment-related nonserious AEs are collected until the 90-day Safety Follow-up Phone Call												
SAE collection[24]		All SAEs are documented until the 90-day Safety Follow-up Phone Call Ongoing SAEs at the 30-day Safety Follow-up Visit will be followed up												
Free T4 and TSH		X				X			X	6-weekly	X	X		
PK sampling[25]		See Table 1-3												
ADA sampling[25]		See Table 1-3												

Assessment		Clinical Screening /Baseline Assessments	Treatment Phase[1]								EOT Visit[2]	Safety Follow-up[2]		Long-term Follow-up[2]
		≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	Until progre.	Within	30 day	Phone	Every
			W1	W3	W5	W7	W9	W11	W13					
			D1	D15	D29	D43	D57	D71	D85					
Survival[26]			X	X	X	X	X	X	X	Every visit	X	X	X	X
Further anticancer therapy[26]												X	X	X

ADA: antidrug antibody; AE: adverse event; CR: complete response; CT: computed tomography; D: Day; DLT: dose-limiting toxicity; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group performance status; EOT: End-of-Treatment; hCG: human chorionic gonadotropin; HIV: Human immunodeficiency virus; ICF: Informed consent form; IMP: investigational medicinal product; MRI: magnetic resonance imaging; PD: progressive disease; CCI PK: pharmacokinetics; PR: partial response; RECIST: response evaluation criteria in solid tumors; SAE: serious adverse event; T4: thyroxine; TSH: thyroid-stimulating hormone; V: Visit; W: Week.

1. A time window of up to 3 days before or 1 day after the scheduled visit day (- 3/+ 1 days) is permitted for all study procedures (except for PK sampling visits on Day 2 and 3, see Table 1-3). The calculation of the dose of avelumab will be based on the weight of the subject determined within 72 hours prior to the day of drug administration.
2. All subjects will have an EOT Visit within 7 days after the decision to discontinue avelumab. In addition, subjects will be followed every 12 weeks (± 7 days) for survival (including assessment of any further anticancer therapy).

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4. If another anticancer therapy is administered before the end of this 7-day period, the EOT Visit should be conducted prior to the start of this new therapy, if possible. The EOT Visit may be performed on the day of the decision to discontinue avelumab.

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CCI [redacted]

7. Medical history should include history of cancer, previous and ongoing medications, previous surgeries, radiotherapies, baseline medical conditions, smoking and alcohol history, and family cancer history.
8. A full physical examination will be conducted at Clinical Screening, at the EOT Visit and at the 30-day Safety Follow-up Visit. During the Treatment Phase, the physical examination will be symptom-directed.
9. If the Clinical Screening ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1/Cycle 1 Day 1.
10. Enrolment will be done after confirmation that the subject meets all screening inclusion criteria (Section 5.3.1) without matching any exclusion criterion (Section 5.3.2).
11. The observation period for DLTs is the 21-day period after the first administration of avelumab for subjects with data used for implementing the dose-escalation algorithm for dose determination (the DLT assessment is not applicable for the 6 subjects in 10 mg/kg once weekly cohort).
12. Core serum chemistry includes liver function panel (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, bilirubin), acute chemistry panel (sodium, potassium, chloride, blood urea nitrogen/total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). If full and core chemistry are scheduled at the same visit, the full chemistry will be performed.
13. Full chemistry panel and other laboratory studies are detailed in Section 7.4.3. Follicle-stimulating hormone at Clinical Screening, if applicable.
14. Full urinalysis (protein content required, and optional parameters albumin and immunoglobulin G to be tested depending on study site capability) at Clinical Screening/baseline, and EOT; basic urinalysis (protein content only) on Days 43 and 85, and then every 6 weeks thereafter prior to administration of avelumab. If urinalysis (full or basic) is positive for protein, sediment will be evaluated.
15. In serum at Clinical Screening; in urine thereafter. Results of the most recent pregnancy test should be available prior to next administration of avelumab.
16. A CT scan or MRI of the chest, abdomen, and pelvis (if MRI is used, CT of chest is mandatory) will be performed within 14 days prior to the first administration of avelumab in order to document baseline status of the tumor disease using RECIST 1.1 target and nontarget lesions. If a CT/MRI scan was performed within 2 weeks prior to the first administration of avelumab and is available and of adequate quality, the screening CT/MRI does not need to be performed. Tumor evaluation at each visit after screening may not exactly be on the same day for study drug treatment, instead it may differ from the scheduled visit date. The tumor evaluation has a tumor assessment window of 5 days prior to the planned tumor assessment date (- 5 days) according to first dosing date throughout the Treatment Phase (Section 7.1.2)
17. Brain CT/MRI scan (either, with contrast preferred) is required at Clinical Screening if not performed within the previous 14 days. Thereafter, brain CT/MRI scan should be done if clinically indicated by development of new specific symptoms. A bone scan should be done at Clinical Screening and beyond as clinically indicated. Bone metastases detected at Clinical Screening need to be followed at tumor evaluation visits.
18. The tumor assessment visit time window is ~~5 days prior to dosing (- 5 days) for tumor evaluation~~ **5 days prior to the planned tumor assessment date (- 5 days) according to first dosing day** during the Treatment Phase, and ± 5 days after the EOT Visit. CT or MRI scan (if MRI is used, CT of chest is mandatory) should always be used. CT/MRI scan will be performed at baseline, every 6 weeks (- 5 days) during the first 12 months of the study, and then every 12 weeks (- 5 days) until progression.

