Integrated Analysis Plan

Clinical Trial Protocol Identification No.	MS100070-0035
Title	A Phase I/Ib Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Chinese Subjects with Locally Advanced Unresectable or Metastatic Solid Tumors with Expansion to Selected Indication(s)
Trial Phase	Phase I/Ib
Investigational Medicinal Product(s)	Avelumab
Clinical Trial Protocol Version	17 May 2019 / Version 4.0 including amendment 3.0
Integrated Analysis Plan Author	Biostatistician PPD PPD PPD
Integrated Analysis Plan Date and Version	13AUG2019, Version Final 2.0
Integrated Analysis Plan Reviewers	PPD Trial Biostatistician Medical Responsible PPD PPD PPD PPD PPD PPD PPD, Merck Serono PPD, Merck Serono PPD, Merck Serono PPD, Merck Serono PPD, Merck Serono PPD, Merck Serono PPD

Signature Page

Integrated Analysis Plan: MS100070-0035

A Phase I/Ib Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Chinese Subjects with Locally Advanced Unresectable or Metastatic Solid Tumors with Expansion to Selected Indication(s)

PPD

PPD, Trial Biostatistician

PPD

Date

PPD

Signature

PPD

PPD

PPD

Date

PPD

Signature

PPD

Merck Serono

Date

Signature

PPD Trial Biostatistician

Merck Serono

PPD, Medical Responsible

PPD

1 Table of Contents

CCI [redacted]

CCI

CCI

2 List of Abbreviations and Definition of Terms

ADA	Antidrug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the concentration-time curve from time zero to time t
AUC_{0-tau}	Area under the concentration-time curve from time zero to tau, the respective dosing interval, i.e., one- or two-week
$AUC_{0-tau/dose}$	Dose-normalized AUC_{0-tau}
$AUC_{extra\%}$	Percentage of area under the serum concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) obtained by extrapolation
BLQ	Below the limit of quantification
BMI	Body mass index
CCI [redacted]	
C_{last}	Last quantifiable concentration
C_{max}	Maximum serum concentration
C_{max}/dose	Dose-normalized C_{max}
C_{min}	Minimum serum concentration
C_{trough}	Serum concentration observed immediately before next dosing
CR	Complete response
CRF	Case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DCR	Disease control rate
DLT	Dose-limiting toxicity

CCI [redacted]	
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End-of-Treatment
GeoCV%	Geometric coefficient of variation
GeoMean	Geometric mean
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonization
IMP	Investigational medicinal product
irAE	Immune-related adverse event
IV	Intravenous(ly)
λ_z	Terminal elimination rate constant
Max	Maximum
Mean	Arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MSI	Microsatellite instability
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not Evaluable
CCI [redacted]	
CCI [redacted]	
PD	Progressive disease/disease progression
CCI [redacted]	
CCI [redacted]	
PK	Pharmacokinetic(s)
CCI [redacted]	

PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SCR	Screening Analysis Set
SDTM	Study Data Tabulation Model
SEM	Standard error of the mean
SOC	System Organ Class
IAP	Integrated Analysis Plan
IRR	Infusion Related Reactions
SD	Stable disease or standard deviation
SOD	Sum of longest diameter for non-nodal lesion and short axis for nodal lesion
$t_{1/2}$	Elimination half-life
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TIL	Tumor infiltrating lymphocyte
t_{max}	Time to reach maximum serum concentration
TTR	Time to response
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
Draft 0.1	03NOV2017	PPD	Not Applicable
Draft 0.2	02MAR2018	PPD	Modified per sponsor's comments received on 22DEC2017 and 02FEB2018
Draft 0.3	11MAY2018	PPD	Modified per sponsor's comments received on 26MAR2018 and 10MAY2018.
Draft 0.4	29MAY2018	PPD	Modified per sponsor's comments received on 21MAY2018 and 24MAY2018.
Final 1.0	01JUN2018	PPD	Modified per sponsor's comments received on 25MAY2018 and 31MAY2018.
Final 2.0	13AUG2019	PPD	1. Add appendix of irAE and IRR 2. Add appendix of Toxicities for Laboratory Evaluations 3. Modify Section 12.2 Medications 4. Clarify ADA in secondary endpoint. 5. Add rule for incomplete date of prior/concomitant medication. 6. Modify definition of re-initiation

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the final analysis of data collected for protocol MS100070-0035.

Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon section 8 (Statistics) of the trial protocol and protocol amendments and is prepared in compliance with ICH E9.

5 Objectives and Endpoints

	Objective	Endpoint	IAP section
Primary Objective	• To evaluate the maximum tolerated dose (MTD) of avelumab (MSB0010718C) monotherapy in Chinese subjects. • To characterize the pharmacokinetics (PK) of avelumab in Chinese subjects.	**Primary Endpoint** • Occurrence of DLTs during the DLT observation period (first 21 days of treatment; excluding 10 mg/kg once weekly cohort). • PK profiles in Chinese subjects.	15 16.1 16.2

Secondary Objective	• To determine the safety and tolerability of avelumab by assessing treatment-emergent adverse events (TEAEs) and treatment-related AEs for all dose groups according to the NCI-Common Terminology Criteria for Adverse Events (CTCAE) v4.03. • To characterize immunogenicity of avelumab in Chinese subjects.	**Secondary Endpoint** • Occurrence of TEAEs for all dose groups according to NCI-CTCAE v4.03. • Occurrence of treatment-related AEs for all dose groups according to NCI-CTCAE v4.03. • Serum titers of ADA against avelumab.	14 15

CCI [redacted]

6 Overview of Planned Analyses

6.1 Interim Analysis

NA.

6.2 Primary Analysis

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

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

6.3 Final Analysis

The final analysis of study data will be conducted after End of Study, which is defined as the last patient complete 90-day safety follow-up phone call or last patient died, whichever comes first.

Additional data from primary analysis up to this cut-off date will be analyzed and presented as an addendum of CSR.

7 Changes to the Planned Analyses in the Clinical Trial Protocol

Biomarker related analysis are not planned in this IAP because biomarker testing will be done at a later time.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Important protocol deviations include:

- Subjects that receive study medication despite not satisfying the inclusion criteria or violating exclusion criteria;
- Subjects that develop withdrawal criteria whilst on the study but are not withdrawn;
- Subjects that receive the wrong treatment or an incorrect dose;
- Subjects that receive an excluded concomitant medication.

The following important deviations will be identified and confirmed prior to or at the Data Review Meeting:

- Deviations from the inclusion and exclusion criteria;
- Deviations post inclusion.

Important protocol deviations are specified in Appendix 18.1, and will be summarized in a table and presented in a data listing. All-important protocol deviations should be documented in SDTM datasets in which identified through sites monitoring, medical review or programming.

8.2 Definition of Analysis Sets

Screening Analysis Set (SCR): all subjects who signed the ICF(s).

DLT Analysis Set (DLT): all subjects with data used for implementing the dose-escalation schedule (excluding 6 subjects in 10 mg/kg once weekly cohort). These subjects should have received all avelumab administrations in the DLT observation period (first 21 days of treatment) or should have stopped treatment because of DLTs in the DLT observation period.

Safety Analysis Set (SAF): all subjects who have received at least 1 dose of avelumab. The Safety Analysis Set will be used for all analyses of safety and efficacy.

Efficacy Population: all subjects who have received at least 1 dose of avelumab and have measurable disease at baseline according to Investigator assessment.

PK Analysis Set: all subjects who receive at least one dose of avelumab, and provide at least one measurable post-dose concentration.

Immunogenicity Analysis Set: The immunogenicity analysis set will include all subjects who receive any dose of avelumab and who have at least one valid ADA result (including negative, positive-TNR).

9 General Specifications for Data Analyses

9.1 Data Handling After Cut-off Date

Data after cut-off date do not undergo the cleaning process. The only exception is the date of death on "DEATH" eCRF page and the date last known to be alive from the "FUPSTAT" eCRF page.

Generally, data others than the date of death and the date last known to be alive obtained after the cut-off will not be displayed in any listings or used for summary statistics, e.g., laboratory values of samples taken after cut-off date, AE with onset date after cutoff date etc. will not be included in any analysis or listing. However, AEs or medications with onset date before the cut-off will be displayed even if their end date is after the cut-off; either as ongoing or the end date will be reported (even though it is after the cut-off).

