Clinical Trial Protocol

Clinical Trial Protocol Number	MS100070-0306
Title	Open-label, Phase I/II study to evaluate pharmacokinetics, pharmacodynamics, safety, and anticancer activity of avelumab in pediatric subjects from birth to less than 18 years of age with refractory or relapsed solid tumors and lymphoma
Short Trial Name	Phase I/II study of avelumab in pediatric cancer subjects
Trial Phase	I/II
IND Number	CCI [redacted]
EudraCT Number	2017-002985-28
Coordinating Investigator	PPD
Sponsor	For all countries except the USA: Merck KGaA, Frankfurter Str. 250 64293 Darmstadt, Germany For sites in the USA: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821, USA Medical Responsible: PPD Office phone: PPD Mobile phone: PPD
Clinical Trial Protocol Version	15 September 2017/Version 2.0
Replaces Clinical Trial Protocol Version	14 August 2017/Version 1.0
Current Clinical Trial Protocol Amendment	Not applicable

Table of Contents

CCI

Table of Tables

Table of Figures

List of Abbreviations

ACTH	Adrenocorticotropic hormone
ADA	Antidrug antibody
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BOR	Best overall response
BUN	Blood urea nitrogen
CL	Clearance
C_{EOI}	Plasma concentration observed at the end of infusion
C_{max}	Maximum plasma concentration observed postdose
C_{trough}	Minimum postdose trough concentration
CR	Complete response
CRO	Contract Research Organization
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DL1	Starting dose level of 10 mg/kg avelumab every 2 weeks
DL -1	Lower dose level of 3 mg/kg avelumab every 2 weeks
DL2	Increased dose level of up to 20 mg/day avelumab every 2 weeks
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full analysis set
^{18}FDG-PET/CT	Fluorodeoxyglucose F 18-positron emission tomography/ computed tomography
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GeoCV	Geometric coefficient of variation
GeoMean	Geometric mean
GGT	Gamma-glutamyltransferase
HBV	Hepatitis B virus

HCV	Hepatitis C virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
IMP	Investigational Medicinal Product
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
CCI	
IRR	Infusion-related reaction
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
CCI	
IRT	Interactive response technology
IV	Intravenous
MCC	Merkel cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival

PD	Progressive disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
CCI	[redacted]
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PR	Partial response
pT	Target probability rate
RBC	Red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	Recommended Phase II dose
SAE(s)	Serious adverse event(s)
SAP	Statistical Analysis Plan
SD	Stable disease
SMC	Safety Monitoring Committee
$t_{1/2}$	Half-life
T4	Free thyroxine
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
TTR	Time to response
ULN	Upper limit of normal

1 Synopsis

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Trial Phase	I/II
IND Number	CCI [redacted]
FDA covered trial	Yes
EudraCT Number	2017-002985-28
Coordinating Investigator	PPD
Sponsor	For all countries except the USA: Merck KGaA, Frankfurter Str. 250 64293 Darmstadt, Germany For sites in the USA: EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821, USA
Trial centers/countries	Approximately 50 sites in North America, Europe, Middle East, South America, and Asia Pacific, including approximately 10 sites in the USA
Planned trial period (first subject in-last subject out)	First subject in: January 2018 Last subject out: January 2022
Trial Registries	EU Clinical Trials Register: https://www.clinicaltrialsregister.eu/ (registration #2017-002985-28) ClinicalTrials.gov (USA): https://clinicaltrials.gov/ (registration # to come)

Objectives:

Primary objectives

Phase I

- To evaluate the safety and tolerability of avelumab
- To determine the recommended Phase II dose (RP2D) of avelumab in pediatric subjects 0 to < 18 years of age with solid tumors and lymphoma

Phase II

- To assess antitumor activity of avelumab by determining the objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and as adjudicated by the Investigator in 2 expansion cohorts in specified tumor types in pediatric subjects treated with avelumab

Secondary objectives

Phase I

- To assess antitumor activity of avelumab by determining the ORR according to RECIST 1.1 and as adjudicated by the Investigator in pediatric subjects with solid tumors and lymphoma treated with avelumab
- To assess progression-free survival (PFS) based on Investigator assessments, duration of response (DOR), time to response (TTR), and overall survival (OS)
- To characterize the pharmacokinetics (PK) of avelumab
- To assess the immunogenicity of avelumab
- To evaluate programmed death ligand 1 (PD-L1) expression; tumor-infiltrating T-cell activity; T-cell population; and T-cell, B-cell, and NK-cell numbers in tumor tissue at Baseline and at confirmed progression (if tumor tissue is obtained)
- To measure changes in vaccination-related antibody concentrations (diphtheria, tetanus, and pneumococcal conjugate)

Phase II

- To evaluate the safety and tolerability of avelumab
- To assess PFS based on Investigator assessments, TTR, DOR, and OS
- To characterize the PK of avelumab
- To assess the immunogenicity of avelumab
- To evaluate PD-L1 expression; tumor-infiltrating T-cell activity; T-cell population; and T-cell, B-cell, and NK-cell numbers in tumor tissue at Baseline and at confirmed progression (if tumor tissue is obtained)
- To measure changes in vaccination-related antibody concentrations (diphtheria, tetanus, and pneumococcal conjugate)

Methodology:

This is a multicenter, open-label, international, Phase I/II study to evaluate the dose, safety and tolerability, antitumor activity, PK, and pharmacodynamics of avelumab in pediatric subjects 0 to < 18 years of age with refractory or relapsed malignant solid tumors (including central nervous system tumors) and lymphoma for which no standard therapy is available or for which the subject is not eligible for the existing therapy.

The study will consist of 2 parts: the dose-finding part (Phase I) and the tumor-specified expansions part (Phase II). In the Phase I dose-finding part of the study, the RP2D of avelumab in children will be determined. Subjects will be enrolled in sequential cohorts of 3 to 6 subjects each. At least 12 subjects must be evaluable for the primary analysis. The starting dose will be the same as the currently recommended dose in adults, 10 mg/kg every 2 weeks. The safety of this dose level and the need for dose de-escalation will be based on the frequency of dose-limiting toxicities (DLTs) to ensure that any given dose level does not exceed the maximum tolerated dose (MTD). The MTD estimate is the highest dose tested of avelumab associated with the occurrence of DLTs within the first 2 cycles of treatment in < 33% of subjects, provided that a higher dose level of avelumab was tested and had an associated DLT rate ≥ 33%. If the DLT rate within the first 2 cycles of treatment is < 33% for all tested dose levels, then the MTD will not have been reached. If the starting dose level is confirmed as safe, this dose will be selected as RP2D if it provides similar exposure in children to those in adults. If exposure is not adequate, a decision can be made to escalate to a dose level up to 20 mg/kg.

Once the RP2D is determined, Phase II will begin with 2 expansion cohorts in 2 specified tumor types. The specified tumor types will be selected based on emerging data from this study and other ongoing studies. These data may include clinical data with avelumab or with other immune checkpoint inhibitors, or preclinical data providing additional rationale for a specific tumor type. Each expansion cohort will follow Simon's Optimal Two-stage Design. If there are 2 or more subjects with confirmed objective responses within the first 23 subjects treated at the RP2D, then an additional 33 subjects will be enrolled and treated at that dose level. If there are 1 or no subjects with confirmed objective responses in the first 23 subjects treated at the RP2D within a minimum follow-up of 16 weeks, then the cohort will be closed for further enrollment.

The study is aimed at defining a single RP2D in the age group 0 to < 18 years. However, if at any time during the study, data suggest a difference in tolerability by age, this will be discussed with the Safety Monitoring Committee (SMC). The following rules will be used:

- The first 3 subjects in the initial cohort will be 1 to < 18 years of age.
- Subsequent cohorts may be open to subjects 0 to <18 years of age, or a narrower age range, based on emerging data, as agreed by the SMC.

Avelumab will be administered every 2 weeks until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurs. A cycle is defined as 2 weeks. In Phase I, the DLT observation period is defined as a 28-day period (2 cycles) beginning with the first avelumab administration. Each subject will be followed for 12 months after his/her end of treatment.

Baseline imaging will be performed within 28 days prior to registration and Cycle 1 Day 1 treatment in order to establish Baseline disease status of target and nontarget lesions according to RECIST 1.1. Acceptable modalities include CT scans (neck, chest, abdomen, and pelvis as

needed), and CT chest with contrast together with MRI of the abdomen and pelvis. The same imaging modality (CT or MRI) should be used throughout the study for a particular subject. A bone scan (bone scintigraphy) or fluorodeoxyglucose F 18-positron emission tomography/CT (^{18}FDG-PET/CT) is required at Baseline in subjects with tumors known to metastasize to bone, with subsequent radiographic disease re-evaluation only if bone metastases are present at Baseline. Baseline CNS imaging will not be required with the exception of symptomatic subjects to evaluate for CNS metastases.

A CT or MRI will be performed every 8 weeks for the first 24 weeks, then every 12 weeks thereafter (a window of 5 days prior to dosing is allowed). If partial response (PR), complete response (CR), or progressive disease (PD) is observed according to RECIST 1.1, a confirmation CT or MRI should be performed according to RECIST 1.1, preferably at the regularly scheduled 8-week assessment interval, but no sooner than 4 weeks after the initial documentation of response or confirmed disease progression. Tumor assessment should be repeated at the End of Treatment Visit if more than 4 weeks have passed since the last evaluation.

Planned number of subjects:

Phase I: 12 to 36 subjects

Phase II: 46 to 112 subjects (23 to 56 subjects per tumor type) for 2 cohorts

Primary endpoints:

Phase I

- Occurrence and severity of treatment-emergent adverse events (TEAEs) ≥ Grade 3 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03
- DLTs to determine the RP2D.

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Secondary endpoints:

Phase I

- Confirmed BOR according to RECIST 1.1 and as adjudicated by the Investigator
- DOR, TTR, PFS per RECIST 1.1 and as adjudicated by the Investigator, and OS
- Occurrence and severity of TEAEs, AEs of special interest, and treatment-related AEs, and incidence of laboratory abnormalities, as graded by NCI-CTCAE v4.03
- Vital signs (including blood pressure and heart rate)
- Single- and multiple-dose PK profiles of avelumab (ie, C_{max}, AUC, $t_{1/2}$, and C_{trough}, as data permit)
- Immunogenicity as measured by avelumab ADA, including neutralizing antibodies (NAbs)
- Assessment of tumor PD-L1 expression; tumor-infiltrating T-cell activity; T-cell population; and T-cell, B-cell, and NK-cell numbers at Baseline and at confirmed progression (if tumor tissue is obtained)
- Vaccination-related antibody concentrations.

[redacted]

Pharmacokinetics:

Samples for PK assessments will be collected from all subjects in the study, as per the Schedule of Assessments - PK and ADA Sampling, and initially stratified by weight (< 10 kg and ≥ 10 kg). For the first 36 subjects, PK samples will be collected during treatment Cycles 1, 2, 3, 5, 7, 8, 13, 19, 25, and every 6 cycles thereafter; at the End of Treatment Visit; and at the 30-Day Safety Follow-up Visit. For the rest of the subjects, more sparse PK samples will be collected.

Other assessments:

Blood samples for analysis of ADA (including NAbs) will be drawn predose at Cycles 1, 2, 3, 5, 7, 13, 19, 25, and every 6 cycles thereafter, as well as at the End of Treatment Visit and the 30-Day Safety Follow-up Visit. Accompanying PK samples will be collected as the same time. [redacted]

Key inclusion criteria:

Male or female subjects 0 to < 18 years of age at the time of first treatment dose with histologically or cytologically confirmed solid malignant tumors or lymphoma; confirmed progression on or refractory to standard therapy or no standard therapy available; availability of archival formalin-fixed, paraffin-embedded block containing tumor tissue, or slides, or a fresh/recent tumor biopsy prior to avelumab treatment; adequate bone marrow, kidney, and liver function.

Key exclusion criteria:

Prior therapy with any antibody or drug targeting T-cell coregulatory proteins; concurrent anticancer treatment or immunosuppressive agents; prior organ transplantation; significant acute or chronic infections; other significant diseases or conditions that might impair the subject's tolerance of trial treatment.

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

Subjects will receive an intravenous (iv) infusion of avelumab over 1 hour (-10 minutes/+20 minutes, or 50 to 80 minutes) once every 2 weeks. To mitigate infusion-related reactions, a premedication regimen of an antihistamine (H1 receptor blocker such as diphenhydramine) and acetaminophen (paracetamol; iv or oral equivalent) is mandatory 30 to 60 minutes prior to each dose of study drug for the first 4 avelumab administrations. This can be modified based on local treatment standards and guidelines, as appropriate. Steroid premedication specifically for avelumab is not permitted.

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 within 10% of the weight used for the previous dose calculation. Subjects will receive avelumab once every 2 weeks until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurs.

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

Not applicable.

Planned trial and treatment duration per subject:

Treatment with avelumab will continue as per protocol specifications until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurs.

Subjects who have experienced a CR should be treated for a minimum of 12 months based on clinical judgment of benefit and/or until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurs, after confirmation of response as specified in the protocol.

Each subject will be followed for an additional 12 months after the subject's end of treatment.

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Statistical methods:

Descriptive statistics will be used to summarize the trial results. Qualitative variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by confidence intervals. Statistics for continuous variables may include means, medians, ranges, and appropriate measures of variability. In Phase I, descriptive statistics will be examined for indications of DLT. In Phase II, BOR will be evaluated according to RECIST 1.1 based on Investigator assessments of disease at different time points.

Table 1 **Schedule of Assessments – Avelumab**

		Treatment Period[a] (-3/+1 days) 1 Cycle = 14 Days								End Of Treatment/Follow-Up[b]			
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Until EOT	EOT/ Withdrawal Visit[b]	Safety Follow-up[c]		Survival Follow-up[d]
Assessments	Screening (≤ 28 Days Prior to Enrollment)	Week 1 (Day 1)	Week 3 (Day 15)	Week 5 (Day 29)	Week 7 (Day 43)	Week 9 (Day 57)	Week 11 (Day 71)	Week 13 (Day 85)	> Week 13 (Day 85)	Within 7 Days of Decision to Discontinue	Visit 30 Days (± 5 days) After Last Tx	Phone Call 90 Days (± 5 days) After Last Tx	Every 12 Weeks (± 1 Week) After Last Tx
Written informed consent/assent	X												
Written [redacted] informed consent/ assent for optional substudies if applicable	X												
Inclusion/exclusion criteria	X												
Medical history	X												
Disease history (including prior treatment regimens)	X												
Demographic data	X												
Physical examination, weight, and height[e]	X	X	X	X	X	X	X	X	Q2 weeks	X	X		
Vital signs[f]	X	X	X	X	X	X	X	X	Q2 weeks	X	X		
Performance status[g]	X	X	X	X	X	X	X	X	Q2 weeks	X	X		
12-lead ECG[h]Error! Reference source not found.	X	X	X	X						X	X		
Bone growth assessments[i]	X												Performed annually

		Treatment Period[a] (-3/+1 days) 1 Cycle = 14 Days								End Of Treatment/Follow-Up[b]			
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Until EOT	EOT/ Withdrawal Visit[b]	Safety Follow-up[c]		Survival Follow-up[d]
Assessments	Screening (≤ 28 Days Prior to Enrollment)	Week 1 (Day 1)	Week 3 (Day 15)	Week 5 (Day 29)	Week 7 (Day 43)	Week 9 (Day 57)	Week 11 (Day 71)	Week 13 (Day 85)	> Week 13 (Day 85)	Within 7 Days of Decision to Discontinue	Visit 30 Days (± 5 days) After Last Tx	Phone Call 90 Days (± 5 days) After Last Tx	Every 12 Weeks (± 1 Week) After Last Tx
Concomitant medications and procedures[j]	X	Concomitant medications and procedures are collected through the Safety Follow-up Visit									X		
AE collection[k]	AEs are collected through the Safety Follow-up Visit Treatment-related non-serious AEs are collected until the 90-day Safety Follow-up Phone Call.[b]											X	
SAE collection[k]	All SAEs are documented through the 90-day Safety Follow-up Phone Call Ongoing SAEs at the 90-day Safety Follow-up Phone Call will be followed up[b]											X	
Samples and Laboratory Assessments[l]													
Hematology[m]	X	X	X	X	X	X	X	X	Q2 weeks	X	X		
Lymphocyte subset quantification[n]		X		X						X			
Coagulation (hemostaeology)[o]	X	X	X	X		X		X	Q4 weeks (odd-numbered cycles only)	X	X		
Full serum chemistry[p]	X	X								X	X		
Core serum chemistry[p]			X	X	X	X	X	X	Q2 weeks				
Urinalysis[q]	X	X		X		X		X	Q4 weeks	X	X		
Pregnancy test[r]	X	X		X		X		X	Q4 weeks	X	X		
T4 and TSH[s]	X	X			X			X	Q8 weeks	X			
Blood for cytokines[t]		X	X	X		X				X			
Blood for vaccination-related antibodies[u]		X						X		X			
HBV and HCV screening tests[v]	X												

		Treatment Period[a] (-3/+1 days) 1 Cycle = 14 Days								End Of Treatment/Follow-Up[b]			
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Until EOT	EOT/ Withdrawal Visit[b]	Safety Follow-up[c]		Survival Follow-up[d]
Assessments	Screening (≤ 28 Days Prior to Enrollment)	Week 1 (Day 1)	Week 3 (Day 15)	Week 5 (Day 29)	Week 7 (Day 43)	Week 9 (Day 57)	Week 11 (Day 71)	Week 13 (Day 85)	> Week 13 (Day 85)	Within 7 Days of Decision to Discontinue	Visit 30 Days (± 5 days) After Last Tx	Phone Call 90 Days (± 5 days) After Last Tx	Every 12 Weeks (± 1 Week) After Last Tx
[redacted]													
Baseline tumor evaluation/staging (CT/MRI/other established methods)[x]	X												
Tumor evaluation/staging during treatment (CT/MRI/other established methods)[y]						X (every 8 weeks)			Every 8 weeks for the first 24 weeks, then every 12 weeks thereafter	X			
Dosing													
Registration[z]		X											
Pretreatment[aa]		X	X	X	X								

