Signature Page for GCT1015-04_SAP
Study GCT1015-04 v5.0

eSignature for Approval	[redacted]
eSignature for Approval	[redacted]
eSignature for Approval	[redacted]

Signature Page for GCT1015-04_SAP
Study GCT1015-04 v5.0

[redacted]

Confidential

Statistical Analysis Plan

Sponsor:	Genmab
Protocol Title:	A Single arm, Multicenter, International Trial of Tisotumab Vedotin (HuMax®-TF-ADC) in Previously Treated, Recurrent or Metastatic Cervical Cancer
Protocol Version:	V7.0 17-Jun-2019
Trial Code:	GCT1015-04

For [redacted]

Author: [redacted], Senior [redacted]

Reviewer: [redacted], Principal [redacted]

For Sponsor:

Approver: [redacted], [redacted], Biostatistics

Reviewers: [redacted], [redacted] Biostatistics

[redacted], [redacted], Medical

[redacted], [redacted], Translational Research

[redacted], [redacted], Translational Research

[redacted], [redacted], Drug Safety Physician

[redacted], [redacted], Pharmacology

[redacted]

Confidential

Table of Contents

[redacted]

Confidential

[redacted]

Confidential

1. List of Abbreviations and Definition of Terms

Abbreviation	Term
ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FPFV	First Patient First Visit
FU	Follow-Up
GFR	Glomerular Filtration Rate
HRQL	Health Related Quality of Life
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IOC	Intraocular
IRC	Independent Review Committee
ITT	Intention to Treat
IV	Intravenous
LPLV	Last Patient Last Visit
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration

MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethyl Auristatin E
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NE	Not Evaluable
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
QTc	Corrected QT
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Set
SD	Standard Deviation
SOC	System Organ Class
TF	Tissue Factor
TNM	Tumor Nodes Metastasis
TTR	Time to Response
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

[redacted]

Confidential

2. Introduction

This Statistical Analysis Plan was written for the clinical trial GCT1015-04 conducted in eight countries (Belgium, Czech Republic, Denmark, Germany, Italy, Spain, Sweden and the United States). The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of the plan.

3. Trial Design and Objectives

3.1 Trial Objectives

3.1.1 Primary Objectives

- Determine the anti-tumor efficacy in subjects with cervical cancer.

3.1.2 Secondary Objectives

- Evaluate tumor response durability.
- Evaluate clinical response.
- Assess safety and tolerability.

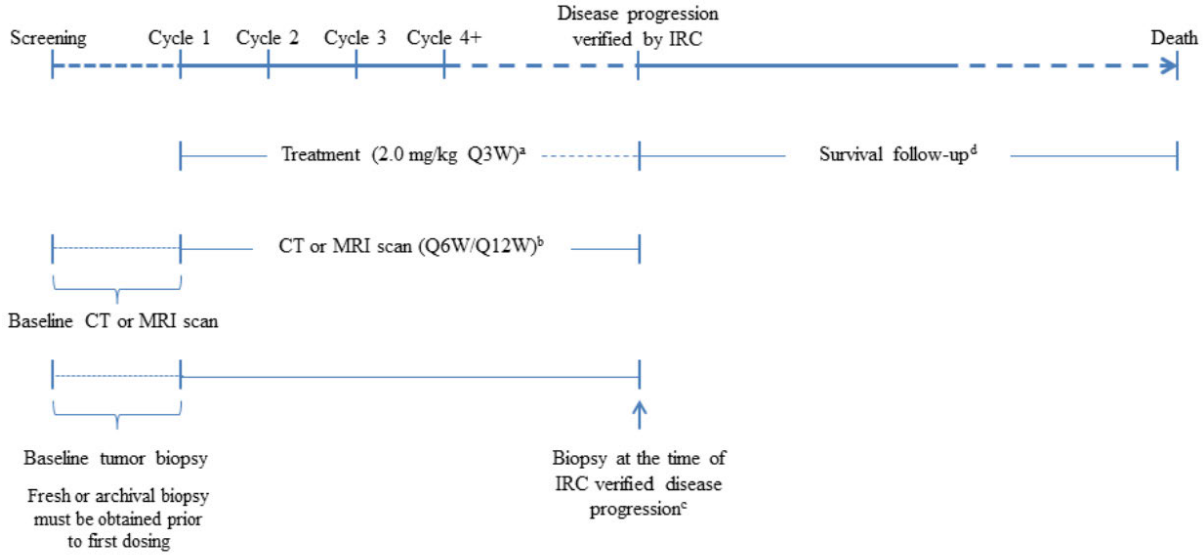
3.1.3 Exploratory Objective

- Assess biomarkers related to clinical response.
- Assess potential pharmacodynamic biomarkers.
- Assess Health Related Quality of Life (HRQL).