The data handling for cut-off date will be implemented at SDTM level.

9.2 Pooling of Centers

In order to provide overall estimates of the treatment effect, data will be pooled across centers. The factor center will not be considered in statistical models.

9.3 Presentation and Definition of General Considerations

9.3.1 Presentation of Continuous and Qualitative Variables

Continuous variables will be summarized using descriptive statistics, i.e.

- number of subjects (N), number of subjects with non-missing values
- mean, standard deviation (SD)
- median, 25th Percentile - 75th Percentile (Q1-Q3)

- minimum (Min) and maximum (Max)

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of subjects of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

9.3.2 Definition of Baseline

The last non-missing measurement (scheduled or unscheduled) prior to the first trial drug administration will be used as the baseline measurement. Definition of baseline value will be used as baseline for all safety and efficacy analysis. If an assessment is planned to be performed on Week 1 Day 1 and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

9.3.3 Definition of Duration

Duration will be calculated by the difference of start and stop date + 1, unless otherwise specified.

9.3.4 Conversion Factors

The following conversion factors will be used to convert days into weeks or months or years, or vice versa:

- 1 week = 7 days
- 1 month = 30.4375 days
- 1 year = 365.25 days

9.3.5 Handling of Missing Data

Unless otherwise specified (Section 11, 13, 14 and 15), missing data will not be imputed.

In all subject data listing imputed values will be presented. In all listings imputed information will be flagged. Partial dates, which are not to be imputed according to this IAP, will be presented in the format like "_____YYYY". In case imputation is defined, imputed date with flag (i.e., D for day, M for month) will be reported.

Missing statistics, e.g. when they cannot be calculated, should be presented as "NA". For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as "NA".

9.3.6 Presentation of PK Concentration Data

Individual PK concentrations will be reported with the same precision as the source data provided by the bioanalytical laboratory or clinical laboratory regardless of how many significant figures or decimal places the data carry. Actual elapsed sample collection times will be rounded to 2 decimal places for reporting purposes only, in by-subject listings.

Pharmacokinetic concentration data will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median), and maximum (Max).

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data, and rounded for reporting purposes only. The following conventions will be applied when reporting descriptive statistics of PK concentration data:

- Mean, Min, Median, Max: 3 significant digits
- SD: 4 significant digits
- CV%: 1 decimal place

Values below the lower limit of quantification (LLOQ) will be taken as zero in the calculation of descriptive statistics for avelumab serum concentrations.

9.3.7 Presentation of PK Parameter Data

Pharmacokinetic parameter data will be descriptively summarized using: number of non-missing observations (n), number of missing observations (n), Mean, SD, CV%, standard error of the mean (SEM), Min, Median, Max, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV%), and the 95% confidence interval (CI) for the GeoMean (LCI 95% GM, UCI 95% GM).

Pharmacokinetic parameter C_{max} will be reported with the same precision as the source data and t_{max} will be reported to two decimal places. All other PK parameters will be reported to 3 significant figures. In export datasets, as well as in the Study Data Tabulation Model (SDTM) PP/XD domain, PK parameters will be provided with full precision, and will not be rounded. Descriptive statistics of PK parameter data will be calculated using full precision values, and rounded for reporting purposes only.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

- Mean, Min, Median, Max, GeoMean, 95% CI: 3 significant digits

- SD, SEM: 4 significant digits
- CV%, GeoCV%: 1 decimal place

9.3.8 Software

All statistical analyses will be performed using SAS® software version 9.4.

Pharmacokinetic parameters will be derived using noncompartmental methods with the validated computer program Phoenix® WinNonlin® 6.4 or higher (Certara, L.P., Princeton, New Jersey, USA). Pharmacokinetic figures will be developed using SigmaPlot® 12.5 or higher (Systat Software, Inc, San Jose, California, USA), Phoenix® WinNonlin® 6.4 or higher, or SAS® Windows Version 9.4 or higher (Statistical Analysis System, SAS-Institute, Cary, North Carolina, USA).

10 Trial Subjects

The subsections in this section include specifications for reporting subject disposition and treatment/trial discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Subjects and Discontinuations

Descriptive statistics will be used to summarize subject disposition and reason for discontinuation by dose level/cohort and in overall, based on the electronic case report form (eCRF) data.

- Number of subjects screened
- Number of subjects who discontinued before treatment overall and by the main reason
- Number of subjects who discontinued from the trial after randomization, grouped by the primary reason
- Number of subjects who discontinued from the trial treatment by the primary reason (e.g. subject did not meet all eligibility criteria, adverse event, lost to follow-up, protocol non-compliance, death, progressive disease, withdrew consent from avelumab, other)
- Number of subjects who received at least 1 dose of trial treatment
- Number of subjects still on treatment
- Number of subjects re-initiated the trial treatment

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

The following summary tables and listings of important protocol deviations will be provided in Screening analysis set (separately for the inclusion/exclusion criteria or post inclusion deviations):

- Frequency table per reason of important protocol deviations
- Listing of important protocol deviations

11 Demographics and Other Baseline Characteristics

Analysis sets: Safety analysis set

11.1 Demographics

Demographic characteristics will be summarized by dose level/cohort and overall as follows:

- Sex: Male, Female.
- Race: Asian, Other.
- Ethnicity: Chinese, Other.
- Age (years): descriptive statistics.
- Age categories: < 65 years, ⩾ 65 years (further break-down: 65 - < 75 years, 75 - < 85 years, ⩾ 85 years).

Specifications for computation:

- Age (years): (date of given informed consent – date of birth + 1) / 365.25. The integer part of the calculated age will be used for reporting purpose.

  - In case of missing day for at least one date, but month and year available for both dates:

  For the derivation of age, the day of informed consent and the day of birth will be set to 1 and the formula above will be used.

  - In case of missing month for at least one date, but year available for both dates:

  For the derivation of age, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used.

- BMI (kg/m^2) = weight(kg)/[height(m)]^2

A supportive demographic listing will be provided.

11.2 Medical History

The summary tables by dose level/cohort and overall for Medical History will also be provided detailing the number and percentage of subjects by Medical Dictionary for Regulatory Activities (MedDRA) in terms of primary System Organ Class (SOC) (ordered alphabetically) and Preferred Term (PT) (ordered alphabetically); each subject will be counted only once within each PT or SOC (eCRF" MEDICAL HISTORY").

Medical history will be displayed in terms of primary SOC and PT in alphabetical order and also listed.

11.3 Other Baseline Characteristics

Information of other baseline characteristics collected at the baseline evaluation visit will be summarized in total and by dose level/cohort. Summary statistics will be presented for:

- Serology: Hepatitis B, hepatitis C, and HIV tests
- Nicotine use status: Never, Regular, Occasional, Former
- Nicotine Consumption: summary statistics
- Alcohol use status: Never, Regular, Occasional, Former
- ECOG performance status

  0: Fully active, able to carry on all pre-disease performance without restriction.

  1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.

  2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

  3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

  4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

  5: Dead.

Baseline characteristics with respect to vital signs, physical examinations, and hematology/biochemistry will be part of Section 15.

Disease history

Disease history is collected in "DISEASE HISTORY" pages.

Summary statistics for the following parameters will be presented by treatment dose

- Site of primary tumor

- Metastatic sites
- Time since initial diagnosis (months)
- Time since documented, locally advanced, inoperable or metastatic disease (months)
- TNM classification at initial diagnosis: each T, N, M category will be described (TX, T0, N1, etc.)
- TNM classification at study entry

Specifications for computation:

- Time since initial cancer diagnosis (months) = (date of first avelumab administration – date of initial cancer diagnosis)/30.4375
- Time since documented, locally advanced, inoperable or metastatic disease (months) = (date of first avelumab administration – date of documented, locally advanced, inoperable or metastatic disease)/30.4375
- Time since progression disease (months) = (date of first administration – date of progression disease) / 30.4375

Incomplete dates for disease history (initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is same as the year of the first study treatment, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

Listing of disease history will be provided with all relevant data (primary site of tumor, sub-site, initial diagnosis date, first occurrence of locally advanced, inoperable or metastatic disease, histopathological classification, metastasis site, TNM classification, etc.) and derived variables used in the above table.