		Treatment Period[a] (-3/+1 days) 1 Cycle = 14 Days								End Of Treatment/Follow-Up[b]			
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Until EOT	EOT/ Withdrawal Visit[b]	Safety Follow-up[c]		Survival Follow-up[d]
Assessments	Screening (≤ 28 Days Prior to Enrollment)	Week 1 (Day 1)	Week 3 (Day 15)	Week 5 (Day 29)	Week 7 (Day 43)	Week 9 (Day 57)	Week 11 (Day 71)	Week 13 (Day 85)	> Week 13 (Day 85)	Within 7 Days of Decision to Discontinue	Visit 30 Days (± 5 days) After Last Tx	Phone Call 90 Days (± 5 days) After Last Tx	Every 12 Weeks (± 1 Week) After Last Tx
Avelumab administration[bb]		X	X	X	X	X	X	X	Q2 weeks				
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AEs: adverse events; βhCG: beta-human chorionic gonadotropin; C1D1: Cycle 1 Day 1; CNS: central nervous system; CR: complete response; CT: computed tomography; ECG: electrocardiogram; eCRF: electronic Case Report Form; EOT: End of Treatment; CCI ; CCI HBV: hepatitis B virus; HCV: hepatitis C virus; IGF: insulin-like growth factor; MRI: magnetic resonance imaging; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PD: progressive disease; PR: partial response; Q: every; QTc: corrected QT; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SAE: serious adverse event; T4: free thyroxine; TSH: thyroid stimulating hormone; Tx: treatment.

a. Treatment period: A time window of up to 3 days before and 1 day after the scheduled visit day (-3/+1 days) will be permitted for all treatment procedures. The biweekly, 14-day treatment schedule should be strictly adhered to, returning to the target date even if the previous visit was off schedule.

b. End of treatment/follow-up: All subjects will have an EOT Visit within 7 days after the decision to discontinue study treatment. All AEs will be documented during the 30-day Safety Follow-Up Visit and the 90-day Safety Follow-up Phone Call. All SAEs and all treatment-related nonserious AEs need to be documented through the study's Safety Follow-up Phone Call, defined at 90 days (± 5 days) after the last IMP administration. Subjects with an ongoing SAE at the 90-day Safety Follow-up Phone Call 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 avelumab must be reported whenever it occurs, irrespective of the time elapsed since the last administration of avelumab. Subjects without PD at the EOT Visit will be followed up for disease progression (CT/MRI scans every 8 weeks for the first 24 weeks of treatment, then every 12 weeks) or the start of subsequent anticancer therapy (whichever comes first). In addition, subjects will be followed every 12 weeks (± 1 week) for survival (including assessment of any further tumor therapy); see footnote d.

c. Safety Follow-up: During the post-treatment Safety Follow-up Visit, serious and non-serious AEs that the Investigator believes to have at least a reasonable possibility of being related to study drug will be recorded in the eCRF. If another antineoplastic therapy is administered before the end of the 30-day period, the 30-day Safety Follow-up visit should be conducted, if possible, prior to the start of this new therapy.

d. Survival follow-up: After discontinuation of study treatment, post-study survival status will be collected every 12 weeks ± 1 week until the subject's death, until 12 months after termination of treatment of the last subject, or until end of study, whichever occurs first. Follow-up will include collection of information on subsequent anticancer therapies. Telephone contact is acceptable.

e. Physical examination: A full physical examination should be performed at Screening and at the EOT Visit. Physical examinations at all other visits should be directed to signs and symptoms. If the physical examination at Screening is performed within 3 days of C1D1, it does not have to be repeated at C1D1. Weight is measured at every visit, and height is measured at Screening and every 4 weeks thereafter.

f. Vital signs: Blood pressure and heart rate will be recorded in a seated position after a 5-minute rest, if applicable. At each clinic visit, 2 blood pressure readings will be taken at least 1 hour apart.

g. Performance status: Lansky performance status ≥ 50% for subjects ≤ 16 years of age, or Karnofsky scale ≥ 50% for subjects > 16 years of age.

h. 12-Lead ECG: All subjects require a single ECG measurement after 5 minutes rest in a supine position at Screening and as indicated. If prolonged QTc interval is suspected, the ECG should be re-evaluated by a qualified person (ie, a cardiologist) at the institution for confirmation. Additional ECGs will be performed as clinically indicated. Clinically significant findings seen on follow-up ECGs should be recorded as AEs.

i. Bone growth assessments: To monitor the effects of treatment on growing bones, the following assessments will be performed at Baseline and annually thereafter: dual-energy X-ray absorptiometry, bone age determination, and blood levels of insulin-like growth factor (IGF)-1, IGF binding protein-3, vitamin D, luteinizing hormone, follicle-stimulating hormone, estradiol, and testosterone.

j. Concomitant medications and procedures: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and through the Safety Follow-up Visit (± 5 days). All concomitant medications should be recorded in the eCRF, including supportive care drugs (eg, antiemetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and nondrug supportive interventions (eg, transfusions).

k. Adverse event assessments: AEs should be documented and recorded at each visit using the NCI-CTCAE version 4.03. For SAEs, the active reporting period will begin from the time that informed consent/assent is provided, which is obtained prior to the subject's participation in the study (ie, prior to undergoing any study-related procedure and/or receiving study treatment) through and including 90 calendar days (± 5 days) after the last dose of study treatment. SAEs occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the Investigator becomes aware of them; at a minimum, all SAEs that the Investigator believes have at least a reasonable possibility of being related to avelumab are to be reported to the Sponsor. Serious and nonserious AEs should be recorded on the eCRF from the time the subject has taken at least 1 dose of study treatment through the subject's last visit. If a subject begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment. During the post-treatment Safety Follow-up (beyond 30 days through 90 calendar days after last dose of study treatment), serious or nonserious AEs suspected to be related to avelumab based on the Investigator's assessment should be recorded on the eCRF.

l. Laboratory assessments: On those weeks when no other assessments are required as per the Schedule of Assessments, a visit to the clinical site is not required unless the Investigator considers it necessary.

m. Hematology: Complete blood count results must be available and reviewed prior to dose administration. No need to repeat on C1D1 if Screening assessments were performed within 7 days prior to that date.

n. Lymphocyte subset quantification: T-cell population; T-cell, B-cell, and NK-cell numbers.

o. Coagulation (hemostaseology): No need to repeat on C1D1 if Screening assessments were performed within 7 days prior to that date.

p. Serum chemistry: Full serum chemistry will be performed during Screening, C1D1 (predose), EOT Visit, and the 30-day Safety Follow-up Visit. No need to repeat on C1D1 if Screening assessments were performed within 7 days prior to that date. Core serum chemistries will be performed during other treatment visits. Core serum chemistry results must be available and reviewed prior to dose administration.

q. Urinalysis: A full urinalysis (dipstick plus microscopic evaluation) is required at Screening and at the EOT Visit, and a basic urinalysis (dipstick only) at each visit indicated prior to administration of trial drug. If the basic urinalysis is abnormal, then a full urinalysis should be performed.

r. Serum/urine pregnancy test: For female subjects of childbearing potential, measure serum βhCG at Screening and urine or serum βhCG thereafter. Results of the most recent pregnancy test should be available prior to the administration of avelumab.

s. T4 and TSH: Perform tests at Screening; C1D1 (predose, if > 14 days after initial Screening); every 6 weeks for 2 subsequent measurements (eg, Week 6/7, Week 12/13); every 8 weeks thereafter (beyond Week 12/13); EOT Visit; and if clinically indicated. There is no need to repeat on C1D1 if Screening assessments were performed within 14 days prior to C1D1.

t. Cytokines: Refer to the Laboratory Manual for the specific cytokines to be measured.

u. Vaccination-related antibodies: Antibody titers for diphtheria, tetanus, and pneumococcal conjugate (PCV-7) will be measured.

v. HBV and HCV screening: The HBV screening panel includes 3 tests: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antigen (HBcAb). The HCV screening test assesses the presence or absence of antibodies to HCV.

[redacted]

x. Baseline tumor evaluation/staging: Tumor assessments will include all known or suspected disease sites. Imaging may include neck, abdomen, pelvis, and chest CT or MRI scans (if MRI is used, CT of chest is mandatory; for trial sites in Germany, only MRI is to be used). Baseline CNS imaging will not be required with the exception of symptomatic subjects to evaluate for CNS metastases. A bone scan (bone scintigraphy) or ^{18}FDG-PET/CT is required at Baseline in subjects with tumors known to metastasize to bone.

y. Tumor assessments post-Baseline: Tumor evaluation has a time window of 5 days prior to dosing (-5 days) and ± 5 days after the EOT Visit. CT or MRI scans will be performed every 4 treatment cycles (every 8 weeks) for the first 24 weeks, then every 12 weeks thereafter. If bone metastases were present at Baseline, or if new bone metastases are suspected, bone scintigraphy or ^{18}FDG-PET/CT will be repeated every 8 weeks for the first 24 weeks, then every 12 weeks thereafter. Bone imaging is also required at the time of CR confirmation for subjects who had bone metastases at Baseline. If PR, CR, or PD is observed according to RECIST 1.1, a confirmation CT or MRI should be performed, preferably at the regularly scheduled 8-week assessment but no sooner than 4 weeks after the first documentation of response or confirmed disease progression. Tumor assessment should be repeated at the EOT Visit if more than 4 weeks have passed since the last evaluation.

z. Registration prior to dosing: Registration of subjects will proceed through the use of an interactive response technology system.

aa. Pretreatment: Premedication with an antihistamine (H1 receptor blocker such as diphenhydramine) and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to the first 4 doses of avelumab is mandatory. Premedication can be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reaction. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

bb. Avelumab administration: Avelumab will be given as a 1-hour infusion every 2 weeks (14 days). The biweekly, 14-day treatment schedule should be strictly adhered to, returning to the target date even if the previous visit was off schedule.

Table 2 **Schedule of Assessments – Pharmacokinetic and Antidrug Antibody Sampling**

	Treatment Period (-3/+1 days) 1 Cycle = 14 Days									Follow-up Visits	
	Cycle 1 (Week 1)	Cycle 2 (Week 3)	Cycle 3 (Week 5)	Cycle 5 (Week 9)	Cycle 7 (Week 13)	Cycle 8 (Week 15)	Cycle 13 (Week 25)	Cycle 19 (Week 37)	Cycle 25 (Week 49) and Every 6 Cycles Thereafter	EOT/ Withdrawal Visit (Within 7 Days of Decision to Discontinue)	30-Day Safety Follow-up (± 5 Days)
First 36 subjects: PK blood samples in subjects < 10 kg at Baseline[a,b]	Predose, EOI, and 48-96 h	Predose	Predose and EOI	Predose	Predose and EOI	Predose	Predose	Predose and EOI	Predose	X	X
First 36 subjects: PK blood samples in subjects ≥ 10 kg at Baseline[a,b]	Predose, EOI, 3 h, and 48-96 h	Predose	Predose and EOI	Predose	Predose and EOI	Predose	Predose and EOI	Predose and EOI	Predose	X	X
PK blood samples in subjects beyond the first 36[a,b]	Predose and EOI	Predose	Predose and EOI	Predose	Predose and EOI	Predose	Predose	Predose and EOI	Predose	X	X
Blood samples for ADA (immunogenicity) testing[c]	Predose	Predose	Predose	Predose	Predose	—	Predose	Predose	Predose	X	X

ADA: antidrug antibodies; EOI: end of infusion; EOT: End of Treatment; PK: pharmacokinetic(s).

a. Predose blood samples for PK determinations will be collected from all subjects within 2 hours prior to trial treatment infusion. PK, ADA, and biomarker samples collected at the same predose time point can be used interchangeably if the dedicated sample has insufficient quantity, as the subject's parent(s)/guardian(s) will have consented to all collections and tests. PK sampling can be adjusted based on the PK data obtained from the first 3 subjects.

b. Postdose samples for PK analysis will be collected at EOI and at the subsequent times indicated. The timepoint window for the EOI and 3-hour samples is ± 30 minutes. Additional PK samples will be collected during the EOT/Withdrawal Visit and at the 30-day Safety Follow-up Visit. PK samples for avelumab will be collected from all subjects in Phase I and Phase II of the study. Every effort should be made to collect PK samples as close to the protocol-prescribed time point as possible, and to record the exact time in source document. Protocol deviations will be captured if samples are not collected, or if sample collection times are not recorded.

c. Blood samples for ADA analysis will be collected within 2 hours prior to the first, second, third, fifth, and seventh doses of avelumab (Cycles 1, 2, 3, 5, and 7) and then every 12 weeks (6 cycles) thereafter while on treatment. Additional samples for ADA analysis will be collected during the EOT/Withdrawal Visit and the 30-day Safety Follow-up Visit. PK, ADA, and biomarker samples collected at the same time point can be used interchangeably if the dedicated sample has insufficient quantity, as the subject's parent(s)/guardian(s) will have consented to all collections and tests.

2 Sponsor, Investigators, and Trial Administrative Structure

The Sponsor of this clinical trial with avelumab is EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), Billerica, MA, in the United States of America (USA), and Merck KGaA, Darmstadt, Germany, outside the USA.

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

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

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

The trial will appear in the following clinical trial registries: EU Clinical Trials Register, https://www.clinicaltrialsregister.eu/ (registration number 2017-002985-28) and ClinicalTrials.gov (USA), https://clinicaltrials.gov/ (registration number to come).

2.1 Investigational Sites

The study will be conducted in approximately 50 sites in North America, Europe, Middle East, South America, and Asia Pacific, including approximately 10 sites in the USA.

2.2 Study Coordination / Monitoring

The Sponsor will coordinate the study and will utilize the support of 1 or more CROs for some activities of the study. The Sponsor will perform oversight of the activities performed by the CROs.

The Clinical Study Supplies department of the Sponsor will supply the study medication of avelumab. Clinical supply is performed by the Clinical Trial Supply function of the Sponsor.

Subject enrollment will be managed by an interactive response technology (IRT) system. Safety laboratory assessments will be performed locally. Results from these local laboratories will be recorded according to the electronic case report form (eCRF) completion guidelines.

Pharmacokinetic (PK), CCI, immunogenicity, and CCI will be performed centrally under the responsibility and/or supervision of the Sponsor.

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

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

The Department of Global Biostatistics will supervise the statistical analyses, which will be outsourced to QuintilesIMS.

2.3 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will review the safety and available PK data on a regular basis. The SMC will consist of permanent members from the Sponsor (Global Drug Safety Product Leader, Medical Responsible, Clinical Pharmacologist, and Biostatistician) and/or CRO (Early Clinical Development Lead, Medical Lead, Biostatistician, and Global Drug Safety Representative), the participating Investigator(s) (for Phase I-recommended Phase II dose [RP2D] portion only), and other optional members with expertise in the management of pediatric cancer subjects. Ad hoc members may be invited as needed. More details will be described in the SMC Charter.

The SMC will decide on relevant dose-limiting toxicities (DLTs) for protocol criteria and will decide by consensus on dose escalation, dose de-escalation, suspension of enrollment, and/or declaration of the maximum tolerated dose (MTD) and/or RP2D, with the final adjudication being a Sponsor prerogative. In addition, the SMC may decide to study a specific cohort.

The SMC may modify the frequency of meetings as deemed appropriate by the SMC during the course of the trial. The specific working procedures will be described in an SMC Charter, which will be established prior to the start of recruitment.

3 Background Information

3.1 Programmed Cell Death and Ligands

The programmed death 1 (PD-1) receptor and PD-1 ligands 1 and 2 (PD-L1, PD-L2) play integral 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 1999; Freeman 2000; Dong 2002; Topalian 2012a) and 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 2002; Iwai 2002). The PD-L1 molecule is expressed as an immune-inhibitory checkpoint on epithelial and vascular endothelial cells, as well as by a number of immune cells, and is employed by tumor cells as immune escape mechanism.

Agents targeting PD-L1, PD-1, and related molecules are collectively referred to as immune checkpoint inhibitors (ICIs). Clinical activity of ICIs, including avelumab, has been observed in

melanoma, non-small cell lung cancer (NSCLC), urothelial cell carcinoma, renal cell carcinoma, ovarian cancer, Merkel cell carcinoma (MCC), and Hodgkin's lymphoma, among others.

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

Several studies with checkpoint inhibitors in pediatric patients with cancer are currently ongoing. In a pediatric study of ipilimumab, no unexpected safety findings were noted, and early signs of clinical activity were seen in pediatric patients with cancer (Merchant 2016). A Phase II study of nivolumab showed no objective responses in patients with relapsed/refractory osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma; Phase I data in relapsed/refractory solid tumors was not reported (Davis 2017). A Phase I/II study of pembrolizumab in pediatric patients with advanced melanoma or PD-L1+ advanced, relapsed, or refractory solid tumors or lymphomas showed low toxicity and durable antitumor activity in various tumor types, specifically Hodgkin's lymphoma, mesothelioma, malignant ganglioglioma, lymphoepithelial carcinoma, and adrenocortical carcinoma (Geoerger 2017a). The iMATRIX-Atezolizumab study examined atezolizumab in pediatric and young adult patients with refractory/relapsed solid tumors (Geoerger 2017b). Preliminary anti-tumor activity was seen in Hodgkin's lymphoma and in single patients with Ewing sarcoma and atypical malignant rhabdoid tumor. The pharmacokinetic and safety profiles for all drugs were similar in children as in adults. PD-L1 expression was variable across pediatric solid tumors subtypes.

3.2 Avelumab

The Investigational Medicinal Product (IMP) for this trial is avelumab, the International Nonproprietary Name for the Sponsor's anti-PD-L1 monoclonal antibody MSB0010718C. Avelumab is being developed in oncological settings by Merck KGaA, Darmstadt, Germany, and by its subsidiary, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA.

Avelumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to PD-L1 and competitively blocks its interaction with PD-1. Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells. Therefore, it is hypothesized to have fewer side effects, 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 2001). For complete details of the in vitro and nonclinical studies, refer to the current Investigator's Brochure (IB).

Avelumab is currently under evaluation in several Phase I, II, and III studies in various tumor indications in the adult subject population, including NSCLC, gastric cancer, MCC, renal cell carcinoma, urothelial cancer, and ovarian cancer. In March 2017, the US Food and Drug Administration granted accelerated approval to avelumab for the treatment of patients 12 years of age and older with metastatic MCC. In May 2017, the indication was extended via accelerated approval to include patients with locally advanced or metastatic urothelial carcinoma, who have

disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (Bavencio 2017).