3.2 Trial Design

The trial design is available in section 4 Trial Design of the protocol.

Figure 1. Overview of trial design



a: Administration of tisotumab vedotin 2.0 mg/kg on day 1 of each cycle. Each treatment cycle is 3 weeks (Q3W).
b: CT or MRI scan every 6 weeks (±7 days) for the first 30 weeks and every 12 weeks (±7 days) thereafter.
c: Optional
d: Survival follow-up should be performed every 60 days (±7 days) or more frequently around the time of database lock.

[redacted]

3.3 Sample Size Justification

In GEN701 there were 9 confirmed responders among the first 34 cervical cancer subjects (26%).

Applying a one-sided exact binomial test at the 0.025 significance level, the planned sample size of 100 subjects provides ≥ 80% power to reject an ORR of 11%, the combined ORR for available second-line therapies (See section 2.2 of the protocol), or less for true ORRs in the range 21% - 25%, representing clinically relevant improvements over available second-line treatments (See Table 1).

Table 1. Power for a range of clinically relevant true confirmed ORRs

True ORR	21%	22%	23%	24%	25%
Power	80%	86%	91%	94%	96%

4. General Analysis Definitions

Data will be analyzed using SAS (Version 9.4 or higher). For graphs R (RStudio) can be used in addition.

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation (SD), median, minimum and maximum values.
- Time to event parameters will be described using Kaplan-Meier estimates: Median time along with 95% confidence interval of the median. First and third quartiles will also be added when specified.

The study being a single arm trial, the tables will be created with one treatment arm.

All data will be listed by subject number and visit (if applicable). Data from scheduled and unscheduled visit will be included in listings. Listings will include all data from all subjects unless specified otherwise. Population flag for FAS will be included.

In general, in plots where subject data are grouped together (e.g. boxplots), the ticks on the time-axis will denote the nominal visit numbers (e.g. Scr, C1D1, C2D1, …). Unscheduled visit data will not be included.

In tables and listings presenting data by visit, the visit names (Screening, Cycle 1 Day 1, Cycle 2 Day 1, …, Treatment discontinuation, Safety Follow-up, and Survival Follow-up) will be used or their abbreviated term (Scr, C1D1, C1D2, …, Treat discont, Saf FU, and Surv FU). Unscheduled visit data will not be tabulated unless specified otherwise.

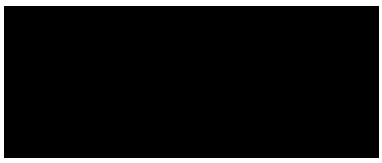
In tables and listings presenting coded data (e.g. medical history, concomitant medication, adverse events …), the dictionary and the version used will be mentioned in the footnote.

4.1 Trial Period and Visit Window Definitions

4.1.1 Trial Periods

The overall observation period will be divided into three mutually exclusive segments:

Pre-treatment period will be defined as the period from the day of subject's informed consent to the day before first IMP administration.



On-treatment period will be defined as the period from day of first dose of IMP to 30 days after last IMP administration.

Post-treatment period will be defined as the period after the On-treatment period (i.e. from 31 days after last IMP administration) and until death, lost to follow-up or withdrawal from the trial.

4.1.2 Visit Windows

Visit windows are defined in the protocol. Those will not be used in the analysis to avoid excluding important data due to dates outside visit windows. Tables will assume that observations are from the recorded visit irrespective of the date specified.

4.2 Planned Analyses

No formal interim analyses are planned. The primary reporting of the trial will be based on a data cut off approximately 6 months after all responders have experienced their first response as assessed by the investigator per RECIST v1.1 (cut-off date).