12 Previous or Concomitant Medications/Procedures

12.1 Prior Anti-Cancer Treatment and Procedures

The prior anti-cancer treatments and procedures are collected under the "PRIOR ANTI-CANCER SURGERIES", "PRIOR ANTI-CANCER DRUG THERAPIES", "PRIOR ANTI-CANCER RADIOTHERAPY", eCRF pages.

The overall summary of presence of prior anti-cancer treatments/procedures tables will include:

- Number of subjects with at least one prior anti-cancer drug therapy
  - Type of therapies: Cytotoxic therapy / Endocrine therapy / Monoclonal antibodies therapy / Molecular Target Therapy / Immunotherapy / Other
  - Intent of therapy: Neoadjuvant / Adjuvant / Metastatic or Locally advanced
  - Best response: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (Non CR/ Non PD) / Not Evaluable / Unknown
  - Time since documented progression disease (months)
- Number of subjects with at least one prior radiotherapy
  - Total dose (Gy), (mCi)
  - Number of fractions
  - Best response: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (Non CR/Non PD) / Not Evaluable / Unknown
- Number of subjects with at least one prior anti-cancer surgery
  - Curative intent for surgery: yes/no
  - Outcome of surgery: No residual tumor after resection (R0) / Tumor/metastases not resected completely with microscopic residual lesions (R1) / Tumor/metastases not resected completely with macroscopic residual lesions (R2) / Metastases not resected (NR) / Other

The following listings of prior anti-cancer treatments and procedures will also be provided:

- Listing of prior anti-cancer drug therapies
- Listing of prior surgeries
- Listing of prior radiotherapy

12.2 Prior or Concomitant Medication and Procedures

Medications

Concomitant medications are medications, other than trial medications, which are taken by subjects any time on-trial (on or after day 1 of treatment); Or any medication which are taken within 30 days after last dose of trial drug. Prior medications are medications, other than trial medications and premedications, which started and stopped before administration of trial drug.

Prior and Concomitant medications will be summarized from the "CONCOMITANT MEDICATIONS DETAILS" eCRF page. ATC-2nd level and PT will be tabulated as given from the WHO-DD dictionary current version. In case multiple ATC's are assigned to a drug, all ATC-2nd level will be used for reporting. Prior and Concomitant medications will be listed. The listing will include: subject identification number, dose level/cohort and all corresponding collected data-field on the corresponding eCRF pages, as well as a flag to identify each medication as Prior or Concomitant.

Incomplete prior/concomitant medication dates will be imputed as follows:

- If the medication date is missing completely, then the medication date will be replaced by the start of study treatment.
- If the day of medication date is missing, but the month and year are equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed medication start date will be 15/JAN/2015.
- If both the day and month of medication start date are missing but the start year is equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed medication start date will be 19/NOV/2014.
- In all other cases the missing medication day or missing medication month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete medication stop date will not be imputed.

Procedures

Prior and concomitant status for Procedures is defined using the same rule as for medications.

Prior and Concomitant procedures will also be listed including: subject identification number, cohort and all corresponding collected data-field on the corresponding eCRF page. A flag will be added to identify each procedure as Prior or Concomitant.

12.3 Anti-cancer Post-treatment

The data collected from the "ANTI-CANCER TREATMENT AFTER DISCONTINUATION, RADIOTHERAPY AFTER DISCONTINUATION DETAILS and SURGERY AFTER DISCONTINUATION DETAILS" eCRF page will be listed.

The anti-cancer treatments after discontinuation will also be summarized in terms of:

Number of subjects with at least one anti-cancer drug therapy after discontinuation

- Type of therapies: Cytotoxic therapy / Endocrine therapy / Monoclonal antibodies therapy / Small molecules / Immunotherapy / Other
- Intent of therapy: Neoadjuvant / Adjuvant / Metastatic or Locally advanced
- Best response: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (Non CR / Non PD) / Not Evaluable/ Unknown

13 Treatment Compliance and Exposure

Analysis Sets: Safety analysis set

13.1 Pre-medication

The number of subjects receiving pre-medication will be summarized for each treatment visit based on "PREMEDICATION DETAILS" eCRF page (subjects for whom the question "Has the subject received premedication before avelumab infusion?" (eCRF PREMEDICATION) is answered "Yes" at the corresponding visit). Percentages will be calculated on the number of subjects who actually received an infusion at the associated visit. In addition, a listing of premedication displaying dose cohort, subject identifier, date and time of administration, name of treatment, dose, unit and route of administration will be provided.

13.2 Exposure to Study Drug

The extent of exposure for avelumab will be characterized by duration (weeks), number of administrations, cumulative dose (mg/kg), dose intensity (mg/kg/cycle), relative dose intensity, number of dose delays.

Descriptive statistics will be used to summarize treatment exposure, based on the data being collected in "AVELUMAB ADMINISTRATION DETAILS" page of eCRF. Summaries will be performed on the safety analysis set. Subjects will receive an IV infusion of avelumab (over 1 hour

[- 10 minutes/+ 20 minutes, i.e., 50 to 80 minutes]) once every 2 weeks or, if 20 mg/kg once every 2 weeks have been established, 10 mg/kg every week for the first 12 weeks and once every 2 weeks thereafter starting at Week 13.

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

(1) Avelumab (3, 10, 20 mg/kg) once every 2 weeks (Q2W):

- **The duration of avelumab (weeks)** during the study is defined as:

$$\left(\frac{\text{date of last dose of avelumab - date of first dose of avelumab + 14}}{7}\right)$$

- **The cumulative actual treatment dose (mg/kg)** of avelumab per subject is the sum of the calculated actual dose levels of avelumab that the subject received (i.e. total dose administered (mg/kg)).

- **The dose intensity of avelumab (mg/kg/cycle)** per subject is defined as:

$$\left(\frac{\text{Cumulative dose of avelumab}}{0.5*[(\text{date of last dose of avelumab} - \text{date of first dose of avelumab} + 14) / 7]}\right)$$

- **Total number of infusions received (n)**

- **Relative dose intensity of therapy (%):** The relative dose intensity per cycle is defined as 100 × actual dose intensity per cycle (mg/kg/cycle)/ (planed dose level per cycle (mg/kg/cycle)]

(2) Avelumab (10 mg/kg) once weekly (Q1W) for 12 consecutive weeks and then starting at Week 13, once every 2 weeks (Q2W):

- **The duration of avelumab (weeks) for first 12 weeks receiving Q1W dose per subject** is defined as:

$$\left(\frac{\text{Date of last dose of avelumab(Q1W)} - \text{ date of first dose of avelumab(Q1W)} + 7}{7}\right)$$

- **The duration of avelumab (weeks) for subsequent weeks receiving Q2W dose per subjec**t is defined as:

$$\left(\frac{\text{Date of last dose of avelumab(Q2W)} - \text{ date of first dose of avelumab(Q2W)} + 14}{7}\right)$$

- **The cumulative actual treatment dose (mg/kg)** of avelumab **receiving Q1W dose** per subject is the sum of the calculated actual dose levels of avelumab that the subject received of Q1W dose (i.e. total Q1W dose administered (mg/kg)).

- **The cumulative actual treatment dose (mg/kg)** of avelumab **receiving Q2W dose** per subject is the sum of the calculated actual dose levels of avelumab that the subject received of Q2W dose (i.e. total Q2W dose administered (mg/kg)).

- **The dose intensity of avelumab (mg/kg/cycle) for first 12 weeks receiving Q1W dose per subject** is defined as:

$$\left(\frac{\text{Cumulative dose of avelumab (Q1W)}}{(\text{date of last dose of avelumab(Q1W)} - \text{ date of first dose of avelumab(Q1W)} + 7) / 7}\right)$$

- **The dose intensity of avelumab (mg/kg/cycle) for subsequent weeks receiving Q2W dose per subjec**t is defined as:

$$\left(\frac{\text{Cumulative dose of avelumab (Q2W)}}{0.5*[(\text{date of last dose of avelumab(Q2W)} - \text{date of first dose of avelumab(Q2W)} + 14) / 7]}\right)$$

- **Total number of infusions received (n) for Q1W dose and Q2W dose, respectively**

- **Relative dose intensity of therapy (%) for Q1W dose:** The relative dose intensity per cycle is defined as 100 × actual dose intensity per cycle (mg/kg/cycle) for Q1W dose/ (planed dose level per cycle(mg/kg/cycle) for Q1W dose

- **Relative dose intensity of therapy (%) for Q2W dose:** The relative dose intensity per cycle is defined as 100 × actual dose intensity per cycle (mg/kg/cycle) for Q2W/ (planed dose level per cycle (mg/kg/cycle) for Q2W dose.