More than 3,720 subjects have been treated with avelumab to date. In the dose-escalation portion of the Phase I study, there was no evidence of differences in the safety profile across all administered dose levels from 1 mg/kg to 20 mg/kg. The MTD was not reached.

The recommended Phase II/III dose in adults was determined to be 10 mg/kg avelumab administered intraveneously every 2 weeks. Avelumab treatment is continued until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurs. Promising clinical activity was observed in several tumor types in adults. Refer to the most recent version of the IB for updated information regarding current clinical studies with avelumab.

3.3 Rationale for the Current Clinical Trial and Overall Benefit and Risk Considerations

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

Based on the available nonclinical and clinical data to date (including modeling and simulation results using adult PK data from ongoing avelumab studies), the conduct of the trial specified in this protocol is considered justifiable.

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

Rationale for the Current Clinical Trial

Based on the success of checkpoint inhibitor therapies in adult tumors, there is a rationale to explore their activity in pediatric malignancies. Pediatric tumors appear to bear the same hallmarks of sensitivity to ICIs, namely the presence of immune cell infiltrates, expression of PD-L1 in tumor and/or infiltrating immune cells (Geoerger, 2017a; Geoerger, 2017b) and high mutation burden in some cases (Marabelle 2015). The pediatric patient population in the Phase I part of this study will include subjects with common pediatric tumors, such as neuroblastoma and sarcomas, as well as rarer tumors occurring in subjects during childhood. Most pediatric tumors share several characteristics: they are predominantly of embryonal origin, have peak incidence in childhood and adolescence, and have well-established guidelines for their diagnosis and management in the first- and second-line settings. In contrast, tumors occurring in adults are generally carcinomas, which are extremely rare in children. These tumors are mostly of epithelial origin, and their incidence rises with age, usually starting in the third decade of life. Diagnosis and management of these tumors are usually extrapolated from adult data. Treatment of these tumors with ICIs have been studied extensively in adults, but very little data are available in children (Davis 2017; Geoerger, 2017a; Geoerger, 2017b).

Based on the acceptable safety and encouraging efficacy data of avelumab in adults, and the preclinical rationale supporting the role of the immune system in the pathogenesis of pediatric malignancies (Marabelle 2015), avelumab will be evaluated in a broad population of pediatric

patients with tumors. At the present time, there is no validated patient selection strategy in pediatric cancers. In the Phase I part of the study, the aims are to define the RP2D and assess the safety and tolerability of avelumab. The Phase II part of the study is designed to enable a formal statistical assessment and characterization of the antitumor activity of avelumab as determined by the ORR, and a robust statistical design to allow for clear conclusions to be drawn regarding the benefit of treatment with avelumab in pediatric patients with specified tumor types.

Overall Benefit and Risk Considerations

The risk-benefit relationship has been carefully considered in the planning of the trial. Based on the available nonclinical and clinical information to date, avelumab provides a positive benefit-risk status with solid tumors, and the conduct of the trial is considered justifiable using the dose and dose regimen of avelumab as specified in this clinical trial protocol.

Specific risks associated with the use of avelumab as a monoclonal antibody have been observed. The primary risks of exposure to avelumab include infusion-related reactions (IRRs) and immune-related AEs (irAEs). Premedication with an antihistamine (H1 receptor blocker such as diphenhydramine) and with acetaminophen (paracetamol) approximately 30 to 60 minutes prior to each dose, once every 2 weeks for the first 4 infusions is mandatory. This regimen may be modified based on local treatment standards and guidelines, as appropriate.

4 Trial Objectives

4.1 Primary Objectives

Phase I

- To evaluate the safety and tolerability of avelumab
- To determine the RP2D of avelumab in pediatric subjects 0 to < 18 years of age with solid tumors and lymphoma

Phase II

- To assess antitumor activity of avelumab by determining the ORR according to RECIST 1.1 and as adjudicated by the Investigator in 2 expansion cohorts in specified tumor types in pediatric subjects treated with avelumab

4.2 Secondary Objectives

Phase I

- To assess antitumor activity of avelumab by determining the ORR according to RECIST 1.1 and as adjudicated by the Investigator in pediatric subjects with solid tumors and lymphoma treated with avelumab
- To assess progression-free survival (PFS) based on Investigator assessments, duration of response (DOR), time to respond (TTR), and overall survival (OS)
- To characterize the PK of avelumab
- To assess the immunogenicity of avelumab

- To evaluate PD-L1 expression; tumor-infiltrating T-cell activity; T-cell population; and T-cell, B-cell, and NK-cell numbers in tumor tissue at Baseline and at confirmed progression (if tumor tissue is obtained)
- To measure changes in vaccination-related antibody concentrations (diphtheria, tetanus, and pneumococcal conjugate)

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a multicenter, open-label, international, Phase I/II study to evaluate the dose, safety and tolerability, antitumor activity, PK, and pharmacodynamics of avelumab in pediatric subjects 0 to < 18 years of age with refractory or relapsed malignant solid tumors (including central nervous system tumors) and lymphoma for which no standard therapy is available or for which the subject is not eligible for the existing therapy.

The study will consist of 2 parts: the dose-finding part (Phase I) and the tumor-specified expansion part (Phase II). During Phase I, the RP2D of avelumab in children will be determined. During Phase II, 2 expansion cohorts will be enrolled, with specific tumors chosen based on available data from the Phase I part of the study, ongoing studies with avelumab and other ICIs, clinical and nonclinical chemotherapy combination data, and any published literature.

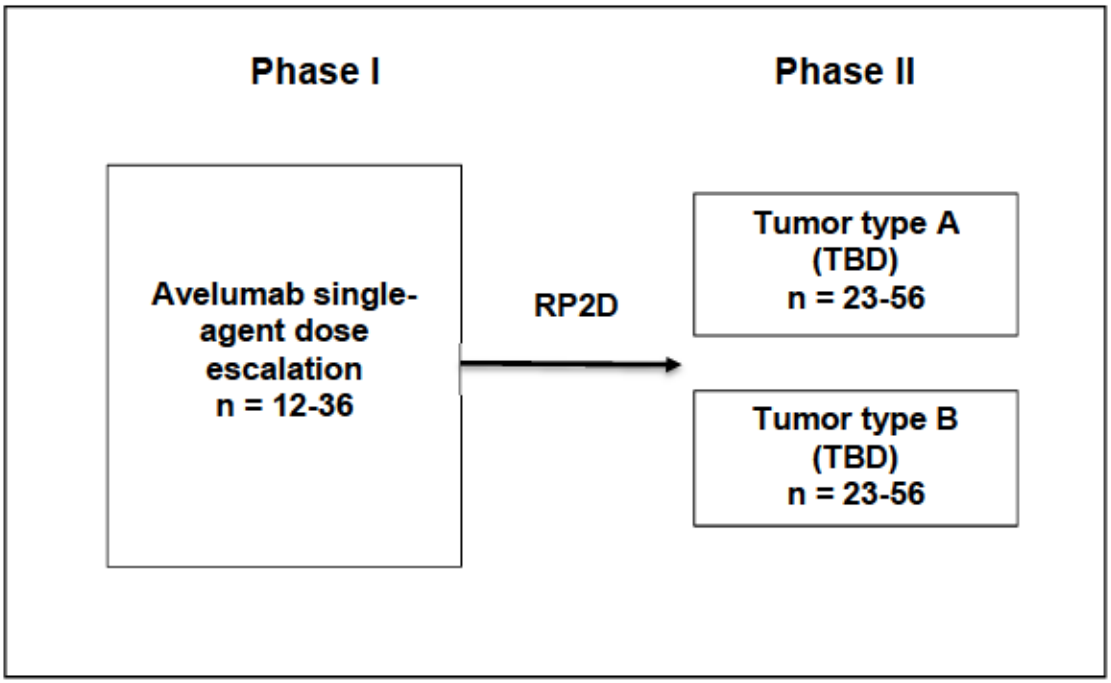
5.1.1 Overall Design

Planned number of subjects:

- Phase I: 12 to 36 subjects
- Phase II: 46 to 112 subjects (23 to 56 subjects per tumor type) for 2 cohorts

The trial design schematic is presented in Figure 1.

Figure 1 Schematic of the Trial Design



RP2D: recommended Phase II dose; TBD: to be determined.

5.1.1.1 Phase I Study Design

In the dose-finding part of the study, subjects will be enrolled in sequential cohorts of 3 to 6 subjects each; the first 3 subjects will be ≥ 1 year old. At least 12 subjects must be evaluable for the primary analysis. Phase I will be completed when at least 12 DLT-evaluable subjects have been treated at a dose level confirmed to be safe. Phase II will then begin.

The starting dose will be the same as recommended dose in adults, 10 mg/kg avelumab administered intravenously (iv) once every 2 weeks, which is based on modeling and simulation results using adult PK data from ongoing avelumab studies as described in Section 5.2. Avelumab will be administered until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurs. In Phase I, the DLT observation period is defined as a 28-day period (2 cycles) beginning with the first avelumab administration.

The first cohort of 3 to 6 subjects will be enrolled at the starting dose level of 10 mg/kg (DL1). Based on the number of subjects experiencing DLTs at the completion of the first cohort, the dose for the next cohort of subjects can be kept the same or modified.

- If DL1 is confirmed as safe, this dose will be selected as RP2D if it provides adequate exposure in children compared with adults.
- If exposure is not adequate (when compared with adult population PK [PopPK]-simulated values for median and distribution of exposure [C_{max}, AUC, and C_{trough}]), a decision can be made to escalate to a dose level up to 20 mg/kg (DL2).
- If at any point the modified toxicity probability interval (mTPI) results indicate a dose de-escalation is warranted, the next subjects will be enrolled at lower dose level of 3 mg/kg every 2 weeks (DL -1). Dose re-escalation can be permitted based on the mTPI results as long as the current dose level has not been determined to have exceeded the MTD. The MTD estimate is the highest dose tested of avelumab associated with the occurrence of DLTs within the first 2 cycles of treatment in $< 33\%$ of subjects, provided that a higher dose level of avelumab was tested and had an associated DLT rate $\geq 33\%$.

Subjects will return to the clinic at regular intervals for assessments (see Section 7.1 and Table 1).

Avelumab treatment will continue until:

- PD (see Section 5.5.1) or death
- Unacceptable toxicity
- Any criterion for withdrawal from the trial or trial treatment is fulfilled (see Section 5.5).

Treatment can continue past the initial determination of confirmed disease progression (see Section 6.2).

Subjects who have experienced a complete response (CR) should be treated for a minimum of 12 months based on clinical judgment of benefit and/or until confirmed progression per irRECIST (Bohnsack 2014), unacceptable toxicity, or any criterion for withdrawal occurs, after confirmation of response as specified in this protocol. In case a subject with a confirmed CR relapses after stopping treatment, during long-term follow-up but prior to the End of Trial, 1 re-initiation of treatment will be allowed at the discretion of the Investigator and agreement of the Medical Monitor. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Prior to re-initiation of the study treatment, malignant disease will be radiologically re-staged to assess all known sites of the disease and to establish a new baseline for subsequent tumor measurements. Relevant safety laboratory results must be available and verified prior to re-initiating treatment. Subjects who re-initiate treatment will stay on study and will be treated and monitored according to the protocol and the Schedule of Assessments (Table 1).

The primary Phase I endpoints are:

- Occurrence and severity of treatment-emergent adverse events (TEAEs) $\geq$ Grade 3 according to NCI-CTCAE v4.03
- DLTs to determine the RP2D

Safety endpoints include incidence of AEs and laboratory abnormalities assessed throughout the trial and evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03, and vital signs.

5.1.1.1.1 Modified Toxicity Probability Interval

Dose escalation/de-escalation rules will follow the mTPI method. Briefly, the mTPI method relies on a statistical probability algorithm to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target probability rate (pT = 0.3), using all subjects treated in prior and current cohorts at the same dose level to determine whether future cohorts should involve dose re-escalation, no change in dose, or dose de-escalation. If the toxicity rate of the current dose is far smaller than pT, the mTPI will recommend escalating the dose; if the toxicity rate is close to pT, the mTPI will recommend continuing at the current dose; and if it is far greater than pT, the mTPI will recommend de-escalation. Decision rules are based on calculating unit probability mass of 3 dosing intervals corresponding to under, proper, and overdosing in terms of toxicity. Specifically, the underdosing interval is defined as (0, pT - e1), the overdosing interval as (pT + e2, 1) and the proper dosing interval as (pT - e1, pT + e2), where e1 and e2 are small fractions. Based on the safety profile of avelumab, e1 is preselected as 0.05, and e2 is selected as 0.03. Therefore, the target interval for the DLT rate is (0.25, 0.33). The detailed dose-finding rules based on the mTPI are illustrated in Table 3.

Table 3 Detailed Dose Re-Escalation/De-Escalation Scheme

		Number of Subjects Treated at Current Dose											
		1	2	3	4	5	6	7	8	9	10	11	12
Number of DLTs	0	NA	NA	E	E	E	E	E	E	E	E	E	E
	1	D	S	S	S	S	E	E	E	E	E	E	E
	2		DU	D	S	S	S	S	S	S	S	S	E
	3			DU	DU	D	D	S	S	S	S	S	S
	4				DU	DU	DU	D	D	S	S	S	S
	5					DU	DU	DU	DU	DU	D	S	S
	6						DU	DU	DU	DU	DU	DU	D
	7							DU	DU	DU	DU	DU	DU
	8								DU	DU	DU	DU	DU
	9									DU	DU	DU	DU
	10										DU	DU	DU
	11											DU	DU
	12												DU

E = Escalate to the next higher dose, or if current dose level is DL1, stay on DL1. Escalation to DL2 is allowed if exposure at DL1 is not adequate.
S = Stay at the current dose.
D = De-escalate to the next lower dose level.
DU = De-escalate to the next lower dose level; the current dose is unacceptably toxic.
Targeted DLT rate at MTD = 33%.

As an example, if the total number of subjects treated at DL1 is 3, then the following dosing rules will be applied:

- 0 or 1 DLT → remain at the same dose level (ie, DL1)
- 2 DLTs → de-escalate to DL -1 and allow for possible re-escalation to DL1
- ≥ 3 DLTs → de-escalate to DL -1, as DL1 is intolerable.

Rules for dose finding using the mTPI method will be the following:

- The target enrollment cohort size will be 3 to 6 subjects.
- The first cohort will initially comprise 3 subjects 1 to < 18 years of age at the time of first treatment dose at 10 mg/kg (DL1). Up to 3 additional subjects (0 to < 18 years of age) can be added if the first 3 subjects experience 0 or 1 DLT at DL1.
- After the first 3 subjects in the initial cohort are treated with DL1, PK data will be evaluated and drug exposure in these subjects versus adults will be analyzed to determine if exposure is adequate. Exposure data are required before any additional subjects are dosed.
- Intrapatient dose escalation is not permitted.
- After each cohort, the number of DLTs will be assessed to determine the dose level for the next cohort using the mTPI design.
- DLTs will be reviewed by SMC members, and the decision to open each new cohort will be made by the SMC.
- The second and later cohorts will be enrolled when all subjects evaluable for DLT at the current dose cohort have been evaluated for at least 2 cycles (28 days), or when more than 1 subject in a cohort experiences a DLT, whichever comes first. The next cohort will receive the dose level as assigned if a dose modification is required.
- If DL1 is confirmed as safe, this dose will be selected as RP2D if it provides adequate exposure in children compared with adults.
- A decision can be made in a cohort defined by the SMC to test a dose level above 10 mg/kg (up to 20 mg/kg) if both of the following conditions are met:
  - Exposure achieved at 10 mg/kg does not reach therapeutic levels established in adults
  - 10 mg/kg was demonstrated to be safe.
- If a subject does not receive at least 2 infusions of avelumab within the DLT observation period (2 cycles = 28 days) for reasons other than study drug-related toxicity, another subject will be enrolled to replace that subject at the current dose level.
- Avelumab treatment will continue until:
  - Confirmed PD (see Section 5.5.1) or death
  - Unacceptable toxicity
  - Any criterion for withdrawal from the trial or trial treatment is fulfilled (see Section 5.5).
- Treatment can continue past the initial determination of confirmed disease progression per irRECIST (see Section 6.2).
- Phase I will be completed when at least 12 DLT-evaluable subjects have been treated at a dose level confirmed to be safe and similar exposure to that in adults is achieved.
- Additional subjects (up to 6 per cohort) can be enrolled at any dose level determined to be below the MTD to further assess variability of PK or safety by age.

5.1.1.1.2 Definition of Dose-limiting Toxicity

Severity of AEs will be graded according to NCI-CTCAE version 4.03. For the purpose of dose finding, any of the following AEs occurring during the primary DLT observation period (28-day period [2 treatment cycles]) that are attributable to avelumab will be classified as DLTs:

Hematologic:

1. Grade 4 neutropenia of > 7 days in duration
2. Grade ≥ 3 neutropenic infection
3. Grade ≥ 3 thrombocytopenia with bleeding
4. Grade 4 thrombocytopenia > 7 days
5. Grade 4 anemia.

Nonhematologic:

1. Any Grade ≥ 3 toxicity, except for any of the following:
   a. Transient (≤ 72 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
   b. Transient (≤ 72 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolves to Grade ≤ 1 or to baseline
   c. Grade 3 diarrhea or Grade 3 skin toxicity that resolves to Grade ≤ 1 in less than 7 days after medical management (eg, immunosuppressant treatment) has been initiated
   d. Grade ≥ 3 amylase or lipase abnormality that is not associated with clinical manifestations of pancreatitis
   e. Tumor flare phenomenon, defined as local pain, irritation, or rash localized at sites of known or suspected tumor
   f. Single laboratory values out of normal range that are unlikely related to trial treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 or Baseline within 7 days with adequate medical management.
2. Inability to complete at least 2 infusions of avelumab during the DLT observation period due to treatment-related toxicity.

While the rules for adjudicating DLTs in the context of dose finding/dose expansion phases are specified above, an AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT observation period, may be defined as a DLT after consultation between Sponsor and Investigator, based on the emerging safety profile.