CCI [redacted]

20. Disease response determinations, including progressive disease assessments associated with study endpoints, will be supported by tumor assessments performed by Investigator.

21. Premedication is mandatory approximately 30 to 60 minutes prior to the first 4 doses of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate. However, the prophylactic use of systemic corticosteroids is not permitted.
22. Concomitant medications and procedures will be documented at each study visit ~~until the EOT Visit~~**until the 30-day Safety Follow-up Visit**.
23. All AEs will be documented at each study visit until the 30-day Safety Follow-up Visit. After this visit, only treatment-related nonserious AEs have to be documented until the 90-day Safety Follow-up Phone Call.
24. All SAEs will be documented at each study visit until the 90-day Safety Follow-up Phone Call. After this, all ongoing SAEs must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as lost to follow-up. Any SAE assessed as related to study drug must be reported whenever it occurs, irrespective of the time elapsed since the last administration of avelumab. At 90 days (± 5 days) after the last dose of avelumab, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related nonserious AEs.
25. Blood samples for PK and ADA will be collected as detailed in Table 1-3.
26. Subjects will be followed every 12 weeks (± 7 days) for survival (including assessment of any further anticancer therapy).

Table 12-3 Schedule of Assessments for Subjects Receiving Avelumab Once a Week for the First 12 Weeks Followed by Once Every 2 Weeks (10 mg/kg Once Weekly Cohort)

Assessment[2]	Clinical Screening /Baseline Assessments	Treatment Phase[1]													
	≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	Until progression
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13 (Roll-over into Once every-2-weeks dosing)	
		D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85	
CCI [redacted]															

Assessment[2]	Clinical Screening /Baseline Assessments	Treatment Phase[1]													
	≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	Until progression
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13 (Roll-over into Once every-2-weeks dosing)	
		D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85	
Written informed consent	X														
Inclusion/exclusion criteria	X														
Medical history[43]	X														
Demographic data	X														
Hepatitis B, hepatitis C and HIV tests	X														
Full physical examination[54]	X														
Symptom-directed physical exam[54]		As indicated throughout the Treatment Phase													
Height	X														
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly
ECOG PS[65]	X	X[65]	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly
Enrolment (if eligible)[76]	X														
12-lead ECG	X	X	X	X	As indicated and decided by Investigator										

Assessment[2]	Clinical Screening /Baseline Assessments	Treatment Phase[1]													
	≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	Until progression
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13 (Roll-over into Once every-2-weeks dosing)	
		D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85	
Hematology and hemostaseology	X		X	X	X	X	X	X	X	X	X	X	X	X	2-weekly
Core serum chemistry[8~~7~~]			X	X	X	X	X		X	X	X	X	X		2-weekly
Full serum chemistry[9~~8~~]	X							X						X	6-weekly
Full urinalysis[10~~9~~]	X														
Basic urinalysis[10~~9~~]								X						X	6-weekly
Serum beta-hCG pregnancy test (if applicable)[11~~10~~]	X														
Urine pregnancy test (if applicable)[11~~10~~]		X				X				X				X	4-weekly
CCI [redacted]															
Premedication[17~~16~~]		X	X	X	X										