Dose reduction is not allowed per protocol and will not be summarized.

Per protocol, Avelumab will be administered as 1-hour intravenous infusion. Subjects will receive the trial treatment once every 2 weeks (excluding 10 mg/kg once weekly cohort). Dose delays will be grouped into the following categories based on the deviation of the actual to the planned treatment administration day (relative to the previous non-zero dose date): no delay (including 1-2 days delays), 3-6 days delay, 7 or more days delay. For example, if one subject receives the study drug on day 1, then the next study drug administration date will be on day 15; however, if the

subject receives the study drug at day 16 or 17, this is considered as 'no delay'. Any zero dose prior to the last treatment administration is considered as a dose interruption.

The summary of dose delays will be based on the safety analysis set and include the following categories:

- No delay
- 3-6 days delay
- 7 or more days delay

The categorization is based on the maximum length of delay, i.e. the worst case of delay if subjects have multiple dose delays.

A listing of study drug administration will include subject identifier, assigned dose level/cohort, number of days relative to previous administration date, dose delay (yes/no), duration of administration and other relevant information collected on the Avelumab Administration Details eCRF page.

13.3 Treatment Re-Initiation

For subjects (Who achieve a confirmed CR on Avelumab and subsequently develop PD after stopping therapy; Who under disease progression due to brain metastasis; Who under disease progression mainly due to a metastatic lesion (nodal or visceral)) will be treated as EOT, but can reinitiate Avelumab therapy if the relevant criteria are met, per investigator and medical monitor decision. Treatment re-initiation and discontinuation after re-initiation will be tabulated and presented in the subject disposition.

For subjects who ever achieved CR, also defined as retreated subjects according to protocol, sparse PK and ADA blood samples will be collected according to the schedule as indicated in protocol Table 1-5. However, for subjects who under disease progression due to brain metastasis or a metastatic lesion (nodal or visceral), PK and ADA blood samples will be collected according to the schedule as indicated in protocol Table 1-3(Table 1-4), or Table 1-5.

CCI

CCI

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

15 Safety Analyses

Safety analyses will be done on the safety analysis set and according to the as-treated principle.

15.1 Dose Limiting Toxicity (DLT)

The primary endpoint of the study is:

- Occurrence of DLTs during the DLT observation period. The number and proportion of subjects experiencing DLTs will be reported by dose level based on the DLT Analysis Set (excluding 10 mg/kg once weekly cohort).

Dose limiting toxicity (DLT) refers to relevant toxicity induced by the drug during the first 21 days of treatment; excluding10 mg/kg once weekly cohort, severity of which is clinically unacceptable, limiting further dose escalation. According to toxicity evaluation criteria in NCI CTCAE V4.03, the observation period for a DLT is the 21-day period after the first administration of avelumab for subjects with data used for implementing the dose-escalation algorithm for dose determination.

DLT data will be captured from the eCRF "ADVERSE EVENTS DETAILS" form.

The Incidence rates of DLT per each dose level during DLT observation will be presented as well as by SOC and PT. DLT summary will be based on DLT set.

15.2 Adverse Events (AE)

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

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

The 5 general grades are:

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

AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded by the investigator using the NCI-CTCAE version 4.03.

Treatment emergent adverse events (TEAEs) are those events that emerge during treatment having been absent pre-treatment, or worsen relative to the pre-treatment state and with onset dates

occurring within the first dosing day of study dose levels until 30 days after the last dose of study treatment.

All analyses described **Error! Reference source not found.**will be based on TEAEs (started during the on-treatment period) if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings. A separate listing including AEs started after the on-treatment period will also be provided.

- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (i.e. no answer to the question "Relationship with study treatment").
- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).
- **Related SAEs**
- **Adverse Events Leading to Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).
- **Related AE Leading to Treatment Discontinuation**
- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).
- **Related AE Leading to Death**
- **Immune Related Adverse Events (irAE):** immune related adverse events are identified via customized MedDRA PT queries and additionally classified by investigator according to case definition (two level approach). Details are included in Appendix 18.2.
- **Infusion Related Reactions (IRR):** IRRs are identified based on a list of MedDRA PTs. The detailed criteria of the timing relationship to infusion are specified in Appendix 18.2.

Incomplete AE-related dates will be handled as follows:

- Incomplete or missing start date:
  - In case the onset date is completely missing or the onset is in the same year (if the onset year is available only) or the onset is in the same month and year (if the day is missing) as start of study treatment, then the onset date will be replaced by the minimum of start of study treatment date and AE resolution date (imputed, if incomplete).
  - In all other cases the missing onset day or onset month will be replaced by 01.
- Incomplete or missing stop date:

- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases, the incomplete stop date will not be imputed.

AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded by the investigator using the NCI-CTCAE version 4.03.

The AE reporting period for safety surveillance begins when the subject is included in the study (date of first signature of informed consent) and continues for all SAEs and treatment-related non-serious AEs through to the study's Safety Follow-up Phone Call, defined as 90 days (± 7 days) after the last administration of avelumab. Any SAE suspected to be related to avelumab must be reported whenever it occurs, irrespective of the time elapsed since the last administration of avelumab.

15.2.1 All Adverse Events

Treatment-emergent Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per subject, using MedDRA (latest version) PT as event category and MedDRA (latest version) SOC body term as Body System category.

Unless otherwise stated adverse events will be displayed in terms of frequency tables: PT and primary SOC in alphabetical order.

If an adverse event is reported for a given subject more than once during treatment, the worst severity and the strongest relationship to trial treatment will be tabulated.

Adverse events related to trial treatment are those events with relationship unrelated or related. In case a subject had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

An overview table of TEAEs will be provided detailing the number and percentage of subjects with:

- Any TEAE
- Any trial drug related TEAE
- Any serious TEAE
- Any trial drug related serious TEAE
- Any TEAE by NCI-CTCAE severity grade (≥3, ≥4)
- Any trial drug related TEAE by NCI-CTCAE severity grade (≥3, ≥4)
- Any TEAE leading to treatment discontinuation
- Any trial drug related TEAE leading to treatment discontinuation

- Any TEAE leading to death
- Any related TEAE leading to death
- Treatment-emergent irAEs
- Related treatment-emergent irAEs
- Treatment-emergent IRRs
- Related treatment-emergent IRRs

The following summary tables will also be provided for TEAEs detailing the number and percentage of subjects by MedDRA primary SOC (ordered alphabetically) and PT (ordered alphabetically):

- TEAEs
- Trial drug related TEAEs
- TEAEs by worst grade (for each subject, maximal grade within the same preferred term)
- Trial drug related TEAEs by worst grade
- Grade 3/4 TEAEs
- Grade 3/4 related TEAEs
- TEAEs leading to death
- Trial drug related TEAEs leading to death

All TEAEs will be listed to support these tables.

15.2.2 Adverse Events Leading to Treatment Discontinuation

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to permanent discontinuation of avelumab, by treatment dose group:

- AEs leading to discontinuation of avelumab by SOC and PT
- Related AEs leading to discontinuation of avelumab by SOC and PT

15.2.3 The listing of all AEs leading to avelumab discontinuation will also be provided Deaths

The frequency (number and percentage) of patients who died during the trial period and who died within 30 days after last dose or 60 days after first dose of avelumab as well as the primary reason for death, will be tabulated based on information from the “DEATH” and “SUBJECT STATUS / SURVIVAL FOLLOW-UP” eCRF page.

The following summaries will be provided:

- All deaths
- Number of deaths within 30 days after last dose of study treatment
- Number of deaths within 60 days after first dose of study treatment
- Primary Reason of death
    - Progressive disease and/or disease related condition
    - Event unrelated to avelumab
    - Event related to avelumab
    - Event related to Physician's Choice
    - Unknown

In addition, date and cause of death will be provided in an individual subject data listing together with selected dosing information (study treatment received, date of first / last administration, number of infusions received for treatment, day relative to first infusion and day relative to most recent infusion) and will include the following information:

- AEs with fatal outcome (list preferred terms of AEs with outcome = Fatal, as well as AEs of Grade 5)
- Flag for death within 30 days of last trial drug treatment
- Flag for death within 60 days of first trial drug treatment

15.2.4 Serious Adverse Events

The following summary tables will be provided for serious TEAEs detailing the number and percentage of subjects by MedDRA primary SOC (ordered alphabetically) and PT (ordered alphabetically); each subject will be counted only once within each PT or SOC:

- SAEs by SOC and PT
- Related SAEs by SOC and PT

The listings of all SAEs will also be provided including a flag for SAEs with onset outside of the on-treatment period.