5.1.1.1.3 Definition of Maximum Tolerated Dose

The MTD estimate is the highest dose tested of avelumab associated with the occurrence of DLTs within the first 2 cycles of treatment in < 33% of subjects, provided that a higher dose level of avelumab was tested and had an associated DLT rate ≥ 33%. If the DLT rate within the first 2 cycles of treatment is < 33% for all tested dose levels, then the MTD will not have been reached.

5.1.1.1.4 Definition of Recommended Phase II Dose

The RP2D is defined as the dose of avelumab chosen for further clinical development in pediatrics. Pharmacokinetics, pharmacodynamics, safety, and antitumor activity data can result in selection of an RP2D level that is lower or higher than the current adult dosage of 10 mg/kg, as long as it does not exceed the MTD.

5.1.1.1.5 Age Range for Each Cohort in Phase I

The study is aimed at defining a single RP2D in the age group of 0 to < 18 years at the time of first treatment dose. However, if at any time during the study, data suggest a difference in tolerability by age, this will be discussed with the SMC. The following rules will be used:

- The initial cohort will be open to subjects 0 to < 18 years of age; the first 3 subjects will be ≥ 1 year of age.
- Subsequent cohorts of 3 to 6 subjects each may be open to subjects 0 to < 18 years of age or a narrower age range, based on emerging data, as agreed on by the SMC.

5.1.1.1.6 End of Phase I

When at least 12 DLT-evaluable subjects have been treated at a dose level confirmed to be safe, enrollment in Phase I will be complete and Phase II will begin.

5.1.1.2 Phase II Study Design

The determination of the RP2D in children will trigger the enrollment of 2 expansion cohorts. Specific tumors will be chosen for the expansion cohorts based on available data from the Phase I part of the study, ongoing studies with avelumab and other ICIs, clinical and nonclinical combination chemotherapy data, and any published literature. These data may include clinical data with avelumab or with other immune checkpoint inhibitors, or preclinical data providing additional rationale for a specific tumor type.

Each expansion cohort will follow Simon's Optimal Two-stage Design (Simon 1989). If there are 2 or more subjects with confirmed objective response among the first 23 subjects treated at the RP2D, then an additional 33 subjects will be enrolled and treated at that dose level. If there is 1 or no subjects with a confirmed objective response among the first 23 subjects treated at the RP2D with a minimum follow-up of 16 weeks, then the cohort will be closed for further enrollment.

Subjects will return to the clinic at regular intervals for assessments (see Section 7.1 and Table 1).

Avelumab treatment will continue until:

- Confirmed PD (see Section 5.5.1) or death
- Unacceptable toxicity
- Any criterion for withdrawal from the trial or trial treatment is fulfilled (see Section 5.5).

Treatment can continue past the initial determination of confirmed disease progression (see Section 6.2).

Subjects who have experienced a complete response (CR) should be treated for a minimum of 12 months based on clinical judgment of benefit and/or until confirmed progression per irRECIST, unacceptable toxicity, or any criterion for withdrawal occurs, after confirmation of response as specified in this protocol. In case a subject with a confirmed CR relapses after stopping treatment, during long-term follow-up but prior to the End of Trial, 1 re-initiation of treatment will be allowed at the discretion of the Investigator and agreement of the Medical Monitor. In order to be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Prior to re-initiation of the study treatment, malignant disease will be radiologically re-staged to assess all known sites of the disease and to establish a new baseline for subsequent tumor measurements. Relevant safety laboratory results must be available and verified prior to re-initiating treatment. Subjects who re-initiate treatment will stay on study and will be treated and monitored according to the protocol and the Schedule of Assessments (Table 1).

Each subject will be followed for additional 12 months after end of treatment.

The primary Phase II endpoint is confirmed best overall response (BOR) according to RECIST 1.1.

Safety endpoints include incidence of AEs and laboratory abnormalities assessed throughout the trial and evaluated using NCI-CTCAE v4.03, and vital signs.

5.1.2 Trial Treatment Administration and Schedule

The trial Schedule of Assessments is presented in Table 1, and the Schedule of Assessments - PK and Antidrug Antibody (ADA) Sampling in Table 2.

Subjects will receive iv infusions of avelumab once every 2 weeks.

To mitigate infusion-related reactions, premedication with antihistamine (H1 receptor blocker such as diphenhydramine) and acetaminophen (paracetamol), based on local treatment standards and guidelines, approximately 30 to 60 minutes prior to each dose, once every 2 weeks for the first 4 doses of avelumab is mandatory. Premedication can be administered beyond the fourth dose of avelumab 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, provided it does not include systemic corticosteroids (steroid premedication specifically for avelumab is not permitted).

The formulation and packaging information of avelumab is provided in Section 6.

5.1.2.1 Standard of Care

Not applicable.

5.1.3 Dose Modification and Adverse Drug Reactions Requiring Treatment Discontinuation

5.1.3.1 Dose Modification for Avelumab

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 within 10% of the weight used for the last dose calculation.

In Phase I, dose escalation/de-escalation rules will follow the mTPI method (see Section 5.1.1.1.1). In Phase II, each subject will stay on the avelumab RP2D dose unless treatment needs to be stopped. There will be no dose reductions in Phase II. Dosing modifications (changes in infusion rate) are described in Section 5.1.3.2 and Section 6.5.5.

5.1.3.2 Adverse Drug Reactions Requiring Avelumab Treatment Discontinuation or Modifications

The following adverse drug reactions (ADRs; for definition, see Section 7.4.1.1) require permanent treatment discontinuation of avelumab:

- Any Grade 4 ADR, except for the following:
  - Grade 4 lipase or amylase abnormality that is not associated with clinical manifestations of pancreatitis. The Medical Monitor must be consulted for such lipase and amylase abnormalities.
  - Grade 4 neutropenia of ≤ 7 days in duration
  - Grade 4 thrombocytopenia without bleeding
  - Other single laboratory values out of normal range that do not have any clinical correlate and resolve to baseline within 7 days with adequate medical management.
- Any Grade 3 ADR except for any of the following:
  - Transient (≤ 72 hours) Grade 3 flu-like symptoms or fever, which are controlled with medical management
  - Transient (≤ 72 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolve to Grade ≤ 1 or baseline with appropriate medical management
  - Grade 3 diarrhea or Grade 3 skin toxicity that resolves to Grade ≤ 1 in less than 7 days after medical management (eg, immunosuppressant treatment) has been initiated
  - Grade 3 lipase or amylase abnormality that is not associated with clinical manifestations of pancreatitis. The Medical Monitor must be consulted for such lipase and amylase abnormalities.

  - Other single laboratory values out of normal range that do not have any clinical correlate
  - Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Any Grade 2 ADR should be managed as follows:
  - Infusion should not be given in case of ongoing Grade 2 ADR on the day of trial treatment administration.
  - Treatment can be resumed according to original schedule once ADR resolves 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 study Medical Monitor.

See the guidelines for handling infusion-related reactions (Section 6.5.5.1), severe hypersensitivity reactions and flu-like symptoms (Section 6.5.5.2), and irAEs (Section 6.5.5.3).

5.2 Discussion of Trial Design

In the Phase I dose-finding part of the study, the RP2D in children 0 to < 18 years of age will be determined. In Phase II, 2 expansion cohorts will be opened in 2 specified tumor types selected based on emerging data from this and other ongoing studies. These data may include clinical data with avelumab or with other ICIs, or preclinical data providing additional rationale in a specific tumor type.

Subjects will not be selected for enrollment in either Phase I or Phase II part of the study based on any molecular characteristics, such as PD-L1 expression, because the optimal strategy for selection of pediatric subjects who derive maximum benefit from avelumab is currently unknown.

Because the benefit of avelumab in pediatric subjects with cancer has not yet been established, eligibility criteria are aimed to ensure that the subjects have exhausted available standard therapy. In addition, a standard set of criteria for avelumab studies has been incorporated, such as exclusion of subjects previously treated with an ICI, absence of active autoimmune disease that can be exacerbated by avelumab, and adequate organ function.

Justification for Dose

The Phase I, dose-finding part of the study will establish the RP2D of avelumab in pediatric subjects. The starting dose will be the same as the recommended adult dosing regimen, 10 mg/kg every 2 weeks. Treatment will continue until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurs. The adult dose was selected as the starting dose in this study for several reasons, as described below.

In a clinical trial of adult cancer subjects treated with avelumab at doses ranging from 1 mg/kg to 20 mg/kg (Study EMR100070-001), the MTD was not reached. A dose of 10 mg/kg every 2 weeks was chosen as the dose regimen expected to achieve > 95% target occupancy in all subjects (refer to Section 5.2 of the IB).

Simulation was conducted based on the adult PopPK model to find a dose that would have exposure similar to that observed in adult population. First-cycle PK data showed that the

exposures were similar or tended to be lower in subjects with lower body weights following administration of avelumab 10 mg/kg iv every 2 weeks. In the first simulation, the clearance (CL) was assumed to be related to body weight as a power function, with exponents of 0.85 on CL and of 1 on volume of distribution (V) as reported in the literature (Deng 2011). An alternative model using estimated exponent (0.565 for CL and 0.472 for central volume) from the adult Pop PK model had been also explored. It had been noted that allometric exponents estimated from data within species (such as adult subjects) were typically smaller than those observed for between-species scaling, which was likely due to a narrower body weight range in adults for a given species (approximately 2- to 3-fold) (Bai 2012). For this reasons, the first simulation with fixed exponents for CL (0.85) and V (1) was considered to be more relevant for a population like children with a wide range of body weights. This model predicted that 10 mg/kg was needed to achieve similar or relatively lower exposure in children to that in adults, and 15 to 20 mg/kg dose would potentially lead to a higher exposure in children than that in the adults. Therefore, 10 mg/kg was recommended for the starting dose to avoid potential overexposure in some of the body weight groups.

Ongoing pediatric studies with other PD-L1 antibodies (nivolumab, pembrolizumab, atezolizumab) were initiated at the adult approved dose (Bristol Myers Squibb 2013; Merck, Sharp & Dohme 2015; Geoerger 2017b). This is also consistent with recent experience with other targeted agents in pediatric oncology. A recent study examined dose-finding studies of 15 predominately small molecular targeted agents (Paoletti 2013). For 75% of the compounds, the pediatric RP2D was between 90% and 130% of the adult dose, and the findings were similar to those reported in adults in terms of either MTD/MAD or RP2D, and PK conclusions. The traditional approach of starting below the adult dose resulted in more than 60% of children being underdosed. Of note, 3 monoclonal antibodies were among the 15 molecular targeted agents. For all 3, the pediatric RP2D was the same as in adults (Paoletti 2013). Taken together, these data suggest that for biologics in general, and for ICIs in particular, selection of the adult dose as the starting dose in children is appropriate.

Similarly, there is no evidence to indicate that the avelumab safety profile should be different in children compared with adults. In the pediatric studies of ipilimumab, pembrolizumab, atezoliumab, and nivolumab, the nature and timing of irAEs was similar to that seen in adults (Merchant 2016). Therefore, there are limited data to suggest that children are at increased risk of irAEs (Davis 2017; Geoerger, 2017a; Geoerger, 2017b). The safety of avelumab in pediatric subjects will be characterized using standard methods (eg, characterization of AEs, laboratory abnormalities, vital signs).

Avelumab is characterized by 2 main recognized types of adverse events: irAEs and IRRs (refer to IB, Section 5.3.1.3.1.6 and Section 5.3.1.3.1.7). Because inhibition of PD-L1 stimulates the immune system, inflammatory reactions collectively referred to as irAEs might occur (Weber 2015; Postow 2015; Naidoo 2015). Immune-related AEs are a known class effect of ICIs and may include pneumonitis, colitis, hepatitis, endocrinopathies, dermatitis, nephritis and renal dysfunction, encephalitis, eye disorders (including uveitis and iritis), and other immune-mediated reactions (including myositis and myocarditis). The majority of irAEs have been mild and respond to immunosuppressive treatment (ie, glucocorticoids). Guidance is provided to Investigators that any AE suspected to have an underlying immune-mediated mechanism, and without other confirmed etiology, should be considered immune related and managed according to guidelines described in the protocol.

In addition to irAEs, the other recognized toxicity of avelumab is IRRs (refer to the IB for additional information). Infusion-related reactions frequently occur with other monoclonal antibodies commonly used in children, including rituximab and infliximab. Studies suggest that the rate of infusion reactions is similar in adults and in children, including children ≤ 5 years old (Dale 2014; Aeschlimann 2014).

Little is known about the long-term effects of checkpoint inhibition on the developing immune system, although preclinical data suggest a role for PD-L1 in the development and function of T cells (Francisco 2009). Reassuringly, there were no changes in absolute lymphocyte count and in frequency of immune-cell subsets in peripheral blood mononuclear cells obtained from adult cancer subjects pre- and post-treatment with avelumab (Lepone 2015). Given the expected poor survival of the subject population to be enrolled on this trial, the potential benefit of therapeutic effect outweighs the theoretical risk of long-term immune dysfunction.

In summary, based on the wide therapeutic index and the lack of specific safety concerns in the pediatric age group, the starting dose in the dose-finding part of the study was selected to be the adult RP2D, 10 mg/kg every 2 weeks. Detailed guidelines on the early recognition and management of irAEs and IRRs will be provided to the Investigators, subjects, and caregivers.

Rationale for Phase I Endpoint

One of the objectives of the Phase I dose-finding part of the study will be to determine RP2D of avelumab in pediatric cancer subjects 0 to < 18 years of age. The RP2D will be chosen based on the overall safety profile, PK, and pharmacodynamics. Determination of the RP2D is commonly the primary objective of dose-finding studies in oncology, including pediatric studies (Doussau 2012). The endpoint corresponding to this objective will be DLTs to determine the RP2D.

5.2.1 Inclusion of Special Populations

All subjects in this study belong to a special population, namely children. See Section 5.2 for the rationale to include this population.

5.3 Selection of Trial Population

Only individuals who fulfill all inclusion criteria without matching any exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject's parent(s)/legal guardian(s) have provided written informed consent and the subject has provided written assent (when age appropriate and per local regulations), following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

Subject eligibility should be reviewed and documented by the Investigator or delegate of the Investigator's study team before subjects are included in the study.

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

1. Signed written informed consent form (ICF) before any trial-related procedure is undertaken that is not part of the standard patient management. The signed ICF indicates that the minor subject's parent(s)/legal guardian(s) have been informed of all pertinent aspects of the study, based on local regulations. Subjects also must provide assent when age appropriate and per local regulations.

2. Male and female subjects 0 to < 18 years of age at the time of first treatment dose.

3. Availability of formalin-fixed paraffin-embedded (FFPE) block containing tumor tissue or a minimum of 10 (preferably 25) unstained tumor slides (cut within 1 week) suitable for PD-L1 expression assessment, from a recently obtained (within 6 months) biopsy from a non-irradiated area. If tissue is unavailable in block or slides, a mandatory tumor biopsy must be performed prior to avelumab treatment for subjects in Phase II.

4. Subjects with histologically or cytologically proven diagnosis of malignant solid tumor (including CNS tumors) or lymphoma in Phase I, or specified tumor types in Phase II with measurable disease at Baseline (at least 1 unidimensional, radiographically measurable lesion based on RECIST v1.1).

5. Confirmed progression on or refractory to standard therapy, or no standard therapy available.

6. Lansky performance status ≥ 50% for subjects ≤ 16 years of age, or Karnofsky scale ≥ 50% for subjects > 16 years of age.

7. Adequate bone marrow function, including:
    a. Absolute neutrophil count ≥ 1,000/mm^3 or ≥ 1 x 10^9/L at least 5 days following the last dose of granulocyte colony stimulating factor
    b. Platelets ≥ 50,000/mm^3 or ≥ 50 x 10^9/L
    c. Hemoglobin ≥ 8 g/dL (may have been transfused).

8. Adequate hepatic function, defined by:
    a. a total serum bilirubin level ≤ 1.5 × the upper limit of normal range (ULN)
    b. an aspartate aminotransferase (AST) level ≤ 3.0 × ULN
    c. an alanine aminotransferase (ALT) level ≤ 3.0 × ULN or, for subjects with documented metastatic disease to the liver, AST and ALT levels ≤ 5 × ULN.

    Patients with documented Gilbert disease are allowed if total bilirubin is < 3 × ULN.

9. Adequate renal function, defined by an estimated creatinine clearance ≥ 50 mL/min (Phase I) or ≥ 30 mL/min (Phase II) according to the Cockcroft-Gault formula or by 24-hour urine collection for creatinine clearance or according to local institutional standard method.

10. Negative serum pregnancy test at Screening for all postmenarchal girls, girls ≥ 10 years of age, or per local or institutional guidelines.

11. Highly effective contraception (ie, methods with a failure rate of less than 1% per year) for both male and female subjects if the risk of conception exists. In this trial, a subject is considered to be of childbearing potential if, in the opinion of the Investigator, he/she is biologically capable of having children and is sexually active. (Note: The effects of the trial treatment on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use highly effective contraception, defined in Appendix I or as stipulated in national or local guidelines. Highly effective contraception must be used for the duration of trial treatment, and at least for 60 days after stopping trial treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this trial, the treating physician should be informed immediately).

12. Estimated life expectancy of at least 3 months.

5.3.2 Exclusion Criteria

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

1. Prior therapy with any antibody or drug targeting T-cell coregulatory proteins (immune checkpoints), such as PD-1, PD-L1, or cytotoxic T-lymphocyte antigen-4.

2. Concurrent anticancer treatment (eg, cytoreductive therapy, radiotherapy, immune therapy, cytokine therapy, monoclonal antibody, targeted small molecule therapy) or any investigational drug **within 2 weeks** prior to start of study treatment, or not recovered from AEs related to such therapies, with the following exceptions:

    a. Short-course, bone-directed, palliative radiotherapy delivered in a normal organ-sparing technique is permitted (concurrently or within the pretreatment period).

    b. Erythropoietin and darbepoetin-α are permitted.

    c. Hormonal therapies acting on the hypothalamic-pituitary-gonadal axis are permitted (ie, luteinizing hormone-releasing hormone agonists/antagonists). No other hormonal anticancer therapy is permitted.

3. Major surgery for any reason, except diagnostic biopsy, within 4 weeks prior to start of study treatment and/or if the subject has not fully recovered from surgery within 4 weeks of the trial treatment.