Since subjects will be treated until they met one of the discontinuation criteria, some subjects may still be ongoing at the time of primary analysis. In that case the entire trial will be reported again including all available data (no cut-off date applied) when the last subject dies or when tisotumab vedotin becomes available in the subjects country, whichever comes first. However, maximum trial duration is 5 years (starting from when the first subject signed the ICF).

4.3 Definition of Populations (Analysis Sets)

4.3.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all subjects who received at least one dose of IMP.

4.3.2 Safety Set

The Safety Set (SAF) includes all subjects who received at least one dose of IMP. Since the full analysis set and the safety set are identical, all safety analyses will use the term full analysis set as the analysis population.

Data from subjects who were screened but never started treatment or from screening failures will be listed, but will not be included in any of the analyses and summary tables.

4.4 Subgroup Definitions

Subgroup analyses for the following baseline factors are planned as supportive analyses of ORR:

- Histology (Squamous or Non-squamous)
- Prior radiation administered to the pelvis (Yes or No)
- Prior lines of systemic regimen (1 or 2). Systemic regimen refers to systemic regimen administered in the extra-pelvic metastatic or recurrent setting in this document.
- Response to last systemic regimen (Yes or No)
- Prior first line combination of Paclitaxel + Cisplatin/Carboplatin + Bevacizumab or Paclitaxel + Topotecan + Bevacizumab (Yes or No)
- ECOG (0 or 1)

- Age (< 50, >=50 to <65 or >=65)
- Region (EU or US)

4.5 Treatment Assignment and Treatment Arms

This is an open-label single-arm trial and all subjects will be assigned the same treatment. Tisotumab vedotin at 2.0 mg/kg will be administered as an IV infusion over a minimum of 30 minutes on day 1 of each treatment cycle (one treatment cycle is 21 days). It's recommended that the infusion completes within 60 minutes.

Each subject's dose will be calculated based on the subject's weight (please refer to section 9.3.2 of the protocol for more details on assessment of weight) rounded to the nearest kilogram, i.e., 2.0 mg/kg x body weight in kg. For subjects who weigh >100 kg, the calculation of IMP dose should be normalized to 100 kg (i.e., 2.0 mg/kg x 100 kg = 200 mg).

Preventive eye therapy must be administered in relation to each infusion as described in section 6.2.2 of the protocol.

4.6 Calculated Variables

- Baseline is defined as the latest available measurement made before the first treatment with tisotumab vedotin. Measurements done on the same date as the first IMP administration will be considered as done before the first IMP administration unless specified otherwise. For PK variables, the first IMP administration will be time 0.
- Change from baseline is defined as the post-baseline value – baseline value.
- Percent change from baseline is defined as the 100*(post-baseline value – baseline value)/baseline value. When the baseline value=0, the percent change from baseline will be missing.
- Time (in months) from last systemic regimen to start of IMP: (start date of IMP – end date of last systemic regimen)/30.4375.
- Time (in months) from biopsy to start of IMP: (start date of IMP – date the biopsy was obtained)/30.4375.
- Duration of exposure (months): (end date of IMP – start date IMP + 1) / 30.4375, End date of IMP related to min (last IMP intake date +20 days, last contact date, date of death, cut-off date).
- Actual cumulative dose (mg): sum of all actual doses administered.
- Planned cumulative dose (mg): 2.0 mg x weight x number of cycles reached. If weight >100 kg, 100 kg will be used in the calculation (i.e. corresponding to a dose of 200 mg per cycle).
- Dose intensity (mg/kg/3 weeks): (actual cumulative dose received (mg/kg) / (last dose date of IMP + 21 – start date of IMP)) * 21 days.
- Relative dose intensity (%): 100 * actual dose intensity (mg/kg/3 weeks) / planned dose intensity (2 mg/kg/3 weeks).
- Follow-up time (months): max (last contact date, date of death) – start date of IMP + 1) / 30.4375.

4.7 Partial/Missing Dates

Partial or missing dates in general will not be imputed (medical history, previous cancer treatment).