15.2.5 Adverse Events of Special Interest

Any AE that is suspected to be a potential irAE and infusion related reactions will be considered an adverse event of special interest (AESI). The frequency (number and percentage) of patients with each of the following will be presented for treatment emergent irAEs, by dose level/cohort:

- Any irAEs

- Any related irAEs
- Any serious irAEs
- Any related serious irAEs
- Any irAEs by NCI-CTCAE severity grade (≥3, ≥4)
- Trial treatment related irAEs by NCI-CTCAE severity grade (≥3, ≥4)
- Any irAEs leading to treatment discontinuation
- Any related irAEs leading to treatment discontinuation
- Any irAEs leading to death
- Any related irAEs leading to death

The frequency (number and percentage) of patients with each of the following will be presented for treatment emergent IRRs, by treatment cohort:

- Any IRRs
- Any related IRRs
- Any serious IRRs
- Any related serious IRRs
- Any IRRs by NCI-CTCAE severity grade (≥3, ≥4)
- Trial treatment related IRRs by NCI-CTCAE severity grade (≥3, ≥4)
- Any IRRs leading to treatment discontinuation
- Any related IRRs leading to treatment discontinuation
- Any IRRs leading to death
- Any related IRRs leading to death

15.3 Clinical Laboratory Evaluation

All laboratory assessments are performed at local laboratories and comply with local requirements.

Laboratory values (including corresponding normal ranges) from local laboratories will be converted into the standard units by data management. The results in standard units will be used for the analyses.

Laboratory results will be classified according to the NCI-CTCAE toxicity grading version 4.03. If toxicities for high and low values of a specific parameter are defined, these toxicities will be analyzed separately for the parameter as "Parameter low" and "Parameter high" (appendix 18.3).

Laboratory results that are not part of the NCI-CTCAE will be presented according to the categories: below normal limits, within normal limits and above normal limits (according to the local laboratories normal ranges).

- **Hematology**: Hematocrit, Hemoglobin, Platelet count, Red blood cells (RBC) count, White Blood Cell Count, Absolute lymphocytes count, Lymphocytes, Absolute Neutrophils count, Neutrophils, Absolute monocyte count, Monocytes, Absolute eosinophil count, Eosinophils, Absolute basophil count, Basophils, RBC morphology, Absolute reticulocytes count, Reticulocytes, Mean corpuscular hemoglobin (MCH), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin concentration (MCHC).
- **Hemostaseology:** Activated partial thromboplastin time (aPTT), Prothrombin time (PT), International Normalized Ratio (INR).
- **Biochemistry**: Albumin, Alkaline phosphatase, Alanine Aminotransferase (ALT), Amylase, Aspartate Aminotransferase (AST), Gamma Glutamyl Transpeptidase (GGT), Blood Urea Nitrogen (BUN), Urea, Calcium, Chloride, Cholesterol, Creatine kinase, Creatinine, C-Reactive Protein (CRP), Glucose, Lactate dehydrogenase (LDH), Lipase, Phosphorus, Magnesium, Potassium, Sodium, Total bilirubin, Protein total, Uric acid, Triglycerides, Hemoglobin A1c.
- **Hormonal tests**: Free Thyroxine (T4), Thyroid-Stimulating Hormone (TSH), Follicle-stimulating hormone.
- **Urinalysis**: pH, Specific gravity, Protein content, Sediment analysis, Albumin, Immunoglobulin G.

NCI-CTCAE grades available:

The laboratory toxicities will be tabulated by the worst on-treatment CTCAE grade or the shift of CTCAE grade from baseline to worst grade during on-treatment period using descriptive statistics (count and percentage). The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary.

- The worst grade during the on-treatment period will be summarized considering only patients with post baseline laboratory samples: Laboratory tests by NCI-CTCAE grade (0, 1, 2, 3, 4, and missing).

The shift table will summarize baseline CTCAE grade vs. the worst on-treatment CTCAE grade (grade = 0, 1, 2, 3, 4, missing). The above analyses apply to the following hematology and biochemistry parameters which can be graded per NCI-CTCAE:

- Hematology: Hemoglobin, Lymphocytes, Neutrophils, Platelets, White Blood Cell.

- Biochemistry: Creatinine, Alanine Aminotransferase, Aspartate Aminotransferase, Gamma Glutamyl Transferase, Total Bilirubin, Lipase, Amylase, Albumin, Alkaline Phosphatase, Glucose, Uric Acid, Sodium, Potassium, Calcium, Magnesium, Cholesterol, Creatine kinase, Triglyceride, Phosphorus.

Tables will summarize, separately for hematology and biochemistry parameters, the shift from baseline grade to worst on-treatment grade by parameters and dose level.

NCI-CTCAE grades not available:

The worst on-treatment value for hematology and biochemistry parameters which cannot be graded per NCI-CTCAE will be summarized by parameter according to the local laboratories normal ranges as follows:

- Shift from baseline value (low, normal, high) to above normal during on-treatment period
- Shift from baseline value (low, normal, high) to below normal during on-treatment period.

The above analyses apply to the following hematology and biochemistry parameters which cannot be graded per NCI-CTCAE:

- Hematology: Hematocrit, Red Blood Cells, RBC morphology, Monocytes, Eosinophils, Basophils, Reticulocytes, MCH, MCV,MCHC.

- Biochemistry: Total Protein, Blood Urea Nitrogen, Blood Urea, Chloride, C-Reactive Protein (CRP), Glucose, Lactate dehydrogenase, Hemoglobin A1c.

Quantitative data will also be examined for trends using descriptive statistics (n, missing, mean, SD, median, Q1, Q3, minimum, and maximum) of actual values, absolute changes and percent changes from baseline to each visit over time. This summarization will apply to hematology and chemistry parameters with numeric results assessed at baseline, post-baseline, discontinuation, end of treatment, and safety follow-up visits.

Listing of clinically significant hematology values and listing of clinically significant biochemistry values will also be provided. Clinically significant values are defined as values with associated NCI-CTCAE grade greater or equal to 3. The following information will be included in those listings:

- Selected dosing information: date of first/last administration
- Laboratory parameter with unit
- Visit of laboratory parameter measurement
- Collection date of laboratory parameter
- Value of laboratory parameter
- Local laboratories normal ranges for laboratory parameter (lower limit of normal and upper limit of normal)

- Normal range indicator for value of the laboratory parameter (Low, Normal, High)
- Associated grade for value of the laboratory parameter according to NCI-CTCAE if applicable.

Other laboratory parameters

The following laboratory parameters collected in the CRF will be presented in specific listing presenting all collected data-fields in the CRF.

- Hemostaseology: Activated partial thromboplastin time (aPTT), Prothrombin time (PT), International Normalized Ratio (INR)
- Hormone: Free T4 and TSH
- Urinalysis: all urinalysis parameters
- Pregnancy test
- Serology

15.4 Vital Signs

The following Vital Signs measurements will be reported for this study:

- Heart rate (beats/min)
- Body temperature (^{0}C)
- Respiration rate (breaths/min)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Weight (kg)

The maximum changes of vital sign measurements screening/baseline to maximum changes after start of 1st treatment will be grouped as follows:

Body temperature increase	< 1°C, 1-<2°C, 2-<3°C, ≥ 3 °C
Heart rate increase from baseline <100 beats/min ; ⩾ 100 beats/min	≤20 beats/min, >20 – 40 beats/min, >40 beats/min
Heart rate decrease from baseline <100 beats/min; ⩾ 100 beats/min	≤20 beats/min, >20 – 40 beats/min, >40 beats/min
SBP increase from baseline <140 mmHg; ⩾ 140 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
SBP decrease from baseline <140 mmHg; ⩾ 140 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP increase from baseline <90 mmHg; ⩾ 90 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg

DBP decrease from baseline <90 mmHg; ⩾ 90 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
Respiration rate increase from baseline <20 breaths/min; ⩾ 20 breaths/min	≤5 breaths/min, >5 – 10 breaths/min, >10 breaths/min
Respiration rate decrease from baseline <20 breaths/min; ⩾ 20 breaths/min	≤5 breaths/min, >5 – 10 breaths/min, >10 breaths/min

Quantitative data will also be examined for trends using descriptive statistics (n, missing, mean, SD, median, Q1, Q3, minimum, and maximum) of actual values, and absolute changes from baseline to each visit.