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

    a. Subjects with adrenal insufficiency may continue corticosteroids at physiologic replacement dose.

b. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intra-ocular, or inhalation) is permitted.

c. Previous or ongoing administration of systemic steroids for the management of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the dose after 14 days will be equivalent to the physiologic replacement dose.

5. Previous malignant disease (other than the tumor disease for this trial) within the last 5 years (except adequately treated non-melanoma skin cancers, carcinoma in situ of skin, bladder, cervix, colon/rectum, breast, or prostate) unless a complete remission without further recurrence was achieved at least 2 years prior to study entry and the subject was deemed to have been cured with no additional therapy required or anticipated to be required

6. Prior organ transplantation, including allogeneic stem cell transplantation.

7. Significant acute or chronic infections, including, among others:
   a. Known history of human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.

   b. Hepatitis B virus or hepatitis C virus (HCV) infection (defined as HBV surface antigen positive and HBV core antibody positive with reflex to positive HBV DNA or HBV core antibody positive alone with reflex to positive HBV DNA; or positive HCV antibody with reflex to positive HCV RNA).

   c. Active tuberculosis (history of exposure or history of positive tuberculin test; plus presence of clinical symptoms, physical or radiographic findings). Subjects with latent tuberculosis infection who are deemed to require treatment by the Investigator are not eligible.

8. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:
   a. Subjects with diabetes type 1, vitiligo, psoriasis, or hypothyroid/hyperthyroid disease not requiring immunosuppressive treatment are eligible.

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

9. Known prior severe hypersensitivity to investigational product or any component in its formulations.

10. Persisting toxicity related to prior therapy of Grade > 2 NCI-CTCAE v4.03 (except neuropathy [see exclusion criterion #11] and alopecia).

11. Neuropathy ≥ Grade 3

12. Pregnancy or lactation

13. Known alcohol or drug abuse as determined by the Investigator

14. History of uncontrolled intercurrent illness, including but not limited to:
    a. Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower)
    b. Uncontrolled active infection.
    c. Uncontrolled diabetes (eg, hemoglobin A1c $\geq$ 8%).

15. Clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke or myocardial infarction (< 6 months prior to enrollment), unstable angina pectoris, congestive heart failure (New York Heart Association Classification Class $\geq$ II), clinically significant ventricular arrhythmia (ie, ventricular tachycardia, ventricular fibrillation, or Torsades de pointes), diagnosed or suspected congenital or acquired prolonged QTc syndrome, or serious uncontrolled cardiac arrhythmia requiring medication/active intervention.

16. All other significant diseases (eg, severe gastrointestinal conditions such as diarrhea, colitis, inflammatory bowel disease, ulcer, or pneumonitis; end-stage kidney disease or chronic kidney disease requiring hemodialysis; or uncontrolled asthma), which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment.

17. Any psychiatric condition, including recent (within 10 days) or active suicidal ideation or behavior that would prohibit the understanding or rendering of informed consent or that would limit compliance with trial requirements.

18. Administration of a live vaccine within 28 days prior to study entry and while on trial.

19. Rapidly progressive disease.

20. Known congenital immunodeficiency.

5.4 Criteria for Initiation of Trial Treatment

The inclusion and exclusion criteria will be checked at the Screening Visit. Individuals who do not meet the criteria for initiating treatment (screen failures) may be rescreened. The parent(s)/legal guardians of rescreened participants will sign a new ICF, a new subject number will be assigned, and the Screening procedures will be conducted.

5.5 Criteria for Subject Withdrawal

Subjects who have experienced a complete response (CR) should be treated for a minimum of 12 months based on clinical judgment of benefit and/or until confirmed progression per irRECIST, unacceptable toxicity, or any criterion for withdrawal occurs, after confirmation of response as specified in this protocol. Each subject will be followed for additional 12 months after end of treatment.

5.5.1 Withdrawal from Trial Therapy

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

- Subject or his/her parent(s)/legal representative(s) withdraw consent.
- Subject lost to follow up.
- Participation in another clinical trial.
- Any events that unacceptably endanger the safety of the subject.
- Subjects meeting the definition of confirmed PD while on treatment based on irRECIST. Subjects who experience confirmed disease progression may be permitted to continue treatment with avelumab per Section 6.2.1.
- Significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms.
- Unacceptable toxicity.
- Occurrence of an exclusion criterion that is clinically relevant and affects the subject's safety, if trial treatment discontinuation is considered necessary by the Investigator and/or Sponsor.
- Therapeutic failure requiring urgent additional drug (if applicable).
- Occurrence of any Grade $\geq$ 3 ADRs or as defined in Section 5.1.3.2.
- Occurrence of AEs resulting in the discontinuation of the trial treatment being desired or considered necessary by the Investigator and/or the subject.
- Occurrence of pregnancy.
- Use of a prohibited concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from the trial treatment if considered necessary by the investigator or the Sponsor.
- Noncompliance (see Section 6.9).

5.5.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time without giving a reason and at their own request or the request of their legally acceptable representative. They may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety or behavioral reasons or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

Withdrawal of consent will be considered withdrawal from the trial unless the subject and/or his/her parent(s)/legal representative(s) agree to be followed for survival, which may include verification of medical records. Subjects should be explicitly asked at the time of withdrawal of consent if they would allow survival information to be collected, including verification of medical/public records as permitted by local regulations. These response should accordingly be captured in the eCRF.

In case of withdrawal from the trial, the assessments scheduled for the last visit (End of Treatment Visit) should be performed, if possible, with focus on the most relevant assessments. In any case, the appropriate End of Safety Follow-up eCRF page must be completed. In case of withdrawal, subjects will be asked to continue safety and survival follow-up, which includes the collection of data on survival and subsequent anticancer therapy.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject or his/her legal representative. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The Investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject or legal representative refuses further visits, the subject should continue to be followed for survival unless the subject or legal representative withdraws consent for disclosure of future information or for further contact. In this case, no further study-specific evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

5.6 Premature Termination of the Trial

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable benefit risk assessment for avelumab. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of avelumab or withdrawal of avelumab from the market for safety reasons.

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

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

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

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

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

5.7 Definition of End of Trial

The end of the trial will be defined as 1 year after the last subject completes his/her End of Treatment Visit.

A clinical trial protocol may not be considered closed as long as:

- Any subject is still receiving avelumab.
- Visits specified by the protocol are still taking place.
- Procedures or interventions according to the protocol are still being undertaken in any subject.
- The post-treatment Follow-up Period, defined in the clinical trial protocol as being part of the trial, has not yet been completed for any subject.

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

6 Investigational Medicinal Product and Other Drugs Used in the Trial

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

6.1 Description of 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 single-use glass vials closed with a rubber stopper and sealed with an aluminum/yellow polypropylene flip-off seal.

6.2 Dosage and Administration

6.2.1 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.

The dose of avelumab will be calculated based on the weight of the subject determined within 72 hours prior to administration. The dose of avelumab used for the previous administration can be repeated if the change in the subject's weight is within 10% of the weight used for the last dose

calculation. Subjects will receive avelumab once every 2 weeks until the criteria in Sections 5.4, 5.5.1, and 5.5.2 are met.

Rules for dose modifications during the Phase I part of the study are described in Section 5.1.1.1. Modifications of the infusion rate due to infusion-related reactions are described in Section 6.5.5.1.

In order to mitigate infusion-related reactions, premedication with an antihistamine (H1 receptor blocker such as diphenhydramine) and with acetaminophen (paracetamol) approximately 30 to 60 minutes prior to each dose of study drug for the first 4 infusions is mandatory. This regimen may be modified based on local treatment standards and guidelines, as appropriate. Steroid premedication specifically for avelumab is not permitted.

Avelumab treatment may continue past the initial determination of confirmed progression per irRECIST as long as the following criteria are met:

- No new symptoms or worsening of previous symptoms
- Tolerance of avelumab
- Stable performance status (Lansky performance status $\geq$ 50% for subjects $\leq$ 16 years of age, or Karnofsky scale $\geq$ 50% for subjects > 16 years of age)
- Treatment will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)

The decision to continue treatment should be discussed with the Medical Monitor and documented in the trial records.

A radiographic assessment should be performed within 8 weeks of original PD to determine whether there has been a decrease in the tumor size, or confirmed PD per irRECIST. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with avelumab.

If the Investigator feels that the subject will continue to achieve clinical benefit by continuing treatment, and after discussion with the Medical Monitor, the subject can remain on the trial, continue to receive avelumab treatment, and continue to undergo monitoring according to the Schedule of Assessments (Table 1). The decision to continue treatment beyond confirmed progression should be approved by the Sponsor and documented in the trial records.

For subjects who continue avelumab beyond confirmed PD per irRECIST, further progression is defined as an additional 10% increase in tumor burden volume from time of confirmed PD. This includes an increase in the sum of all target lesions and/or the development of new measurable lesions. Further progression beyond confirmed PD will require discontinuation of avelumab therapy.

Additionally, subjects receiving avelumab who have experienced a CR should be treated for a minimum of 12 months based on clinical judgment of benefit and/or until confirmed disease progression, unacceptable toxicity, or any criterion for withdrawal occurs, after confirmation of response and at the discretion of the Investigator. In case such subject's disease relapses after

stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment will be allowed at the discretion of the Investigator and agreement with the Medical Monitor. To be eligible for retreatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Prior to re-initiation of the study treatment, malignant disease will be radiologically re-staged to assess all known sites of the disease and to establish a new baseline for subsequent tumor measurements. Relevant safety laboratory results must be available and verified prior to re-initiating treatment. Subjects who re-initiate treatment will stay on study and will be treated and monitored according to the protocol and the "Until EOT" schedule in the Schedule of Assessments (Table 1).

Immediate access to an intensive care unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, iv antihistamines, bronchodilators, and oxygen) must be available for use in the treatment of IRRs. Infusion of avelumab will be stopped in case of Grade ≥ 2 infusion-related, allergic, or anaphylactoid reaction. Following the first 4 avelumab infusions, subjects must be observed for 2 hours postinfusion for potential IRRs.

As with all monoclonal antibody therapies, there is a risk of allergic reaction. Avelumab should be administered in a setting that allows for immediate access and administration of therapy for severe allergic/hypersensitivity reactions, such as the ability to implement immediate resuscitation measures. Steroids, epinephrine, allergy medications (antihistamines), or equivalents should be available for immediate access.

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

6.2.2 Standard of Care

Not applicable.

6.3 Assignment to Treatment Groups

Once the subject or legal representative has provided a signed ICF and meets all inclusion criteria and does not meet any exclusion criterion, the Investigator or delegate will request trial registration using the IRT immediately prior to the first treatment. The trial is fully controlled by the IRT, which assigns treatment individual (unique) vial numbers for each subject. The vial number is linked via the GMP-qualified system to the corresponding treatment as well as to the subject.

Subject identifiers will comprise 17 digits, the first 10 digits representing the trial number, the following 3 digits representing the site number, and the last 4 digits representing the subject number, which is allocated sequentially starting with 0001.

In the Phase I dose-finding part of the study, subjects will be assigned to sequential cohorts of 3 to 6 subjects each. Phase II will have 2 expansion cohorts, with specific tumors chosen based on available data from the current study, other ongoing studies with avelumab or other ICIs, clinical and nonclinical combination chemotherapy data, and any published literature.

6.4 Noninvestigational Medicinal Products to Be Used

Mandatory premedication with an antihistamine (H1 receptor blocker such as diphenhydramine) and acetaminophen (paracetamol) for the first 4 doses is required in all subjects to be treated with avelumab (see Section 5.1.2 for details).

6.5 Concomitant Medications and Therapies

6.5.1 Permitted Medicines

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

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

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

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

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

6.5.2 Prohibited Medicines

Prohibited prior and concomitant drugs and treatments include the following (see Exclusion Criteria in Section 5.3.2):

- Systemic anticancer therapy ≤ 2 weeks prior to start of study treatment
- Immunosuppressive medication within 7 days prior to registration and Cycle 1 of treatment, except the following (see Section 6.5.5):
  - Intranasal, inhaled, and topical steroids, and local steroid injections (eg, intra-articular injection)
  - Systemic corticosteroids at physiologic doses
  - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication, transfusion of blood products; steroid premedication specifically for avelumab is not permitted).

- Vaccination 4 weeks prior to the first dose of avelumab and while on trial, except for administration of inactivated vaccines (eg, inactivated influenza vaccines)
- Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (or any other antibody or drug specifically targeting T cell co-stimulation or immune checkpoint pathways).
- Abuse of alcohol or other drugs during the trial.

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

- Immunotherapy, immunosuppressive drugs (ie, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of irAEs), or other experimental pharmaceutical products. Steroids with no or minimal systemic effect (topical, inhalation) are allowed.
- Growth factors (granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor). Exception: erythropoietin and darbepoietin-α may be prescribed at the Investigator's discretion.
- Herbal remedies with immunostimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin).

Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment (at Days 30 and 90 post-treatment ± 5 days). All concomitant medications, including supportive care drugs (eg, antiemetic treatment and prophylaxis), the drugs used to treat AEs or chronic diseases, and nondrug supportive interventions (eg, transfusions), should be recorded in the appropriate section of the eCRF, noting the name, dose, duration, and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

6.5.3 Other Interventions

The following nondrug therapies must not be administered during the trial and within 28 days before the start of trial treatment: major surgery (excluding prior diagnostic biopsy).

Prior palliative radiotherapy to metastatic lesions is permitted, provided it has been completed 48 hours prior to subject registration.

Palliative short-course, limited-field, bone-directed radiotherapy may be administered during the trial. The assessment of PD will be made according to RECIST 1.1 (Eisenhauer 2009) and as adjudicated by the Investigator and not based on the necessity for palliative bone-directed radiotherapy.

6.5.4 Special Precautions

As a routine precaution, subjects enrolled in this trial must be observed for 2 hours postinfusion for the first 4 infusions (except for conditions defined in Section 6.4), in an area with resuscitation equipment and emergency agents. At all times during avelumab 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 hypersensitivity reactions, methylprednisolone and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

Infusion of avelumab will be stopped in case of Grade ≥ 2 hypersensitivity, inflammatory response, or IRR. The treatment recommendations for IRRs and severe hypersensitivity reactions according to the NCI are as outlined in Sections 6.5.5.1 and 6.5.5.2, respectively.

Investigators should also monitor subjects closely for potential irAEs, which may become manifest earliest after weeks of treatment. Such events may consist of, but are not limited to, persistent rash, diarrhea and colitis, pneumonitis, endocrinopathies, myositis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of hypothetical irAEs also includes formation of auto-antibodies like antinuclear antibodies or anti-neutrophil cytoplasmic antibodies. See Section 6.5.5.3 for details on the management of irAEs.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

6.5.5.1 Infusion-Related Reactions

In order to mitigate infusion-related reactions, subjects must be premedicated with an antihistamine (H1 receptor blocker such as diphenhydramine) and with acetaminophen (paracetamol) approximately 30 to 60 minutes before the first 4 infusions of avelumab, or according to local standards (excluding steroids). 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 4.

Table 4 Treatment Modification for Symptoms of Infusion-related Reactions Associated with Avelumab

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the 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, NSAIDs, narcotics, iv 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. Infusion time should be extended to 2 hours, and subject should receive the full dose.
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.

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

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If a subject experiences a Grade 3 or Grade 4 infusion-related reaction at any time, the subject must discontinue avelumab. If an infusion reaction occurs, all details about drug preparation and infusion must be recorded.

6.5.5.2 Severe Hypersensitivity Reactions and Flu-like Symptoms

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

A. Symptoms

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

- Cyanosis.

B. Management

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

For prophylaxis of flu-like symptoms, indomethacin or comparable nonsteroidal anti-inflammatory drug dose (eg, ibuprofen or naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of avelumab iv infusion. Alternative treatments for fever (eg, acetaminophen [paracetamol]) may be given to subjects at the discretion of the Investigator.

6.5.5.3 Immune-related Adverse Events

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

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

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

Table 5 Management of Immune-related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over Baseline 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 ADL Colitis: abdominal pain; blood in stool	Delay 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 ADL 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 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)	**Management**	**Follow-up**
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 Delay avelumab therapy 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 Covering > 30% body surface area; life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3 Consider skin biopsy Dermatology consult	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume avelumab therapy following steroids taper (for initial Grade 3).

	1.0 to 2.0 mg/kg/day prednisone or equivalent	
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
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 Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and then resume 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 equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (eg, infliximab, cyclophosphamide, iv immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue 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 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 1 to 2 days	If returns to Baseline: Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper.

	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 worsens: Treat as Grade 3-4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone iv or iv equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted (for trial sites in Germany, only MRI is to be used)	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 600 mg/m^2 (for subjects 2 to 18 years of age) 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 – 1.5 x 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 – 6 x 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 Baseline: 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 x 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 Baseline: Taper steroids over at least 1 month.

Cardiac irAES		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory 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 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.	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.
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.	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A)
a Local guidelines, or (for example) ESC (European Society of Cardiology) or American Heart Association (AHA) guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	—	Continue hormone replacement/ suppression and monitoring of endocrine function as appropriate

Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency), or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve (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 T4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, prolactin, testosterone in men, estrogens in women) • Start hormone replacement/ suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild or moderate symptoms with normal MRI. Repeat the MRI in 1 month	Resume avelumab once symptoms and hormone tests improve (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI scan is documented. Continue hormone replacement/ suppression therapy as appropriate.

	• Withhold avelumab if severe symptoms or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate high-dose corticosteroids (1 to 2 mg/kg/day methylprednisolone iv or equivalent) followed by corticosteroids taper during at least 1 month.	
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4.03)	**Grade of other irAEs (NCI-CTCAE v4.03)**	**Grade of other irAEs (NCI-CTCAE v4.03)**
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 Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade 1: Taper steroids over at least 1 month
Grade 4	Permanently discontinue 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; ADL: activities of daily living; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BNP: B-type natriuretic peptide; CK-MB: creatine kinase-myocardial fraction b; CT: computed tomography; FSH: follicle stimulating hormone; GH: growth hormone; IGF-1: insulin-like growth factor; irAE: immune-related adverse event; LH: luteinizing hormone; MRI: magnetic resonance imaging; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Event; T4: free thyroxine; TSH: thyroid-stimulating hormone; ULN: upper limit of normal.

6.6 Packaging and Labeling of the Investigational Medicinal Product

Avelumab is formulated as a 20.0 mg/mL solution and is supplied by the Sponsor in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum/yellow polypropylene flip-off seal.