For the calculation of the time (in months) from the date the biopsy was obtained to start date of IMP and the time (in months) from end date of last systemic regimen to start date of IMP, the following imputation rules will be applied when respectively the date the biopsy was obtained or the end date of last systemic regimen is incomplete:

- If the day is missing: first day of the month
- If the day and month are missing: first day of July.
- If the day and month are missing and if the year is the same as the start year of IMP: leave missing.

For the assignment to prior or concomitant medication the following rules will be applied in case of incomplete or missing dates:

- If end date is missing, the end date will be set to the last contact date.
- If end date is incomplete: if the day is missing: the end date will be imputed with the last day of the month; if the day and month are missing: the end date will be imputed with min (31 December of the year, last contact date, date of death).
- If start date is missing: if the (imputed) end date is before the date of first IMP administration, the start date will remain missing; if the (imputed) end date is after or on the date of first IMP administration, the start date will be imputed by the date of first IMP administration.
- If start date is incomplete: the start date will be imputed as minimum of last day/last month and the (imputed) end date.

The imputed dates will only be used for the assignment to prior or concomitant and will not be used in any other calculation and will not be listed.

For the assignment of adverse events (AE) the following rules will be applied in case of incomplete or missing start date:

- If end date is before the date of first IMP administration, the start date will remain missing/incomplete (medical history);
- If start date is missing and end date is after or on the date of first IMP administration or the end date is missing, the start date will be imputed by the date of first IMP administration (AE).
- If start date is incomplete and end date is after or on the date of first IMP administration or the end date is missing, the start date will be imputed as follows: if the day is missing and if the start date and date of first dose share the same month and year, the missing start day will be imputed as the day of first dose. If the start date month is after the month of first dose, day will be imputed as the first (i.e. 01-MMM-YY); if the day and month are missing and if the start date and date of first dose share the same year, day and month will be imputed as the day and month of first dose. If the start date year is after the year of first dose, the month and day will be imputed as January first (i.e. 01-JAN-YY) (AE).

The imputed date will only be used for the assignment of the treatment emergent flag and will not be used in any other calculation (unless specified otherwise) and will not be listed.

[redacted]

4.8 Methods to Be Used For Handling Missing Data

All available data will be included in data listings and/or tabulations.

No imputation of missing data is planned for safety endpoints, PK or biomarker endpoints. If outliers are detected, a robustness analysis where the outlier effect is reduced or eliminated may be considered.

4.8.1 Primary Endpoint

Any subjects with missing information regarding response to treatment will be counted as non-responders. This also includes subjects with response that cannot be confirmed according to RECIST v1.1 criteria.

4.8.2 Pharmacokinetics

Missing concentration values will be reported as is in data listings. Concentration values below the lower limit of quantification will be handled as LLOQ/2 in summary statistics, and reported as is in data listings. Any missing concentration data will not be imputed.

4.8.3 Biomarkers (TF expression, cTF)

Missing data for TF expression or cTF will be reported as is in data listings, and will not be included in any summary charts or graphs. TF expression or cTF values below the lower limit of quantification will be handled as LLOQ/2 in summary statistics, and reported as is in data listings. Any missing TF expression or cTF data will not be imputed.

4.8.4 Health Related Quality of Life

Missing data at an individual item level will not be imputed, however the following rule will be used for the computation of the scores at the scale level (per the EORTC guideline). For a particular scale, if at least half of the items from the scale have been answered then use the items that were completed and apply the standard equations (per EORTC guideline; see in section 16.3 for more details) for calculating the scale score (ignore items with missing values when making the calculations). If less than half of the items from the scale have been answered then set the scale score to missing (For single-item measures, the score will then be set to missing).

4.9 Changes to Protocol

Some subgroup analyses were updated compared to the ones planned in the protocol:

- Histology which was planned for three subgroups (Adenocarcinoma, adeno-squamous and squamous cell carcinoma) will be done for two subgroups (Squamous and Non-squamous).
- Prior radiation for localized disease has been updated to Prior radiation administered to the pelvis.
- Bevacizumab (Yes and No) has been updated to Prior first line combination of Paclitaxel + Cisplatin/Carboplatin + Bevacizumab or Paclitaxel + Topotecan + Bevacizumab.
- Prior lines of therapy has been updated to Prior lines of systemic regimen administered in the extra-pelvic metastatic or recurrent setting (1 and 2).
- Response to last therapy has been updated to response to last systemic therapy.