A listing of vital signs will be prepared in addition. The listing will also include dose level/cohort, subject identifier, vital sign parameter (unit), visit, date/time, value, baseline value, and change from baseline, and flags for potentially clinically meaningful changes. The listing will be sorted by dose level/cohort, subject identifier, vital sign parameter and vital sign measurement date/time.

15.5 Other Safety or Tolerability Evaluations

15.5.1 ECG

A shift table from baseline to the worst on-treatment conclusion will be tabulated with the subsequent categories:

- Normal ECG
- Abnormal ECG
    - ECG abnormalities non-clinically significant
    - ECG abnormalities clinically significant
- Missing
- Overall

Conclusions are sorted as Normal/Abnormal non-clinically significant/Abnormal clinically significant, the latest one being considered as the worst. If no post-baseline data are available the worst on-treatment result will be accounted as missing. If significance is not provided, the conclusion will be classified as “Abnormal ECG”. This “Abnormal ECG” category will count abnormal conclusion with missing significance only.

Quantitative data will also be examined for trends using descriptive statistics (n, missing, mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and absolute changes from baseline to each visit.

A listing of ECG values will be provided with all information included from the ECG where the abnormality was observed.

15.5.2 Eastern Cooperative Oncology Group/ ECOG Performance Status

Shifts in ECOG performance status from baseline to worst on-treatment performance status will be summarized by dose level/cohort. Missing category will also be included.

A listing will also be provided for ECOG performance status.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

Serum concentrations and PK parameters will be listed by dose level, study day, and/or scheduled time point, as appropriate, and summarized using descriptive statistics as described in Section **Error! Reference source not found.**.

Graphical displays of individual and mean (± SD for linear profiles only) serum concentration-time profiles will be presented on linear and semi-logarithmic scales by dose level up to 336 hours post-dose for the bi-weekly cohorts. Mean (± SD, linear profiles only) trough serum concentration-time profiles will be prepared for the once-weekly and bi-weekly cohorts. Individual serum concentration-time profiles will be presented on linear scale by study day for the once-weekly cohort.

For the PK analysis, pre-dose sample concentrations that are below the limit of quantification (BLQ) will be assigned a numerical value of zero for the calculation of AUC. On Day 1, any missing pre-dose value will also be assigned a numerical value of zero for the calculation of AUC. Any anomalous concentration values observed at pre-dose will be used as such in the PK analysis and identified in the CSR. All post-dose BLQ concentrations will be set to ‘zero’ in all cases.

Noncompartmental computation of PK parameters will be performed for the 3 mg/kg, 10 mg/kg, and 20 mg/kg once every 2 weeks dose escalation cohorts. Pharmacokinetic parameters will be evaluated and listed for all patients who provide sufficient concentration-time data. At least 3 valid, post-dose concentrations will be required in the PK profile to obtain any PK parameter estimate.

Individual PK parameters will be calculated using actual elapsed time from dose with a maximum of 14 significant digits in the time data (or using scheduled time if actual time is not available). The pre-dose sample will be considered as if it had been taken simultaneously with the administration of IMP. For any interim analyses, nominal time from dose will be used to calculate PK parameters.

Partial area $AUC_{0\text{-}tau}$ should be calculated using the scheduled dosing interval, as defined in the CTP. The actual dosing interval calculated from CRF time data should not be used. The following rules apply when calculating the partial area $AUC_{0\text{-}tau}$ within the observed time interval fromT_1 to T_2:

- If the start time of the interval (T_1) occurs before the first observation, the observation at T_1 will be estimated using the linear interpolant between the first data point and C0. For single dose data C0 = 0 when the drug was administered via an extravascular route or via infusion, and C0 is the estimated dosing time intercept when the drug was administered as an IV bolus.
- If either T_1 or T_2 falls within the time range in which samples were taken, but does not coincide with an observed data point, then a linear interpolation is performed to estimate the corresponding concentration value.
- If the end time of the interval (T_2) occurs after the last measurable concentration and the terminal regression (λ_z) is estimable, then λ_z is used to estimate the concentration at T_2. The linear trapezoidal rule will be used to calculate the area from the last observation time to the end time of the partial area (T_2). If λ_z cannot be estimated the partial area will not be calculated.

For each subject in the PK analysis set the following PK parameters will be calculated for avelumab on Day 1 in the bi-weekly cohorts, if possible:

AUC_{0-t} The area under the concentration-time curve from time zero (dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log linear trapezoidal rule (linear up, log down). Units: h*µg/mL.

AUC_{0-tau} The area under the serum concentration-time curve from time zero (dosing time) to tau (336 hours), calculated using the mixed log linear trapezoidal rule (linear up, log down). Units: h*µg/mL.

$AUC_{0-\infty}$ The area under the serum concentration-time curve from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λ_z determination. $AUC_{0-\infty}=AUC_{0-t}+C_{last\ pred}/\lambda_z$. Units: h*µg/mL.

$AUC_{extra\%}$ The AUC from time t_{last} extrapolated to infinity given as a percentage of $AUC_{0-\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0-\infty}$)*100. The predicted $AUC_{0-\infty}$ should be used. Units: %.

λ_z Terminal elimination rate constant, determined from the slope of the regression line of log(concentration) versus time. Units: h^{-1}.

C_{max} Maximum serum concentration observed, obtained directly from the concentration versus time curve. Units: µg/mL.

C_{last} Last quantifiable serum concentration observed, obtained directly from the concentration versus time curve. Units: µg/mL.

C_{trough} The concentration observed immediately before next dosing. Units: µg/mL.

t_{max} Time to reach maximum serum concentration, obtained directly from the concentration versus time curve. Units: h.

$t_{1/2}$ Terminal elimination half-life, determined as $\ln(2)/\lambda_z$. Units: h.

AUC_{0-t}/dose Dose-normalized AUC_{0-t}. Actual mg/kg dose administered will be used in the calculation of this parameter. Units: (h*µg/mL)/(mg/kg).

AUC_{0-tau}/dose Dose-normalized AUC_{0-tau}. Actual mg/kg dose administered will be used in the calculation of this parameter. Units: (h*µg/mL)/(mg/kg).

C_{max}/dose Dose-normalized C_{max}. Actual mg/kg dose administered will be used in the calculation of this parameter. Units: (µg/mL)/(mg/kg)

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression ($\lambda_{z\ low}$, $\lambda_{z\ upp}$) to determine $\lambda_{z\ (t1/2,\ Interval)}$.
- Number of data points (N_λ) included in the log-linear regression analysis to determine λ_z.
- Goodness of fit statistic (Rsq) for calculation of λ_z.

The regression analysis should contain data from at least 3 different time points in the terminal phase consistent with the assessment of a straight line on the log-transformed scale. Phoenix WinNonlin best-fit methodology will be used as standard. The last quantifiable concentration should always be included in the regression analysis, while the concentration at t_{max} and any concentrations <LLOQ which occur after the last quantifiable data point should not be used.

The coefficient of correlation (Rsq) should be $\geqslant$0.800 and the observation period over which the regression line is estimated should be at least twofold the resulting $t_{1/2}$ itself. If%AUC_{extra} is greater than 20%, the rate constants and all derived parameters (e.g., $t_{1/2}$, $AUC_{0-\infty}$) will be included in the parameter outputs and descriptive statistics but will be flagged and discussed appropriately. Any flags should be included in the study specific SDTM.

Scatter-plots of individual patient data and GeoMean values of C_{max}/dose, AUC_{0-tau}/dose, and AUC_{0-t}/dose versus dose will be prepared.

Dose proportionality of PK parameters will be assessed graphically based on exposure data (AUC_{0-tau} and C_{max}).

The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

16.2 Pharmacodynamics

NA.