Avelumab will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines. Each box of avelumab will contain 1 vial. The information on the label will be in accordance with approved submission documents.

Avelumab will be shipped in suitable transport containers according to its storage and shipping conditions. Shipments are monitored with temperature control devices.

CCI [redacted]

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.

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

Avelumab stored at room temperature CCI [redacted] or at elevated temperatures CCI [redacted] for extended periods is subject to degradation. Avelumab must not be frozen. Rough shaking of avelumab must be avoided.

For application in this trial, avelumab must be diluted with 0.9% saline solution (sodium chloride injection) or as indicated in the Pharmacy Manual. 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 Pharmacy Manual.

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

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 trial drug, including reconciliation of drugs and maintenance of drug records.

- Upon receipt of trial drug, 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.
- The dispensing of the trial drug will be carefully recorded on the appropriate drug accountability forms provided by the Sponsor, and an accurate accounting will be available for verification by the Sponsor's Monitor at each monitoring visit.
- Trial drug accountability records will include:
  - confirmation of trial drug delivery to the trial site.
  - the inventory at the site of trial drug provided by the Sponsor and prepared at the site.
  - the use of each dose by each subject.
  - dates, quantities, batch numbers, expiry dates and (for trial drug prepared at the site) formulation, as well as the subjects' trial numbers.
- The Investigator should maintain records that adequately document that:
  - the subjects were provided the doses specified by the clinical trial protocol.
  - all trial drug provided by the Sponsor was fully reconciled.

Unused trial drug must not be used for any purpose other than the current trial. Any trial drug that has been dispensed to a subject must not be redispensed to a different subject.

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

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

- all administered units.
- all unused units.
- all destroyed units (during the trial).
- all destroyed units at the end of trial.
- date of destruction(s).
- name and signature of the Investigator/pharmacist.

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

- after the expiry date.
- after the retest date unless the trial drug is reanalyzed and its retest date extended.

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

6.9 Assessment of Investigational Medicinal Product Compliance

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

Noncompliance is defined as a subject missing > 1 cycle of trial treatment for nonmedical reasons and barring any extenuating circumstances in the opinion of the Investigator. If 1 cycle was missed, and the interval between the subsequent treatment cycle and the last administered treatment cycle was longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance are met as well.

6.10 Blinding

This is an open-label trial. Therefore, trial treatment is not blinded.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose 5% or more than the calculated dose for that particular administration. Any overdose must be recorded in the trial drug section of the eCRF.

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

6.13 Medical Care of Subjects after End of Trial

After a subject has completed the trial or has withdrawn early, usual treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice and depending on the subject's individual medical needs. The Sponsor will not provide any additional care to subjects after they leave the trial because such care should not differ from what is normally expected for subjects with solid tumors unless it differs from local laws and regulations.

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

If the trial is not terminated for a reason given in Section 5.6, the survival follow-up will continue until up to 1 year after the last subject receives the last dose of avelumab or the last subject dies, whichever comes first. The Sponsor may terminate the study at any time, and there may be allowance for subjects to enter a rollover study, expanded access, or other mechanism for avelumab access as appropriate.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

A complete Schedule of Assessments is provided in Table 1. The Schedule of Assessments-Pharmacokinetic and Antidrug Antibody Sampling is provided in Table 2, and the PK/ADA procedures are discussed in Section 7.5.

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

7.1.1 Screening and Baseline Procedures and Assessments

The Screening procedures and Baseline assessments will be completed within 28 days before trial treatment starts.

During the Screening period and before any trial-related investigations and assessments are started, the subject's parents/legal guardians will be asked to sign the ICF. A discussion about conducting tumor sampling at the time of progression should be part of the initial informed consent process.

The Screening procedures and Baseline assessments will be completed within 28 days of signing the ICF and prior to registration and avelumab infusion on Cycle 1 Day 1. Failure to establish eligibility within 28 days would result in Screening failure, and the subject will be excluded from the trial. However, subjects can be rescreened based on the Investigator's judgment and following Sponsor approval. In this case, the parent(s)/legal guardian(s) of rescreened participants will sign

a new ICF, a new subject number will be assigned, and the Screening procedures will be conducted.

The subjects' information that will be documented during Screening includes demographic information (birth date, sex, and race as permitted by local regulations), and the complete medical history, including the history of solid tumor or lymphoma, previous and ongoing anticancer therapies, and baseline medical condition (concomitant medications and procedures and AEs will be monitored throughout the trial treatment period). Moreover, an Emergency Medical Support card will be handed out at the Baseline Assessments Visit.

During Screening, subjects will undergo a complete physical examination, including recording body height and weight, vital signs, 12-lead ECG, and a determination of performance status (using Lansky performance status for subjects ≤ 16 years of age or Karnofsky scale for subjects > 16 years of age). Baseline data information should be completed before the collection of blood samples, tumor biopsies, or any invasive procedure other than the aforementioned vital signs, demographics, and clinical history information.

The Screening laboratory examination includes hematology, hemostaseology, full serum chemistry, and full urinalysis (dipstick plus microscopic evaluation). Free thyroxine (T4) and thyroid-stimulating hormone (TSH) will also be assessed at Screening for all subjects.

During Screening, a serum beta-human chorionic gonadotropin (βhCG) pregnancy test will be performed for females of childbearing potential, and blood HBV and HCV screening tests will be performed for all screened subjects, as these conditions are trial entry exclusion criteria (see Section 5.3.2).

As permitted by local or institutional regulations, subjects who are of childbearing potential (defined as, in the opinion of the Investigator, the subject is biologically capable of having children and is sexually active) will be asked to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception (see Appendix I). As permitted by local or institutional regulations, the Investigator or his or her designee will discuss with the subject the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the subject's chart. In addition, the Investigator or his or her designee will instruct the subject to call immediately if 1 or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the subject or the subject's partner.

Baseline tumor evaluation (type and staging, etc.) will be performed using CT or MRI (see Section 7.2.5 for details). The tumor evaluation will include all known or suspected disease sites. Imaging may include neck, chest, abdomen, and pelvis CT or MRI scans (if MRI is used, CT of chest is mandatory; for trial sites in Germany, only MRI is to be used). Baseline CNS imaging will not be required with the exception of symptomatic subjects to evaluate for CNS metastases. A bone scan (bone scintigraphy) or fluorodeoxyglucose F 18-positron emission tomography/CT (^{18}FDG-PET/CT) is required at Baseline in subjects with tumors known to metastasize to bone.

Subjects are required to provide tumor tissue samples, see Section 7.6.1 for details. Tumor tissue can be archival tissue (blocks preferable) or from a biopsy performed during screening (blocks or slides, blocks preferable).

Blood samples will be collected prior to the first dose of avelumab to determine baseline lymphocyte subset quantification (ie, T-cell, B-cell, and NK-cell numbers and T-cell population) and for assessing baseline vaccination-related antibody titers and cytokines.

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7.1.2 Treatment Period

In this trial, trial treatment will be given until confirmed disease progression, significant clinical deterioration (confirmed clinical progression), death, unacceptable toxicity, or any criterion for withdrawal from the trial or trial treatment is fulfilled (see Section 5.5.1). Treatment may continue past the initial determination of confirmed disease progression according to irRECIST if the subject's performance status has remained stable and if, in the opinion of the Investigator, the subject will benefit from continued treatment (see Section 6.2). Additionally, subjects who have experienced a CR should be treated for a minimum of 12 months based on clinical judgment of benefit and/or until confirmed disease progression or unacceptable toxicity, after confirmation of response, at the discretion of the Investigator.

In case such subject's disease relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment will be allowed at the discretion of the Investigator and with the agreement with the Medical Monitor. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Prior to re-initiation of the study treatment, malignant disease will be radiologically re-staged to assess all known sites of the disease and to establish a new baseline for subsequent tumor measurements. Relevant safety laboratory results must be available and verified prior to re-initiating treatment. Subjects who re-initiate treatment will stay on study and will be treated and monitored according to the protocol and the "Until EOT" schedule in the Schedule of Assessments. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol (see Table 1).

Study treatment must begin within 28 days of Screening. While on trial treatment, subjects will be asked to visit the trial site once every 2 weeks during the treatment period. A time window of up to 3 days before or 1 day after the scheduled visit day will be permitted for all trial procedures; however, the biweekly, 14-day treatment schedule should be strictly adhered to, and subjects should return to the target date even if the previous visit was off schedule.

Tumor evaluation (see Section 7.3) will be performed every 8 weeks starting at Cycle 5 for the first 24 weeks, then every 12 weeks until the end of treatment or withdrawal from the study, and at the End of Treatment/Withdrawal Visit if more than 4 weeks has passed since the last evaluation.

Subjects will receive avelumab by iv infusion following pretreatment with an antihistamine (H1 receptor blocker such as diphenhydramine) and acetaminophen (paracetamol; oral or iv), approximately 30 to 60 minutes prior to each dose, once every 2 weeks for the first 4 infusions (see Section 5.1.2).

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

7.1.3 End of Treatment

Subjects who discontinue treatment will have End of Treatment and Safety Follow-up Visits as indicated in Table 1. All AE information for subjects who discontinue avelumab should be collected as described in Section 7.4.1.2.

The possibility of the subject undergoing optional tumor sampling at confirmed progression will be discussed with the subject's parent(s)/legal guardian(s) and the subject (when age appropriate and per local regulations) during the initial informed consent discussion. The appropriate timing of the optional tumor sampling should be discussed with the Sponsor and Medical Monitor.

7.1.3.1 End of Treatment Visit

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

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

- Documentation of AEs, serious AEs, and concomitant medication and procedures
- Physical examination, including vital signs, body weight, and height
- Performance status (Lansky performance status for subjects ≤ 16 years of age, or Karnofsky scale for subjects > 16 years of age)
- 12-lead ECG
- Laboratory hematology, hemostaseology (coagulation), full serum chemistry, full urinalysis (dipstick plus microscopic evaluation), and T4 and TSH levels
- Pregnancy test for female subjects of childbearing potential
- Blood sample for lymphocyte subset quantification
- Blood sample for PK determinations
- Blood sample for measuring cytokines and vaccination-related antibodies

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7.1.4 Safety Follow-up

Follow-up with each subject will be conducted 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab. The 30-Day Safety Follow-up Visit should be performed at the trial site; the 90-Day Safety Follow-Up can be performed via telephone contact. Each follow-up will include an assessment of safety parameters as described in Table 1. All SAEs and all treatment-related nonserious AEs need to be documented through the study's 90-day Safety Follow-up Phone Call.

During the post-treatment safety follow-up period, AEs and SAEs that the Investigator believes have at least a reasonable possibility of being related to study drug are to be recorded on the eCRF.

Any SAE assessed as related to study treatment must be reported whenever it occurs, irrespective of the time elapsed since the last administration of study treatment. Subjects or their legal representative will also be asked about any antitumor therapy.

7.1.5 Long-term Follow-up

After discontinuation of study treatment, poststudy survival status will be collected every 12 weeks (± 1 week) until death, until 12 months after termination of treatment of the last subject, or until end of study, whichever occurs first. This follow-up will include collection of information on subsequent anticancer therapies. Telephone contact is acceptable.

Subjects with ongoing SAEs reported at the 90-Day Safety Follow-up telephone call or reported during survival follow-up telephone calls 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."

Any subsequent anticancer therapies and the date of any response and subsequent progression should be captured in the eCRF.

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7.2 Demographic and Other Baseline Characteristics

7.2.1 Demographic Data

At Screening, the following demographic data will be collected:

- Date of birth (based on local regulations); sex (gender); race and ethnicity (when permitted by local regulations); childbearing potential in girls and the ability to father children in boys; height; and weight
- Medical history and disease history: previous illness, concomitant illness at entry into the trial, allergies, prior therapies and regimens for the target indication (relevant previous medications), concomitant therapies to be continued during the trial, and treatments stopped or changed at entry into the trial
- Performance status (Lansky performance status for subjects ≤ 16 years of age, or Karnofsky scale for subjects > 16 years of age).

7.2.2 Diagnosis of Solid Tumors or Lymphomas

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

- Detailed history of the malignancy, including histopathological diagnosis, grading, and staging in accordance with the appropriate staging system for each tumor type
- All therapy used for prior treatment of the malignancy (including surgery, radiation therapy, chemotherapy, and immunotherapy)
- Any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy
- Current signs and symptoms of the malignancy and AEs from current and previous anticancer treatments
- Current disease status.

7.2.3 Medical History

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

- Past and concomitant nonmalignant diseases and treatments
- All medications taken and procedures carried out within 28 days prior to Screening.

7.2.4 Vital Signs and Physical Examination

The assessments listed below will be performed during Screening and as indicated in the Schedule of Assessments (Table 1).

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

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

Body weight and height will be recorded.

7.2.5 Computed Tomography or Magnetic Resonance Imaging Scans for Tumor Assessment

Baseline imaging will be performed within 28 days prior to registration and Cycle 1 Day 1 treatment in order to establish Baseline disease status of target and nontarget lesions according to RECIST 1.1. Acceptable modalities include CT scans (neck, chest, abdomen, and pelvis as needed), and CT chest with contrast together with MRI of the abdomen and pelvis. The same imaging modality (CT or MRI) should be used throughout the study for a particular subject. Computed tomography images from a whole-body PET/CT may be used as long as imaging quality and the slice thickness of the CT images are of the quality from a dedicated CT scan. The use of iv contrast is preferred unless there is a history of allergy or other risk in the opinion of the Investigator (chest X-ray is not acceptable). Other imaging modalities may be performed at the discretion of the Investigator and as clinically indicated.

Baseline tumor burden should be determined as outlined in Section 7.3. In general, lesions detected at Screening/Baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

A bone scan (bone scintigraphy) or ^{18}FDG-PET/CT will be required at Baseline in subjects with tumors known to metastasize to bone, with radiographic disease re-evaluation only if bone metastases are present at Baseline. Otherwise, bone imaging will be required only if new bone metastases are suspected. Additional imaging may need to be performed in case bone metastasis are detected, and these should be followed in accordance with RECIST 1.1. Baseline CNS imaging will not be required with the exception of symptomatic subjects to evaluate for CNS metastases.

7.2.6 Cardiac Assessments

All subjects require a single 12-lead ECG at Baseline and at other visits as indicated in the Schedule of Assessments (Table 1) after the subject has been in a supine position breathing quietly for 5 minutes. The ECG results will be used to evaluate the heart rate, atrial ventricular conduction, QR and QT intervals, and possible arrhythmias. If prolonged QTc is suspected, then the ECG should be re-evaluated by a qualified person (ie, a cardiologist) at the institution for confirmation.

7.2.7 Clinical Laboratory Tests

Blood samples will be collected at Screening for clinical laboratory parameter evaluations. These clinical laboratory test results will serve not only as the Baseline values for subsequent safety

clinical laboratory evaluations during the trial, but also help to make sure that each enrolled subject fulfills all the trial entry criteria and does not meet any of the trial exclusion criteria for laboratory parameters as listed in Section 5.3. Detailed description of laboratory assessments is provided in Section 7.4.3.

7.3 Efficacy Assessments

To determine the ORR, the anticancer activity of avelumab will be evaluated by performing CT/MRI scans until confirmed disease progression or the start of new anticancer therapy.

A CT or MRI will be performed every 8 weeks for the first 24 weeks, then every 12 weeks thereafter (a window of 5 days prior to dosing is allowed, and ± 5 days at the End of Treatment Visit). In case partial response (PR), complete response (CR), or progressive disease (PD) is observed according to RECIST 1.1, a confirmation CT or MRI should be performed according to RECIST 1.1, preferably at the regularly scheduled 8-week assessment interval, but no sooner than 4 weeks after the initial documentation of response or confirmed disease progression. Tumor assessment should be repeated at the End of Treatment Visit if more than 4 weeks have passed since the last evaluation.

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Treatment decisions will be made by the Investigator based on the Investigator's assessment of disease status. Investigator's assessment of objective tumor response to treatment will be performed according to RECIST 1.1 (all measurements should be recorded in metric notation, as described in RECIST 1.1).

7.4 Assessment of Safety

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

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the trial, from the time of the subject's assent (when age appropriate and per local regulations) and the subject's legal representative signature of informed consent. Trial site personnel will report any AE, whether observed by the Investigator or reported by the subject and/or his/her parent(s)/legal representative(s) (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 IRR. 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 the Schedule of Assessments (see Table 1).

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

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

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

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

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

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

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

The 5 general grades are:

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

According to Sponsor convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets 1 of the serious criteria described below.

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

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

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

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

Treatment-emergent Adverse Event (TEAE)

Treatment-emergent adverse events are defined as events with onset dates occurring on treatment or events that worsen on treatment.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

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

Adverse Drug Reaction (ADR)

Adverse drug reactions are defined in this study as any AEs suspected to be related to study treatment 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" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.)
- Requires inpatient hospitalization or prolongs an existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise considered to be medically important.

Note: important medical events that may not result in death, be life threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they

may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE, as described in Section 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

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

Events Not to Be Considered as AEs/SAEs

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

AE/SAEs Observed in Association with Disease Progression

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

7.4.1.2 Methods of Recording and Assessing Adverse Events

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

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

It is important that each AE report include a description of the event, its duration (onset and resolution dates [and times when it is important to assess the time of AE onset relative to the

recorded treatment administration time]), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the trial treatment, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

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

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance will begin when the subject is initially included in the trial (date of first signature of informed consent) and continue through the 90-Day Safety Follow-up Phone Call, which is defined as occurring 90 days (± 5 days) after last study drug administration.

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

7.4.1.4 Procedure for Reporting Serious Adverse Events

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

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

Relevant pages from the eCRF may be provided in parallel (eg, medical history or 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 request for follow-up information (eg, additional information, outcome, final evaluation, or other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the Global Drug Safety Department of the Sponsor may contact the Investigator directly to obtain clarification or to obtain further information or to discuss the 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 (particularly deaths) involving trial subjects to the IEC/IRB that approved the trial.

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

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

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

7.4.1.6 Monitoring of Subjects with Adverse Events

Any AE that occurs during the course of a clinical trial must be monitored and followed up and are assessed for final outcome at the Safety Follow-up Phone Call at 90 days (± 5 days) after the last IMP administration. All SAEs and all treatment-related nonserious AEs need to be documented through the study's Safety Follow-up Phone Call.