Assessment[2]	Clinical Screening /Baseline Assessments	Treatment Phase[1]													
	≤ Day -14 to Day -1	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	Until progression
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13 (Roll-over into Once every-2-weeks dosing)	
		D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85	
Avelumab administration		X	X	X	X	X	X	X	X	X	X	X	X	X	2-weekly
Concomitant medication and procedures	Collected at each study visit ~~until the EOT Visit~~ **until the 30-day Safety Follow-up Visit**														
AE collection[18~~17~~]	AEs are collected through the 30-day Safety Follow-up Visit Treatment-related nonserious AEs are collected until the 90-day Safety Follow-up Phone Call														
SAE collection[19~~18~~]	All SAEs are documented until the 90-day Safety Follow-up Phone Call Ongoing SAEs at the 30-day Safety Follow-up Visit will be followed up														
Free T4 and TSH	X							X						X	6-weekly
PK sampling[20~~19~~]	See Table 1-4														
ADA sampling[20~~19~~]	See Table 1-4														
Survival[21~~20~~]		X	X	X	X	X	X	X	X	X	X	X	X	X	Every visit
Further anticancer therapy[21~~20~~]	Collected through Safety Follow-up and Long-term Follow-up														

ADA: antidrug antibody; AE: adverse event; CR: complete response; CT: computed tomography; D: Day; DLT: dose-limiting toxicity; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group performance status; EOT: End-of-Treatment; hCG: human chorionic gonadotropin; HIV: Human immunodeficiency virus; ICF: Informed consent form; IMP: investigational medicinal product; MRI: magnetic resonance imaging; PD; progressive disease; CCI; PK: pharmacokinetics; PR: partial response; RECIST: response evaluation criteria in solid tumors; SAE: serious adverse event; T4: thyroxine; TSH: thyroid-stimulating hormone; V: Visit; W: Week.

1. A time window of 1 day before or 1 day after the scheduled visit day (- 1/+ 1 days) is permitted for all study procedures while subjects receiving avelumab once weekly (12 consecutive weeks). A time window of up to 3 days before or 1 day after the scheduled visit day (- 3/+ 1 days) is permitted for all study procedures while subjects receiving avelumab once every 2 weeks (Week 13 and thereafter). The calculation of the dose of avelumab will be based on the weight of subject determined within 72 hours prior to the day of drug administration.
2. **Columns of EOT Visit, Safety Follow-up, and the Long-term Follow-up Visits are omitted due to layout readability. The procedures at EOT Visit, Safety Follow-up, and the Long-term Follow-up are identical to the procedures planned for subjects receiving avelumab once every 2 weeks (as shown in Table 1-1).**
3. ~~2.~~ Mandatory for study entry. A recently obtained formalin-fixed, paraffin-embedded block containing tumor tissue (biopsy from a non-irradiated area within 6 months) or 12 or more slides (preferably, approximately 25 slides) is required for all subjects. Endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies, and surgical specimens are suitable. Fine needle aspiration biopsies are not suitable. Samples can be provided as block or slides.
4. ~~3.~~ Medical history should include history of cancer, previous and ongoing medications, previous surgeries, radiotherapies, baseline medical conditions, smoking and alcohol history, and family cancer history.
5. ~~4.~~ A full physical examination will be conducted at Clinical Screening, at the EOT Visit and at the 30-day Safety Follow-up Visit. During the Treatment Phase, the physical examination will be symptom-directed.
6. ~~5.~~ If the Clinical Screening ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Visit 1/Cycle 1 Day 1.
7. ~~6.~~ Enrolment will be done after confirmation that the subject meets all screening inclusion criteria (Section 5.3.1) without matching any exclusion criterion (Section 5.3.2).
8. ~~7.~~ Core serum chemistry includes liver function panel (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, bilirubin), acute chemistry panel (sodium, potassium, chloride, blood urea nitrogen/total urea, creatinine, glucose), and mineral panel (magnesium, phosphorus, calcium). If full and core chemistry are scheduled at the same visit, the full chemistry will be performed.
9. ~~8.~~ Full chemistry panel and other laboratory studies are detailed in Section 7.4.3. Follicle-stimulating hormone at Clinical Screening, if applicable.
10. ~~9.~~ Full urinalysis (protein content required, and optional parameters albumin and immunoglobulin G to be tested depending on study site capability) at Clinical Screening/baseline, and EOT; basic urinalysis (protein content only) on Days 43 and 85, and then every 6 weeks thereafter prior to administration of avelumab. If urinalysis (full or basic) is positive for protein, sediment will be evaluated.
11. ~~10.~~ In serum at Clinical Screening; in urine thereafter. Results of the most recent pregnancy test should be available prior to next administration of avelumab.