- TF expression in biopsy as measured by IHC has been removed. Based on the available data from GEN701, it was observed that there is rarely a scenario where the subject is Tissue Factor "negative". Therefore, a simply positive to negative comparison is insufficient. This analysis is then out of the scope of this clinical SAP.
- Additional subgroup analyses have been added for ECOG and age.

Regarding the efficacy endpoint time to response, it was decided to analyse it only for the FAS population restricted to subjects with a confirmed response using descriptive statistics.

For the efficacy endpoint progression free survival, it was decided to present the PFS rates at 3 and 6 months rather than at 6 and 12 months.

Regarding the pharmacokinetic data, the plasma concentrations will be listed. No further summary is planned.

For the adverse events, it was decided to remove the tabulation of non-serious AEs, as tabulations for all AEs and serious AEs were considered to provide sufficient information. The deaths won't be tabulated in a separate table to avoid duplication of information; on-treatment deaths will be recorded on the AE form and tabulated in the fatal AEs tabulation; and the post-treatment deaths will be included in the overall survival analyses.

Regarding the laboratory data, summary tables for continuous parameters were removed and information was presented in box plots.

No analysis is planned for the vital signs data while the protocol mentioned a table and a listing.

5. Trial Subjects

5.1 Disposition of Subjects

Screening failures including failure reason, protocol version and re-screening information will be presented in a listing. Subjects screened but never started IMP will also be listed.

The frequency of subjects with ongoing treatment and the frequency of subjects who discontinued from treatment will be summarized for the full analysis set (FAS) together with the reasons for treatment discontinuation. The frequency of subjects ongoing in the study and the frequency of subjects discontinued from study (combining the ones who withdrew from study (including subjects who withdrew consent, subjects withdrawn by investigator and lost to follow-up subjects) and the ones who died) will be also given for the full analysis set (FAS).

The details of the 'other reason' will be included in the listing together with the reason for not attending the treatment discontinuation visit and the safety follow-up visit.

Subject dispositions will also be presented in flow diagram in accordance with the current CONSORT statement[1].

5.2 Protocol Deviations

Important protocol deviations will be summarized for the FAS. The details of all deviations will be listed.

Protocol deviations will be defined in the protocol deviations plan.

5.3 In- and Exclusion Criteria

Listing of all in- and exclusion criteria not met will be provided for the FAS.

[redacted]

6. Demographic Characteristics

Descriptive statistics with respect to subject characteristics at baseline will be displayed for the FAS.

The variables to be summarized are:

- Age (years, continuous and categorical: age<50 years and age ≥50 years including also subcategory age ≥65 years)
- Region (EU or US)
- Race (White, Black or African American, Native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska native, Other)
- Ethnic origins (Hispanic or Latino, Not Hispanic or Latino)
- Weight (kg)

Details of the other categories mentioned above will be added to the listings.

7. Baseline Disease Characteristics

Descriptive statistics with respect to subject disease characteristics at baseline will be displayed for the FAS.

- ECOG performance status score. (Note: at entry, only subjects with an ECOG performance status of 0 and 1 are allowed).
- Recurrent disease at time of screening (Yes, No).
- Site(s) of disease at time of screening (Cervix, Uterus, Vagina, Bladder, Rectum, Pelvic lymph nodes, Extra-pelvic lymph nodes, Liver, Bowel, Lung, Bone, Other).
- Histology (Squamous cell carcinoma, Adenocarcinoma, Adenosquamous carcinoma)
- Time (in months) from last systemic regimen* to start date of IMP

Descriptive statistics for the following subgroup data will also be displayed for the FAS.

- Prior radiation administered to the pelvis (Yes or No)
- Prior lines of systemic regimen* (1 or 2)
- Response to last systemic regimen* (Yes or No)
- Prior first line combination of Paclitaxel + Cisplatin/Carboplatin + Bevacizumab or Paclitaxel + Topotecan + Bevacizumab* (Yes or No)

Lastly, descriptive statistics with respect to biopsy information will be displayed for the FAS.

- Biopsy provided (Yes, No) at screening
- Type of Biopsy (Before vs After last systemic regimen*)
- Time from the date the biopsy was obtained to start of IMP (months)

* Given in the setting of recurrent or extra-pelvic metastatic cervical cancer.