All SAEs ongoing at 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." Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

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

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

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

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

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

7.4.3 Laboratory Assessments

Clinical laboratory samples, as detailed in the Schedule of Assessments (see Table 1) and listed in Table 6, will be collected and analyzed locally. Local laboratory samples and results will be recorded in the eCRFs according to the eCRF completion guidelines. The report of the results must be retained as a part of the subject's medical record or source documents. Blood samples for the full safety tests listed in Table 6 will be taken from nonfasted subjects as detailed in the Schedule of Assessments (Table 1). Urinalysis, and T4 and TSH tests will be performed only at the time points defined in Table 1.

Sample collection, details of blood volume by visit and assessment, labeling, and storage requirements will be summarized in a separate Laboratory Manual or Manual of Operations.

Table 6 Clinical Laboratory Assessments

Full Chemistry	Core Chemistry[a]	Hematology
Albumin	Alkaline phosphatase	Absolute lymphocyte count
Alkaline phosphatase	ALT	Absolute neutrophil count
ALT	AST	Hematocrit
Amylase	BUN/total urea	Hemoglobin
AST	Calcium	Platelet count
GGT	Chloride	RBC count
BUN/total urea	Creatinine	White blood cell count and differential count
Calcium	Glucose	
Chloride	Phosphorus/Phosphates	
Cholesterol	Magnesium	
Creatine kinase	Potassium	
Creatinine	Sodium	
CRP	Total bilirubin	
Glucose	Lipase	**Hemostaseology**
LDH	Amylase	aPTT
Lipase	Creatine kinase	Prothrombin time/INR
Phosphorus/Phosphates		
Magnesium		**Basic Urinalysis** (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) **Full urinalysis** (dipstick plus microscopic evaluation) to be performed only at the Screening and End of Treatment Visit
Potassium		
Sodium		
Total bilirubin		
Total protein		
Uric acid		Totality of binding ADA
Triglycerides		
		TSH and T4
Hormone		

ADA: antidrug antibody; ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CRP: C-reactive protein; GGT: gamma-glutamyltransferase; INR: international normalized ratio; LDH: lactate dehydrogenase; RBC: red blood cell; TSH: thyroid-stimulating hormone; T4: free thyroxine.

a. Core serum chemistries.

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

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

Vital signs, performance status, and 12-lead ECG will be assessed according to the Schedule of Assessments (see Table 1).

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

Body weight will be recorded at Screening and at subsequent visits as indicated in the Schedule of Assessments (see Table 1) and documented in the eCRF. Height will be measured at Screening and every 4 weeks thereafter.

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

For female subjects of childbearing potential, a serum βhCG pregnancy test will be carried out during Screening, and urine or serum βhCG pregnancy tests will be carried out at the visits indicated in the Schedule of Assessments (see Table 1).

7.5 Pharmacokinetics

Blood samples for population PK determinations after a single dose as well as multiple doses of avelumab will be collected from all subjects in the study (Phase I and Phase II).

Samples for PK assessments will be collected as per the Schedule of Assessments - PK and ADA Sampling (see Table 2) and stratified by weight (< 10 kg and ≥ 10 kg) for the first 36 subjects. Pharmacokinetic samples will be collected during treatment Cycles 1, 2, 3, 5, 7, 8, 13, 19, 25, and every 6 cycles thereafter. Additional PK samples will be collected at the End of Treatment Visit and the 30-Day Safety Follow-up Visit. Serum concentrations of avelumab will be determined by a validated method. After the first 36 subjects, a more sparse PK sampling schedule will be followed.

7.5.1 Body Fluid(s)

Sample collection, details of blood volume by visit and assessment, labeling, storage, and shipment requirements will be summarized in a separate Laboratory Manual or Manual of Operations.

7.5.2 Pharmacokinetic Calculations

The methodology and software for PK calculations and PK parameter estimation will be specified in the Statistical Analysis Plan (SAP).

7.6 Biomarkers

Storage and analyses of biomarker samples will be handled according to the specifications as described in the ICF.


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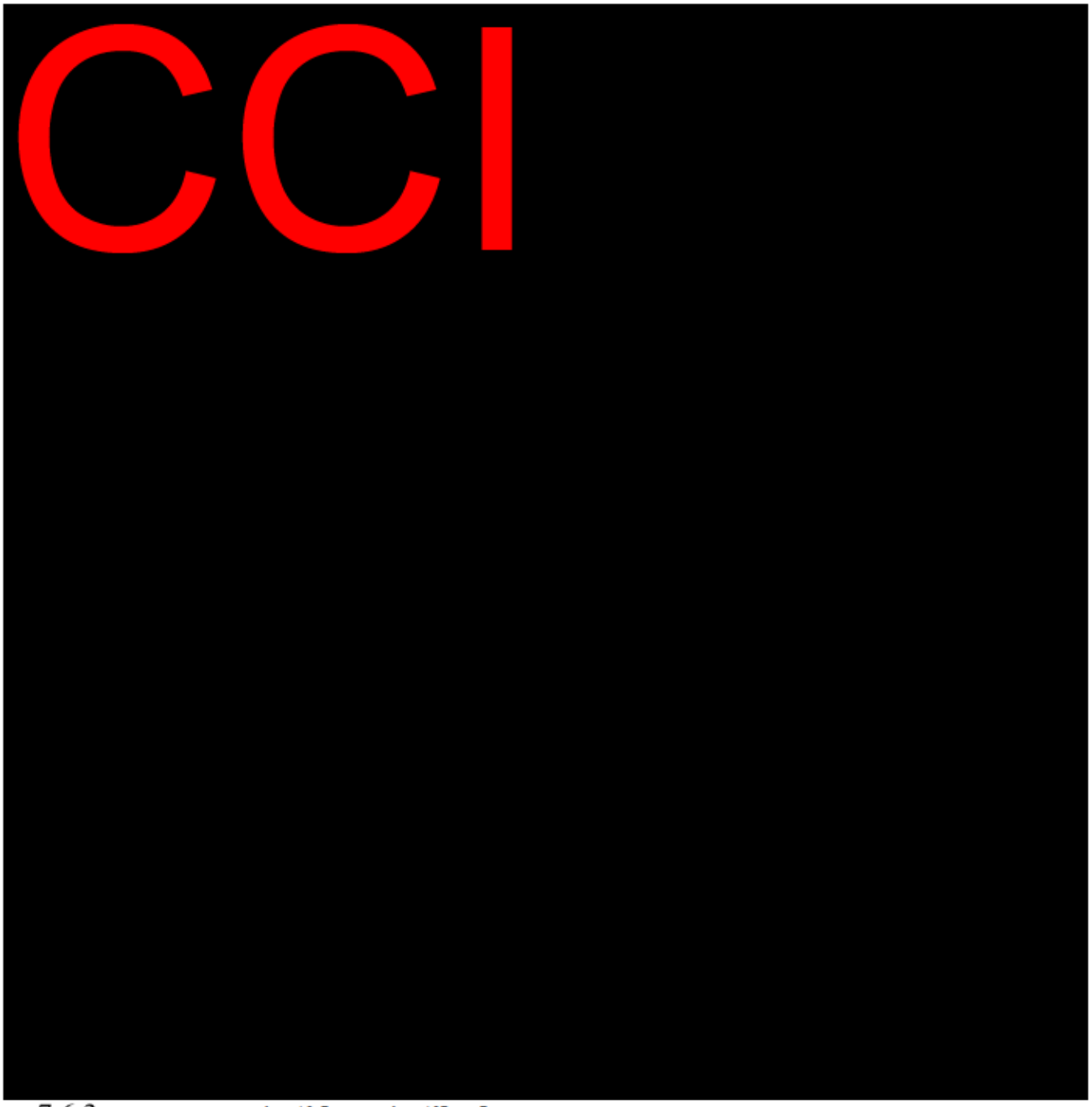

7.6.3 Antidrug Antibody

An overview of human ADA immunogenicity assessments (including neutralizing antibodies [NAbs]) planned in the trial is provided in the Schedule of Assessments - PK and ADA Sampling (see Table 2).

A blood sample for baseline ADA analysis will be collected within 2 hours prior to trial treatment administration on Cycle 1 Day 1. Further blood samples for ADA analysis will be collected predose (within 2 hours prior to trial treatment) during Cycles 2, 3, 5, 7, 13, 19, 25, and every 6 cycles thereafter for as long as the subject is receiving trial treatment; at the End of Treatment

Visit; and at the 30-day Safety Follow-up Visit. Samples positive for ADA will be re-analyzed to determine the titer and tested for neutralizing capacity.

7.7 Other Assessments

7.7.1 Subject-reported Outcomes/Quality of Life

See Appendix III for the Lansky and Karnofsky performance scales. Detailed methodology will be included in the Manual of Operations.

8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Primary Endpoints

Phase I and Phase II primary endpoints are as follows.

Phase I

- Occurrence and severity of TEAEs ≥ Grade 3 according to NCI-CTCAE v4.03
- DLTs to determine the RP2D

Phase II

- Confirmed BOR according to RECIST 1.1 and as adjudicated by the Investigator.

Dose-limiting toxicities are described in Section 5.1.1.1.2, and the RP2D is defined in Section 5.1.1.1.4.

Best overall response is defined as the best response obtained among all tumor assessment visits after the date of the first dose of avelumab until confirmed disease progression. It will be determined according to RECIST 1.1 and as adjudicated by the Investigator. Only tumor assessments performed before the start of any further anticancer treatment will be considered in the assessment of BOR. Clinical deterioration will not be considered as documented disease progression.

If deemed appropriate based on emerging data from this trial, an Independent Review Committee may be added at a later date following a protocol amendment.

8.3.2 Secondary Endpoints

Phase I and Phase II secondary endpoints are as follows.

Phase I

- Confirmed BOR according to RECIST 1.1 and as adjudicated by the Investigator
- DOR, TTR, PFS per RECIST 1.1 and as adjudicated by the Investigator, and OS
- Occurrence and severity of TEAEs, AEs of special interest, and treatment-related AEs, and incidence of laboratory abnormalities, as graded by NCI-CTCAE v4.03
- Vital signs (including blood pressure and heart rate)
- Single- and multiple-dose PK profiles of avelumab (ie, C_{max}, AUC, $t_{1/2}$, and C_{trough}, as data permit)
- Immunogenicity as measured by avelumab ADA, including NAbs
- Assessment of tumor PD-L1 expression; tumor-infiltrating T-cell activity; T-cell population; and T-cell, B-cell, and NK-cell numbers at Baseline and at confirmed progression (if tumor tissue is obtained)
- Vaccination-related antibody concentrations.

Phase II

- DOR, TTR, PFS per RECIST 1.1 and as adjudicated by the Investigator, and OS
- Occurrence and severity of TEAEs, AEs of special interest, and treatment-related AEs, and incidence of laboratory abnormalities, as graded by NCI-CTCAE v4.03
- Vital signs (including blood pressure and heart rate)
- Single- and multiple-dose PK profiles of avelumab (ie, C_{max}, AUC, $t_{1/2}$, and C_{trough}, as data permit)
- Immunogenicity as measured by avelumab ADA, including NAbs

- Assessment of tumor PD-L1 expression; tumor-infiltrating T-cell activity; T-cell population; and T-cell, B-cell, and NK-cell numbers at Baseline and at confirmed progression (if tumor tissue is obtained)
- Vaccination-related antibody concentrations.

Duration of response is defined, for subjects with an OR, as the time from first documentation of OR (CR or PR) to the date of first documentation of objective PD or death due to any cause, whichever occurs first. If a subject has not had an event (PD or death), DOR is censored at the date of last adequate tumor assessment. Censoring rules are the same as for PFS.

Time to response is defined, for subjects with an OR, as the time from the date of first dose of avelumab to the first documentation of OR (CR or PR), which is subsequently confirmed.

Progression-free survival is defined as the time from the date of first dose of avelumab to the date of the first documentation of objective PD per RECIST 1.1 or death due to any cause, whichever occurs first. Progression-free survival data will be censored on the date of the last adequate tumor assessment for subjects who do not have an event (PD or death), for subjects who start a new anticancer therapy prior to an event, or for subjects with an event after 2 or more missing tumor assessments. Subjects who do not have a Baseline tumor assessment or who do not have any post-Baseline tumor assessments will be censored on the start date unless death occurred on or before the time of the second planned tumor assessment, in which case the death will be considered an event.

Overall survival is defined as the time from the date of first dose of avelumab to the date of death due to any cause. Subjects last known to be alive will be censored at date of last contact.

8.4 Analysis Sets

Full Analysis Set (FAS): All subjects enrolled in the study and receive at least 1 dose of avelumab.

Safety Analysis Set (SAF): All subjects who receive at least 1 dose of avelumab. In this trial, the SAF = FAS.

Per-Protocol (PP) Analysis Set: A subset of the FAS; will include all FAS subjects who did not have any clinically important protocol deviations.

DLT Analysis Set (Phase I only): All subjects with data used for implementing the dose escalation schedule. These subjects will have received all trial treatment administrations in the DLT evaluation period (first 2 cycles of treatment) or stopped treatment because of DLTs in the DLT evaluation period.

PK Analysis Set: All subjects who complete at least 1 administration of avelumab and who provide at least 1 sample with measurable concentrations of avelumab (at least 1 predose and 2 postdose from 2 or more treatment cycles).

Immunogenicity Analysis Set: All subjects who complete at least 1 administration of avelumab, and who have provided a blood sample prior to any avelumab treatment and at least 1 post-treatment sample.

Biomarker Analysis Sets: All subjects who complete at least 1 administration of avelumab, and who have provided the appropriate blood/serum/plasma samples for biomarker assessments.

8.5 Description of Statistical Analysis

8.5.1 General Considerations

Full details of all planned analyses will be described in the trial SAP.

Analyses for Phase I will be presented by dose level and overall, and analyses for Phase II will be presented by expansion cohort and overall, if not stated otherwise.

All data recorded during the trial will be presented in individual data listings performed on the SAF. All data will be evaluated as observed, and no imputation method for missing values will be used unless otherwise specified in the SAP. All data will be presented in a descriptive manner. Each cohort will be analyzed separately, and no multiplicity adjustment across cohorts will be performed.

Descriptive statistics will be used to summarize the trial results, ie, statistics for continuous variables may include number of subjects (n); mean, standard deviation; median, 25th Percentile - 75th Percentile (Q1-Q3), minimum, and maximum . Qualitative variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by confidence intervals (CIs). Unless otherwise specified, the calculation of proportions will be based on the number of subjects in the analysis set 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.

Baseline

In general the last nonmissing measurement prior to randomization will serve as the Baseline measurement for efficacy. If no such a value is available, the last measurement prior to the first trial drug administration will be used as the Baseline measurement with the exception of pre-

randomization assessments used for the derivation of efficacy endpoints (eg, tumor assessment at baseline, which will be set to missing, if not done prior to randomization).

The last available assessment prior to the start of study treatment is defined as "Baseline" value or "Baseline" assessment for safety.

On-Treatment

On-treatment Period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer therapy – 1 day), unless otherwise stated.

The DLT Analysis Set is the underlying data set for the MTD determination. Safety analyses will be performed on the SAF. Baseline summaries and efficacy analyses will be performed on the FAS. Analyses of PK variables will be performed on the PK Analysis Set. Analysis of peripheral blood mononuclear cell pharmacodynamic data will be performed on the Immunogenicity Analysis Set. Analyses of biomarkers will be performed on the respective Biomarker Analysis Sets.

The estimation of PK parameters will be performed using the validated software tool Phoenix® WinNonlin 6.3® (or later). All other statistical analyses will be performed using SAS® Version 9.2 or higher.

8.5.2 Analyses of Primary Endpoints

8.5.2.1 Phase I: Occurrence and Severity of Treatment-emergent Adverse Events ≥ Grade 3

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

Adverse events (serious and nonserious) will be considered TEAEs when emerging or worsening in the on-treatment period, defined as the time from the first trial drug administration to the last drug administration date + 30 days or the earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurs first, unless otherwise stated.

The frequency of subjects experiencing TEAEs ≥ Grade 3, regardless of relatedness to trial treatment, will be summarized by system organ class and preferred term at each dose level and described in terms of severity. Similar summaries will also be provided for TEAEs ≥ Grade 3 related to trial treatment.

8.5.2.2 Phase I: Determination of Recommended Phase II Dose

For determination of RP2D, individual subject data from the dose escalation part of the study will be reported by dose level.

In addition, the following will be analyzed:

- At each dose level, the number and proportion of subjects in the DLT Analysis Set who experienced a DLT during the DLT evaluation period
- At each dose level, the number and proportion of TEAEs experienced by subjects in the DLT Analysis Set during the DLT evaluation period
- At each dose level and overall, the number and proportion of TEAEs ≥ Grade 3 by subjects in the DLT Analysis Set during the DLT evaluation period.

The MTD is defined as the highest dose tested of avelumab associated with the occurrence of DLTs within the first 2 cycles of treatment in < 33% of subjects, provided that a higher dose of avelumab was tested and had an associated DLT rate ≥ 33%. If the DLT rate within the first 2 cycles of treatment is < 33% for all tested dose levels, then the MTD will not have been reached.

8.5.2.3 Phase II: Confirmed Best Overall Response According to RECIST 1.1 and Investigator

Best overall response will be evaluated according to RECIST 1.1 and based on the Investigator's assessments of disease at different evaluation time points from the first trial administration date until confirmed disease progression.

Only tumor assessments performed before the start of any further anticancer treatment will be considered in the assessment of BOR. Clinical deterioration will not be considered progression.

Subjects who do not have an on-treatment radiographic tumor assessment due to early progression, who receive antitumor treatments other than the trial treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR, will be counted as nonresponders in the assessment of OR.

Objective response is defined as CR or PR according to RECIST 1.1 from the date of first dose of avelumab until documented disease progression. Both CR and PR must be confirmed by repeat assessments according to RECIST 1.1, preferably at the regularly scheduled 8-week assessment interval, but no sooner than 4 weeks after the initial documentation of response or confirmed disease progression. Subjects who do not have an on-treatment radiographic tumor assessment due to early progression, who receive antitumor treatments other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR, will be counted as nonresponders in the assessment of OR

The analysis of the BOR will be conducted using the FAS. The ORR, defined as the proportion of subjects with BOR of PR or CR, will be tabulated by cohort. A 2-sided 95% Clopper-Pearson CI will be constructed.