CCI [redacted]

CCI [redacted]

17. ~~16.~~ Premedication is mandatory approximately 30 to 60 minutes prior to the first 4 doses of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate. However, the prophylactic use of systemic corticosteroids is not permitted.
18. ~~17.~~ All AEs will be documented at each study visit until the 30-day Safety Follow-up Visit. After this visit, only treatment-related nonserious AEs have to be documented until the 90-day Safety Follow-up Phone Call.
19. ~~18.~~ All SAEs will be documented at each study visit until the 90-day Safety Follow-up Phone Call. After this, all ongoing SAEs must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as lost to follow-up. Any SAE assessed as related to study drug must be reported whenever it occurs, irrespective of the time elapsed since the last administration of avelumab. At 90 days (± 5 days) after the last dose of avelumab, subjects will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related nonserious AEs.
20. ~~19.~~ Blood samples for PK and ADA will be collected as detailed in Table 1-4.
21. ~~20.~~ Subjects will be followed every 12 weeks (± 7 days) for survival (including assessment of any further anticancer therapy).

Table 12-4 Schedule of Assessments – Pharmacokinetic and Antidrug Antibody Sampling for Subjects Receiving Avelumab Once Every 2 Weeks

Assessment	Treatment Phase														EOT Visit	Safety Follow-up
	V1					V2		V3		V4		V7		Until Progression	Within 7 days after decision to discontinue IMP	30 days (±5 days) after last IMP
	W1 D1		W1 D2	W1 D3	W2 D8	W3 D15		W5 D29		W7 D43		W13 D85				
	Prior to infusion	End of infusion				Prior to infusion	End of infusion	Prior to infusion	End of infusion	Prior to infusion	End of infusion	Prior to infusion	End of infusion			
PK sampling[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	6-weekly up to W25 (D169), then 12-weekly	X	X
ADA sampling[2]	X					X		X		X		X		6-weekly up to W25 (D169), then 12 weekly to EOT		X

ADA: antidrug antibody; D: Day; EOT: End-of-Treatment; IMP: investigational medicinal product; PK: pharmacokinetics; V: Visit; W: Week.

1. For subjects receiving avelumab once every 2 weeks, PK serum samples will be collected at the following time points:
   - Day 1: within 2 hours prior to and at the end of the 1-hour infusion, and at 0.5, 1, 2, 4, 6, and 12 hours after the end of the infusion.
   - Day 2: 2 samples will be collected 24 and 36 hours after the end of the infusion.
   - Day 3: a single sample will be collected 48 hours after the end of the infusion.
   - Day 8: a single sample will be collected 168 hours after the end of the infusion.
   - Days 15, 29, 43, 85, 127, and 169 (Week 25): samples will be collected within 2 hours prior to infusion (trough value) and immediately after the infusion is completed (peak value).
   - Every 12 weeks beyond Week 25: a single sample will be collected within 2 hours prior to infusion (trough value).
   - EOT Visit.
   - 30-day Safety Follow-up Visit.

*The time window for PK sampling timepoints are: + 10 minutes for the end of infusion sample collection on Day 1; ± 10 minutes for 0.5 and 1 hour after the end of infusion; ± 20 minutes for 2, 4, and 6 hours after the end of infusion; ± 2 hours for 12, 24, 36, 48, and 168 hours after the end of infusion. **The time window for PK sampling time points is applicable for all scheduled PK sample collection for all subjects**.

2. For subjects receiving avelumab once every 2 weeks, ADA serum samples will be collected at the following time points:
   - Day 1 (baseline): the baseline sample should be collected within 2 hours prior to the first administration of avelumab, ie, either during Clinical Screening or predose on Day 1.
   - Days 15, 29, 43, 85, 127 and 169: samples will be collected within 2 hours prior to infusion.
   - After Day 169, 1 sample (within 2 hours prior to infusion) every 12 weeks until the EOT Visit.
   - 30-day Safety Follow-up Visit.