16.3 Immunogenicity

Antidrug antibody (ADA) are assessed before the trial treatment infusion on Days 1, 15, 29, 43, 85, 127, 169. After Day 169, 1 sample (within 2 hours prior to infusion) every 12 weeks until the EOT visit and at the safety follow-up visit (30 days ± 5 days after last treatment) for subjects receiving Avelumab once every 2 weeks. For 10 mg/kg once weekly cohort, ADA are assessed before the trial treatment infusion on Days 1, 15, 29, 43, 85, 127, 169, and then every 12 weeks while on treatment, and at the safety follow-up visit. If the sample is positive for ADA, it will be re-analyzed to determine the titer. The ADA results will be derived based on the algorithm as the following table.

Algorithm for the Derivation of ADA Results

Sample Screen Result	Confirmatory	Titer	ADA Result
Negative	NA	NA	Negative
NR	NA	NA	NR
Positive	Negative	NA	Negative
Positive	NR	NA	NR
Positive	Positive	Number	Number
Positive	Positive	NA	Positive-TNR

NR = no result, NA = not applicable, TNR = titer no result.

Negative, number, or positive-TNR are valid results while number and positive-TNR are considered as positive. Subjects will be characterized into different categories based on the below criteria.

Category	Definition	Subject at Risk (Denominator for Incidence)
Never positive	No positive results at any time point	Number of subjects with at least one valid result at any time point
Ever positive	At least one positive result at any time point	Number of subjects with at least one valid result at any timepoint
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*baseline titer while on avelumab treatment	Number of subjects with valid baseline and at least one valid post-baseline result
Treatment emergent	Not positive prior to treatment with avelumab and with at least one positive post-baseline result	Number of subjects with at least one valid postbaseline 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 one valid postbaseline 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 one valid postbaseline result and without positive baseline results (including missing, NR)

The frequency and percentage of each category will be presented by dose level/cohort and overall in tables based on Safety Analysis Set.

Listings of ADA results from ever positive ADA subjects will be prepared.

- Overview on ADA status: Subject ID, dose level, age, gender, ADA Status, Study Day of Start of ADA response, Duration of ADA immunogenicity response (weeks)
- Listing of ADA and Ctrough concentrations: Subject ID, dose level, age, Visit and Visit Date, ADA result, Date of last prior avelumab infusion, Days since last avelumab infusion, Date of last available predose drug concentration at or before ADA assessment and corresponding drug concentration
- Listing of all PK concentrations, Subject ID, dose level, age, Visit and Visit Date, Nominal time, observed avelumab serum concentration, Actual date/time; Hours since last avelumab infusion.
- Listing of immunogenicity data and adverse events (AEs): Subject ID, dose level, age, sex, study treatment start and stop date, all dates with positive ADA result, AE start date, stop date, preferred term, CTCAE toxicity grade, seriousness, and applicable flags for immune-related adverse event (irAE), infusion related reaction (IRR), serious adverse event (SAE), or reason for permanent treatment discontinuation.
- Listing of immunogenicity data and efficacy endpoints: Subject ID, dose level, age, start and stop of treatment, date of onset, time to onset (weeks since treatment start) and last date of ADA positive results, as well as date of onset, confirmed BOR and confirmed BOR date, DOR, PFS time or censoring time and reason for censoring, and OS time or censoring time and reason for censoring.

16.4 Quality of Life

NA.

CCI [redacted]

17 Reference

U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. 14 June 2010.

18 Appendix

18.1 Important Protocol Deviations

Protocol reference text	Category of Protocol Deviation	Description of Protocol Deviations	Deviation Code	Protocol Deviation Category	Protocol Section	Proposed check/comment
Inclusion criteria: For the subject to be eligible for inclusion, each criterion must be checked 'YES':						
Criterion1: Signed written informed consent.	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 1 (signed inform consent form).	PDEV01	Important	Section 5.3.1	If date of written informed consent(I_ICDT) = missing. Or date of written informed consent (I_ICDT) > Start date of First Avelumab administration (I_EXSTDTM). Medical Review Required.
Criterion 4: Histologically or cytologically proven locally advanced unresectable or metastatic solid tumor, for which no standard therapy exists or standard therapy has failed.	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 4 (histologically or cytologically proven metastatic or locally advanced solid tumor).	PDEV02	Important	Section 5.3.1	Medical review required.
Exclusion criteria: For the subject to be eligible for inclusion, each criterion must be checked 'NO':						
Criterion 1: Prior therapy with any antibody/drug targeting T cell coregulatory proteins (immune checkpoints) such as PD-1, PD-L1, cytotoxic T-lymphocyte antigen-4 (CTLA-4), 4-1BB, LAG-3, TIM-3 or anti-CD127.	Eligibility and Entry Criteria	Subject met exclusion criterion 1	PDEV03	Important	Section 5.3.2	Medical Review required.

Criterion 2: Concurrent anticancer treatment(s) (e.g., cytoreductive therapy, radiotherapy [with the exception of *palliative bone-directed radiotherapy and radiotherapy administered to superficial lesions], immune therapy, or cytokine therapy except for erythropoietin). Radiation to more than 30% of the bone marrow or with a wide field of radiation should not be used within 28 days prior to the first administration of avelumab and is prohibited throughout the study	Eligibility and Entry Criteria	Subject met exclusion criterion 2	PDEV04	Important	Section 5.3.2	Medical Review required.
Criterion 18: Clinically significant (that is, active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrolment), myocardial infarction (< 6 months prior to enrolment), unstable angina pectoris, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious cardiac arrhythmia requiring medication (including corrected QT interval prolongation of > 470 msec calculated according to Fridericia and/or pacemaker or prior diagnosis of congenital long QT syndrome)	Eligibility and Entry Criteria	Subject met exclusion criterion 18	PDEV05	Important	Section 5.3.2	Medical Review required.
Subjects that develop withdrawal criteria whilst on the study but are not withdrawn	Other criteria	Subject developed Significant clinical deterioration, but continued on the study	PDEV06	Important	Section 5.5.2	Medical review required/ Programmatically checked.
Subjects that develop withdrawal criteria whilst on the study but are not withdrawn	Other criteria	Subject developed Grade ≥ 4 ADRs, but continued on the study	PDEV07	Important	Section 5.5.2	Medical review required/ Programmatically checked.
Subjects that develop withdrawal criteria whilst on the study but are not withdrawn	Other criteria	Subject developed AE resulting in the discontinuation of avelumab being desired or considered necessary by the Investigator and/or the subject, but	PDEV08	Important	Section 5.5.2	Medical review required.

		continued on the study				
Subjects that develop withdrawal criteria whilst on the study but are not withdrawn	Other criteria	Subject became pregnant, but continued on the study.	PDEV09	Important	Section 5.5.2	Medical review required/ Programmatically check
Non-permitted concomitant medication during the study	Concomitant Medication Criteria	Subject took prohibited medication during the study.	PDEV10	Important	Section 6.5.2	Medical Review/ Programmatically check
Subjects overdosed (>=120% of assigned dose)	IP Compliance	Subject was overdosed.	PDEV11	Important	Section 6.12	Programmatically check with administration page Actual dose (I_EXADOSE) > =120 % of 20mg/kg.

18.2 Description of the Case Definition for Assessment of Immune-Related AEs and IRRs

Immune-Related Adverse Events

Immune-related adverse events (irAEs) will be identified programmatically. AEs which satisfy all of the following criteria will be flagged as immune-related:

1) The AE preferred term matches a preferred term on the list of pre-selected MedDRA terms.

2) The AE onset occurs after the first study drug administration and no more than 90 days after last dose.

3) On the AE details eCRF page [aedt], the question "Were Corticosteroids, Immunosuppressants, or hormonal therapy (e.g. Thyroid, insulin) applied?" has the answer "Yes" selected.

4) On the irAE specific eCRF page [irae], either:

a. The question "Does any of the following provide a clear etiology for the event?" has the answer "No" selected, indicating that the AE is not attributable to underlying cancer disease/PD, prior or concomitant medications/procedures, nor another medical condition such as an infection, pre-existing disease or investigator´s choice of alternative etiology other than irAE.

OR

b. The irAE specific eCRF indicates that a biopsy was performed and the question "Is the histopathology/biopsy consistent with an immune-related event?" has the answer "Yes" selected.

In the case that criteria (1) through (3) are met, and entries for condition (4) are missing, the following rules will be applied:

• If the answer to "Does any of the following provide a clear etiology for the event?" (4a) is missing, the event will be considered as irAE (irrespective of biopsy results).