The response at each scheduled tumor assessment and the BOR will be listed for each subject.

8.5.3 Analyses of Secondary Endpoints

8.5.3.1 Phase I: Confirmed Best Overall Response According to RECIST 1.1 and Investigator

Best overall response will be evaluated according to RECIST 1.1 and based on the Investigator's assessments of disease at different evaluation time points from the first trial administration date until confirmed disease progression.

Only tumor assessments performed before the start of any further anticancer treatment will be considered in the assessment of BOR. Clinical deterioration will not be considered progression.

Subjects who do not have an on-treatment radiographic tumor assessment due to early progression, who receive antitumor treatments other than the trial treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR, will be counted as nonresponders in the assessment of OR.

Objective response is defined as CR or PR according to RECIST 1.1 from the date of first dose of avelumab until documented disease progression. Both CR and PR must be confirmed by repeat assessments according to RECIST 1.1, preferably at the regularly scheduled 8-week assessment interval, but no sooner than 4 weeks after the initial documentation of response or confirmed disease progression. Subjects who do not have an on-treatment radiographic tumor assessment due to early progression, who receive antitumor treatments other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR, will be counted as nonresponders in the assessment of OR.

The analysis of the BOR will be conducted using the FAS. The ORR, defined as the proportion of subjects with BOR of PR or CR, will be tabulated by dose level and overall. A 2-sided 95% Clopper-Pearson CI will be constructed.

The response at each scheduled tumor assessment and the BOR will be listed for each subject.

8.5.3.2 Phase I and Phase II: Other Efficacy Endpoints

The following parameters will be calculated using the FAS:

- DOR in subjects with confirmed BOR of CR or PR: time (in months) from the first occurrence of CR or PR to either PD or occurrence of death due to any cause
- TTR, which is the time (in months) from the date of first dose of avelumab to the first documentation of OR (CR or PR), which is subsequently confirmed
- PFS, which is the time (in months) from first study drug administration to either first observation of PD or occurrence of death due to any cause within 12 weeks of the last tumor assessment, whichever occurs first
- OS time (in months), calculated for all subjects.

Duration of response, PFS, and OS will be presented in subject listings and analyzed using the Kaplan-Meier method in FAS by dose/cohort. Time to response will be presented in subject listings

and summarized including number of subjects (n); mean, standard deviation; median, Q1, Q3, minimum, and maximum by dose/cohort.

8.5.3.3 Phase I and Phase II: Safety Analyses

Safety analyses in Phase I and Phase II will be performed on the SAF. The safety endpoints will be tabulated by dose level or cohort, using descriptive statistics.

Safety assessments will be based on review of the incidence of TEAEs, AEs of special interest, treatment-related AEs, and changes in vital signs, and laboratory values (hematology, coagulation, and serum chemistry).

Adverse Events

All AEs will be coded according to MedDRA. Severity of AEs will be graded using the NCI-CTCAE v4.03 toxicity grading scale.

Treatment-emergent adverse events are defined as events with onset dates occurring on-treatment or events that worsen on-treatment.

The frequency of subjects experiencing TEAEs, regardless of relatedness to trial treatment, will be summarized by system organ class and preferred term for each treatment arm. Similar summaries will also be provided for serious TEAEs, TEAEs leading to permanent discontinuation of trial treatment, TEAEs by maximum severity, TEAEs related to trial treatment, TEAEs with fatal outcome, and treatment-emergent adverse events of special interest, such as irAEs.

Laboratory Values

Laboratory results will be classified by grade according to NCI-CTCAE v4.03. The worst on-treatment grades for chemistry and hematology laboratory results will be summarized. Shifts in toxicity grading from Baseline to highest grade during the on-treatment period will be displayed. For laboratory tests without an NCI-CTCAE grade definition, results will be presented categorically (eg, below, within, or above normal limits).

Vital Signs

Vital signs (body temperature, respiratory rate, heart rate, and blood pressure), recorded according to the Schedule of Assessments (Table 1), will be presented.

Further details will be provided in the SAP based on current safety experience applying the latest version of MedDRA.

8.5.3.4 Phase I and Phase II: Pharmacokinetic Profiles of Avelumab

Single- and multiple-dose PK profiles of avelumab, including C_{max}, AUC, $t_{1/2}$, and C_{trough}, as data permit, will be calculated.

PK Analysis Set

Descriptive statistics of PK data will be calculated for all subjects in the PK Analysis Set.

Avelumab serum concentrations will be provided in listings and descriptively summarized by day and nominal time, along with by body weight, age or actual dose as appropriate, using the number of nonmissing observations, arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum.

Pharmacokinetic concentrations at the end of infusion (C_{EOI}) and trough concentrations (C_{trough}) will be additionally summarized by nominal time day on scheduled visits. Descriptive statistics will additionally show the geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% CI for the GeoMean.

Pharmacokinetic concentration data will be reported using the same precision as the source data.

Descriptive PK analysis will be performed using the computer program Phoenix WinNonlin version 6.4, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).

Population Pharmacokinetic Analysis

Sampled PK profiles from this study may be analyzed jointly with data from other studies by nonlinear mixed effect approach, in order to describe the PK concentration time profile followed by multiple dose infusion of avelumab; to identify covariates explaining (part of) the between subject PK variability; and to estimate the residual PK inter-individual variability. The PK Analysis Set will be used. More details will be given in a separate Data Analysis Plan for Population Pharmacokinetic Analysis. The results will be reported separately.

8.5.3.5 Phase I and Phase II: Avelumab Antidrug Antibodies

Subjects will be characterized into different categories and summarized by dose level or cohort based on the criteria in Table 7.

Table 7 Subject Characterization Based on Antidrug Antibody Results

Category	Definition	Subject at Risk (Denominator for Incidence)
Never positive	No positive results at any time point	Number of subjects with at least 1 valid result at any time point
Ever positive	At least 1 positive result at any time point	Number of subjects with at least 1 valid result at any time point
Pre-existing	A positive ADA result prior to treatment with avelumab	Number of subjects with valid Baseline result
Treatment boosted	A positive ADA result prior to treatment with avelumab and the titer ≥ 8 x Baseline titer while on avelumab treatment	Number of subjects with valid Baseline and at least 1 valid post-Baseline result

Treatment emergent	Not positive prior to treatment with avelumab and with at least 1 positive post-Baseline result	Number of subjects with at least 1 valid post-Baseline result and without positive Baseline results (including missing, NR)
Transient positive	If treatment-emergent subjects have a single positive evaluation, or duration between first and last positive result < 16 weeks and last assessment not positive	Number of subjects with at least 1 valid post-Baseline result and without positive Baseline results (including missing, NR)
Persistent positive	If treatment-emergent subjects have duration between first and last positive result ≥ 16 weeks or a positive evaluation at the last assessment	Number of subjects with at least 1 valid post-Baseline result and without positive baseline results (including missing, NR)

ADA: antidrug antibodies; NR: not recorded.

Drug concentration in serum for ADA ever-positive subjects versus ADA never-positive subjects will be descriptively summarized to evaluate the potential effect of ADA on PK.

8.5.3.6 Phase I and Phase II: Biomarkers

Summary statistics for PD-L1 expression and infiltration by lymphocyte subpopulations in tumor tissue will be provided for all preplanned time points, separately for each dose level, and overall. Changes to baseline levels will also be presented as applicable. Profiles over time will be displayed on a per-subject basis.

Details of the statistical analysis of biomarkers will be presented in the SAP.

8.5.3.7 Phase I and Phase II: Vaccination-related Antibody Concentrations

Changes in antibody concentrations of 3 vaccines (diphtheria, tetanus, and pneumococcal conjugate) will be summarized.

8.5.4.3 Phase I and Phase II: Safety

Safety assessments will also be based on review of ECG and performance status.

12 lead ECG and performance status, recorded according to the Schedule of Assessments (Table 1), will be listed for each subject.

8.6 Interim and Additional Planned Analyses

No interim analysis for efficacy is planned for this trial. There will be periodic safety review by the SMC. Details will be provided in the SMC Charter.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

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

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

9.2 Subject Information and Informed Consent

Adequate information will be provided to subjects and their parent(s)/legal guardian(s), and informed consent(s) will be signed by parent(s)/legal guardian(s). An unconditional prerequisite for a subject's participation in the trial is the written informed consent of her/his parent(s)/legal guardian(s), which must be given before any trial-related activities are carried out. When applicable and as per local regulations, assent will be provided by subjects.

Adequate information must therefore be given to the subject and his/her parent(s)/guardian(s) by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A discussion about tumor sampling at the time of progression should be part of the initial informed consent conversation.

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

If permitted by local regulations, a person other than the Investigator may inform the subject and his/her parent(s)/legal guardian(s) about the trial and sign the ICF, as above.

After the information is provided by the Investigator, the ICF must be signed and dated by the subject's parent(s)/legal guardian(s), the subject (when applicable as per local regulations), and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and it must be safely archived 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 and his/her parent(s)/legal guardian(s) prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to subjects and their parent(s)/legal guardian(s) and submit them to the IRB/IEC for review and opinion. Using the approved revised subject information sheet and other written information, the Investigator will explain the changes to the previous version to each trial subject and his/her parent(s)/legal guardian(s) and obtain new written consent for continued participation in the trial. The subject (when age appropriate and per local regulations) and his/her parent(s)/legal guardian(s) 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.

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9.3 Subject Identification and Privacy

A unique number will be assigned to each subject, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. All subject data collected in the trial will be stored under the appropriate subject number. Only the Investigator will be able to link trial 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.

If the subject meets all inclusion criteria and does not meet any of the exclusion criteria, the subject registration center will receive confirmation, register the subject and inform the Investigator and the Sponsor of the registration number by fax. If the subject is ineligible for the trial, a subject number will be allocated and documented.

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9.4 Emergency Medical Support and Subject Card

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

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, he/she 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 provides the appropriate means to contact a Sponsor physician. This includes the provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency.

9.5 Clinical Trial Insurance and Compensation to Subjects

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

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents to the responsible IEC or IRB for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File at QuintilesIMS.

The IEC or IRB will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

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

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

9.7 Health Authorities

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

10 Trial Management

10.1 Case Report Form Handling

Refer to the Manual of Operations for eCRF completion guidelines.

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

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

10.2 Source Data and Subject Files

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

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, ie, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

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

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor, and kept in a safe place at the site.

10.3 Investigator Site File and Archiving

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

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

10.4 Monitoring, Quality Assurance, and Inspection by Health Authorities

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

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

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Study Report and Publication Policy

10.6.1 Clinical Study Report

After completion of the Phase I and Phase II of the trial, a Clinical Study Report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3.

10.6.2 Publication

Posting of data on the EU Clinical Trials Register and ClinicalTrials.gov sites is planned and will occur 12 months after the last clinic visit of the final trial subject or another appropriate date to meet applicable requirements.

The first publication will include the results of the analysis of the primary endpoints and will include data from all trial sites that provided evaluable data. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

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12 Appendices

Appendix I: Contraceptive Guidance

In this clinical trial of children < 18 years of age, a female or male subject is considered to be of childbearing potential (and therefore required to use 2 highly effective methods of birth control) if, in the opinion of the Investigator, the subject is biologically capable of having children and is sexually active.

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," methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods, such as:

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

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

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

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

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Contraceptive Guidance

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of < 1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] oral intravaginal transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] oral injectable
Highly Effective Methods That Are User Independent
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] Intrauterine device (IUD) Intrauterine hormone-releasing system (IUS) bilateral tubal occlusion
Vasectomized partner (A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)
Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized during the treatment period and for at least 60 days after the last dose of study treatment.

Appendix II: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	Open-label, Phase I/II study to evaluate pharmacokinetics, pharmacodynamics, safety, and anticancer activity of avelumab in pediatric subjects from birth to less than 18 years of age with refractory or relapsed solid tumors and lymphoma
IND Number:	CCI [redacted]
EudraCT Number:	2017-002985-28
Clinical Trial Protocol Date/ Version:	15 September 2017/Version 2.0

Protocol Lead:

I approve the design of the clinical trial:

PPD [redacted]

Signature Date of Signature

Name, academic degree:	PPD [redacted]
Function / Title:	PPD [redacted]
Institution:	EMD Serono Research & Development Institute, Inc.
Address:	45A Middlesex Turnpike Billerica, MA 01820, USA
Telephone number:	PPD [redacted]
Mobile number:	PPD [redacted]
E-mail address:	PPD [redacted]

Signature Page – Coordinating Investigator

Trial Title	Open-label, Phase I/II study to evaluate pharmacokinetics, pharmacodynamics, safety, and anticancer activity of avelumab in pediatric subjects from birth to less than 18 years of age with refractory or relapsed solid tumors and lymphoma
IND Number	CCI [redacted]
EudraCT Number	2017-002985-28
Clinical Trial Protocol Date/Version	15 September 2017/Version 2.0

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

PPD

Signature Date of Signature

Name, academic degree: PPD

Function / Title: PPD

Institution:

Address:

PPD

Telephone number:

Fax number:

E-mail address:

Signature Page – Principal Investigator

Trial Title	Open-label, Phase I/II study to evaluate pharmacokinetics, pharmacodynamics, safety, and anticancer activity of avelumab in pediatric subjects from birth to less than 18 years of age with refractory or relapsed solid tumors and lymphoma
IND Number	CCI [redacted]
EudraCT Number	2017-002985-28
Clinical Trial Protocol Date/ Version	15 September 2017/Version 2.0
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 Harmonisation 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:

Address:

Telephone number:

Fax number:

Sponsor Responsible Persons not Named on the Cover Page

Name: PPD

Function / Title: PPD

Institution: EMD Serono, Inc.

Address: 45A Middlesex Turnpike
Billerica, MA 01821, USA

Telephone number: PPD

E-mail address:

Name: PPD

Function / Title: Senior Clinical Trial Lead

Institution: Merck KGaA

Address: Frankfurter Str. 250
64293 Darmstadt
Germany

Telephone number: PPD

E-mail address: PPD

Appendix III: Lansky and Karnofsky Performance Scales

Lansky Performance Scale

Lansky play-performance scale for pediatric patients

This scale may be used with children age 1-16 who have any type of malignancy. It may be used for both inpatients & outpatients, and for patients undergoing active treatment as well as long-term follow-up. It is rated by parents based on their child's activity over the past week. Parents fill out the assessment based on the directions on the form, and the form is readministered over time to assess for changes in performance status.

An excerpt of the relevant directions for parents is as follows:

"Think about your child's play and activity over the past week. Think about both good days and bad days. Average out this period. Now read the descriptions and pick the one that best describes your child's play during the past week."

Rating	Description
100	fully active, normal
90	minor restrictions with strenuous physical activity
80	active, but gets tired more quickly
70	both greater restriction of, and less time spent in, active play
60	up and around, but minimal active play; keeps busy with quieter activities
50	lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities
40	mostly in bed; participates in quiet activities
30	stuck in bed; needs help even for quiet play
20	often sleeping; play is entirely limited to very passive activities
10	does not play nor get out of bed
0	unresponsive

Karnofsky Performance Scale

The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

References:

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Appendix IV: Protocol Amendments and List of Changes

Amendment #1

Effective 15 September 2017 for all sites.

Rationale

The rationale for this amendment is to make administrative changes and remove a statement included in the protocol.

Major Scientific Changes

None.

Administrative and Editorial Changes

Administrative changes:

- Change IND number from CCI [redacted] per request by the FDA for resubmission.
- Change of address for the coordinating investigator, effective 01 September 2017.
- Correct the name of the Sponsor for Canada from EMD Serono to Merck KGaA
- Update the name and address of the clinical trial lead on the Sponsor Responsible Persons Not Named on the Cover page.
- Update the version and date of the amendment throughout the document.

Editorial changes:

The following statement was inadvertently included in the protocol because of a copy-and-paste error; the statement has been removed in 3 places in the protocol: An independent imaging vendor will be engaged to read and interpret all computed tomography (CT)/magnetic resonance imaging (MRI) data. Responses will be evaluated using RECIST 1.1.

Comparison with Clinical Trial Protocol Version 1.0, 14 August 2017

Change	Section	Page(s)	Previous Wording	New Wording	Rationale
IND Number	Title page, Synopsis title page, signature pages of protocol lead, principal investigator, and coordinating investigator	Pages 1, 11, 107, 108, and 109	CCI [redacted]	CCI [redacted]	CCI [redacted]
Change of title and address of coordinating investigator	Title page, Synopsis title page, Section 2, Coordinating investigator signature page	Pages 1, 11, 25, 108	PPD PPD PPD PPD		Coordinating investigator's new location as of 01 September 2017
Change of sponsor address for Canada	Title page, Synopsis title page, Section 2	Pages 1, 11, 25	For all countries except the USA~~ and Canada~~ For sites in the USA~~ and Canada~~	For all countries except the USA For sites in the USA	Incorrect sponsor address for Canada

Change	Section	Page(s)	Previous Wording	New Wording	Rationale
Update CTP version and date	Title page, signature pages of protocol lead, principal investigator, and coordinating investigator	Pages 1, 107, 108, and 109	~~14 August 2017/Version 1.0~~ 15 September 2017/Version 2.0	15 September 2017/Version 2.0	Administrative change
Removed sentences about independent imaging vendor	5.1.1.1, 5.1.1.2, and 7.2.5	Pages 32, 38, and 72	~~An independent imaging vendor will be engaged to read and interpret all computed tomography (CT)/magnetic resonance imaging (MRI) data. Responses will be evaluated using RECIST 1.1.~~	None	Copy-and-paste error—no independent read for secondary objections are planned.
Name and contact information of clinical trial lead	Sponsor Responsible Persons not Named on the Cover page	Page 111	PPD ~~Lead~~ ~~EMD Serono, Inc.~~ ~~45A Middlesex Turnpike~~ ~~Billerica, MA 01821, USA~~ PPD PPD PPD Senior Clinical Trial Lead Merck KGaA Frankfurter Str. 250 64293 Darmstadt PPD	PPD Senior Clinical Trial Lead Merck KGaA Frankfurter Str. 250 64293 Darmstadt Germany PPD PPD	New trial lead