• If the answer to "Is the histopathology/biopsy consistent with an immune-mediated event?" (4b) is missing, or if no biopsy was performed, and condition (4a) is not satisfied (i.e. "Yes" is selected as the answer to the question "Does any of the following provide a clear etiology for the event?"), the event will be considered as a non-irAE.

Infusion Related Reactions

Infusion related reactions are identified based on a list of MedDRA PTs and criteria on the timely relationship according to table below:

Criteria for infusion related reactions

Infusion related reactions	**Reactions** - Considered when onset is on the day of study drug infusion (during or after the infusion) or the day after the study drug infusion (irrespective of resolution date): • Infusion related reaction • Drug hypersensitivity • Anaphylactic reaction • Hypersensitivity • Type 1 hypersensitivity **Signs and Symptoms** - occurring on the day of study drug infusion (during or after the infusion) and resolved with end date within 2 days after onset • Pyrexia • Chills • Flushing • Hypotension • Dyspnoea • Wheezing • Back pain • Abdominal pain • Urticaria

18.3 CTCAE Toxicities of Laboratory Evaluations

Laboratory Evaluation	Toxicity	Grade	Value
Albumin	LOW	1	<LLN - 30 g/L
	LOW	2	<30 - 20 g/L
	LOW	3	<20 g/L
Alkaline Phosphatase	HIGH	1	>1.0 - 2.5 x ULN
	HIGH	2	>2.5 - 5.0 x ULN
	HIGH	3	>5.0 - 20.0 x ULN
	HIGH	4	>20.0 x ULN
Alanine Aminotransferase	HIGH	1	>1 - 3.0 x ULN
	HIGH	2	>3 - 5.0 x ULN
	HIGH	3	>5 - 20.0 x ULN
	HIGH	4	>20 x ULN
Aspartate Aminotransferase	HIGH	1	>1 - 3.0 x ULN
	HIGH	2	>3 - 5.0 x ULN
	HIGH	3	>5 - 20.0 x ULN
	HIGH	4	>20 IU/L
Calcium	HIGH	1	> ULN - 2.9 mmol/L;
	HIGH	2	>2.9 - 3.1 mmol/L;
	HIGH	3	>3.1 - 3.4 mmol/L
	HIGH	4	>3.4 mmol/L
	LOW	1	< LLN - 2.0 mmol/L
	LOW	2	<2.00 - 1.75 mmol/L
	LOW	3	<1.75 - 1.5 mmol/L
	LOW	4	<1.50 mmol/L
Cholesterol	HIGH	1	>ULN - 7.75 mmol/L
	HIGH	2	>7.75 - 10.34 mmol/L
	HIGH	3	>10.34 - 12.92 mmol/L
	HIGH	4	>12.92 mmol/L
Creatine Kinase	HIGH	1	>1.0 - 2.5 x ULN
	HIGH	2	>2.5 - 5 x ULN
	HIGH	3	>5.0 - 10 x ULN
	HIGH	4	>10.0 x ULN
Creatinine	HIGH	1	>1.0 - 1.5 x ULN
	HIGH	2	>1.5 - 3.0 x ULN
	HIGH	3	>3.0 - 6.0 x ULN
	HIGH	4	>6.0 x ULN
Gamma Glutamyl Transferase	HIGH	1	>1.0 - 2.5 x ULN
	HIGH	2	>2.5 - 5.0 x ULN
	HIGH	3	>5.0 - 20.0 x ULN
	HIGH	4	>20.0 x ULN
Glucose	HIGH	1	>ULN - 8.9 mmol/L
	HIGH	2	>8.9 - 13.9 mmol/L
	HIGH	3	>13.9 - 27.8 mmol/L
	HIGH	4	>27.8 mmol/L
	LOW	1	< LLN - 3.0 mmol/L
	LOW	2	<3.0 - 2.2 mmol/L
	LOW	3	<2.2 - 1.7 mmol/L
	LOW	4	<1.7 mmol/L

Laboratory Evaluation	Toxicity	Grade	Value
Hemoglobin	HIGH	1	> ULN - ULN + 20 g/L
	HIGH	2	> ULN + 20 - ULN + 40 g/L
	HIGH	3	> ULN + 40 g/L
	LOW	1	< LLN - 100 g/L
	LOW	2	<100.0 – 80 g/L
	LOW	3	<80.0 g/L
Lipase	HIGH	1	>1.0 - 1.5 x ULN
	HIGH	2	>1.5 – 2.0 x ULN
	HIGH	3	>2.0 – 5.0 x ULN
	HIGH	4	>5.0 x ULN
Lymphocytes	HIGH	2	>4.00 – 20.00 10^9/L
	HIGH	3	>20.00 10^9/L
	LOW	1	< LLN - 0.8 10^9/L
	LOW	2	<0.80 - 0.5 10^9/L
	LOW	3	<0.50 - 0.2 10^9/L
	LOW	4	<0.20 10^9/L
Magnesium	HIGH	1	>ULN - 1.23 mmol/L
	HIGH	3	>1.23 - 3.30 mmol/L
	HIGH	4	>3.30 mmol/L
	LOW	1	< LLN - 0.5 mmol/L
	LOW	2	<0.50 - 0.4 mmol/L
	LOW	3	<0.40 - 0.3 mmol/L
	LOW	4	<0.30 mmol/L
Neutrophils	LOW	1	< LLN - 1.5 10^9/L
	LOW	2	<1.50 - 1.0 10^9/L
	LOW	3	<1.00 - 0.5 10^9/L
	LOW	4	<0.50 10^9/L
Phosphate; Phosphorus	LOW	1	< LLN - 0.8 mmol/L
	LOW	2	<0.80 - 0.6 mmol/L
	LOW	3	<0.60 - 0.3 mmol/L
	LOW	4	<0.30 mmol/L
Platelets	LOW	1	< LLN - 75.0 10^9/L
	LOW	2	<75 - 50.0 10^9/L
	LOW	3	<50 - 25.0 10^9/L
	LOW	4	<25 10^9/L
Potassium	HIGH	1	>ULN - 5.5 mmol/L
	HIGH	2	>5.5 - 6.0 mmol/L
	HIGH	3	>6.0 - 7.0 mmol/L
	HIGH	4	>7.0 mmol/L
	LOW	2	< LLN - 3.0 mmol/L
	LOW	3	<3.0 - 2.5 mmol/L
	LOW	4	<2.5 mmol/L
Amylase	HIGH	1	>1.0 - 1.5 x ULN
	HIGH	2	>1.5 – 2.0 x ULN
	HIGH	3	>2.0 – 5.0 x ULN
	HIGH	4	>5.0 x ULN
Sodium	HIGH	1	> ULN - 150 mmol/L
	HIGH	2	>150 - 155 mmol/L
	HIGH	3	>155 - 160 mmol/L

Laboratory Evaluation	Toxicity	Grade	Value
	HIGH	4	>160 mmol/L
	LOW	1	< LLN - 130 mmol/L
	LOW	3	<130 - 120 mmol/L
	LOW	4	<120 mmol/L
Total Bilirubin	HIGH	1	>1.0 - 1.5 x ULN
	HIGH	2	>1.5 – 3.0 x ULN
	HIGH	3	>3.0 – 10.0 x ULN
	HIGH	4	>10.0 x ULN
Triglycerides	HIGH	1	>1.71 - 3.42 mmol/L
	HIGH	2	>3.42 - 5.7 mmol/L
	HIGH	3	>5.70 - 11.4 mmol/L
	HIGH	4	>11.40 mmol/L
White Blood Cell	HIGH	3	>100.0 10^9/L
	LOW	1	< LLN - 3.0 10^9/L
	LOW	2	<3.0 - 2.0 10^9/L
	LOW	3	<2.0 - 1.0 10^9/L
	LOW	4	<1.0 10^9/L
Uric Acid	HIGH	3	> ULN – 0.59 mmol/L
	HIGH	4	>0.59 mmol/L

LLN= lower limit of normal; ULN= upper limit of normal

ELECTRONIC SIGNATURES

Document: ctp-ms100070-0035-iap-v2-0

Signed By	Event Name	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Task Completed (Approval eSign): Approved	Technical Approval	16-Aug-2019 02:18