Tumor classification (TNM) and Tumor stage (FIGO) at time of diagnosis, and details of the other categories mentioned above will be added to the listings.

8. Medical and Surgical History

Medical conditions and Surgeries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The medical conditions (separately for ongoing and past conditions) and the surgeries will be tabulated separately by system organ class (SOC) and preferred term (PT) for the FAS. SOC and PT (within SOC) will be ordered by decreasing frequency. As mentioned in the Adverse Events section, the adverse events collected during the pre-treatment period will be tabulated together with the medical history.

All details will be listed.

9. Prior Anti-cancer Therapies

All prior anti-cancer therapies, except for radiation therapies and surgeries, will be listed and tabulated by anatomical therapeutic chemical (ATC) code level 3 and active ingredient (WHO-DD dictionary). ATC class and active ingredient (within ATC class) will be ordered by decreasing frequency.

In addition, subjects with prior lines of systemic regimen administered in the extra-pelvic metastatic or recurrent setting will be summarized for the following:

- Number of subjects who received 1 vs 2 systemic regimens
- The best response to the last systemic regimen
- Number of subjects with 1st line systemic regimen by combination of drugs
- Number of subjects with 2nd line systemic regimen by combination of drugs
- Number of subjects with Paclitaxel + Cisplatin/Carboplatin + Bevacizumab or Paclitaxel + Topotecan + Bevacizumab as 1st line systemic therapy

Prior radiation therapies and prior cancer surgeries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The prior cancer surgeries will be presented by system organ class and preferred term (both levels ordered by decreasing frequency). The prior cancer radiation therapies will be summarized by setting (Early-stage disease, locally advanced disease, and palliative) and preferred term (ordered by decreasing frequency).

All details will be listed.

10. Subsequent Anti-Cancer Therapies

All subsequent anti-cancer therapies will be listed and tabulated by anatomical therapeutic chemical (ATC) code level 3 and active ingredient (WHO-DD dictionary). ATC class and active ingredient (within ATC class) will be ordered by decreasing frequency.

In addition, subsequent systemic cancer therapies will also be summarized by combination of drugs. The combination "Other" will also be detailed by a summary of the standardized procedure name.

All details will be listed.

11. Procedures

Procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

All procedures will be listed.

12. Prior and Concomitant Medications

Prior and Concomitant medications will be classified according to World Health Organization Drug Dictionary (WHO-DD dictionary).

Medications will be reported according to the following two distinct categories:

- Prior when they start and end before the first day of IMP
- Concomitant when they start before the first day of IMP and stop or continue after the first day of IMP, or when they start on or after the first day of IMP.

The number and percentage of subjects receiving a concomitant medication will be displayed by third Anatomical Therapeutic Chemical class (ATC 3) and active ingredient for the FAS.

ATC class and active ingredient (within ATC class) will be ordered by decreasing frequency.

Prior medications will only be listed.

A listing of all medications recorded on the (prior and) concomitant medications eCRF page will provide details including indication, dose, route, frequency, and start and stop dates. Prior and Concomitant medications will be split in two listings.

13. Efficacy Evaluation

Efficacy results will be presented on the full analysis set (FAS).

13.1 Primary Objective

Determine the anti-tumor efficacy in subjects with cervical cancer.

13.1.1 Confirmed Objective Response Rate based upon RECIST v1.1[2], assessed by the independent review committee (IRC)

Confirmed objective response rate (ORR) is defined (based on IRC verified scan results) as an overall response (PR or better) confirmed by a subsequent overall response of PR or better at least four weeks later*. Of note, the best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or start of new anti-cancer therapy.

[* The following sequences will be counted as confirmed response:

- CR-CR = CR confirmed
- CR-PR = PD (confirmed) - because of reappearance of disease. Imaging charter must make sure that prior scan is corrected to PR if believed when seeing the following scan to be only PR at subsequent scan. This way CR-PR should not occur if the reader interprets this as a PR confirmed, it would be corrected to PR-PR in this case. Otherwise it would be CR-PD which would qualify as confirmed SD if minimum duration criteria for SD met.
- PR-PR = PR confirmed
- PR-CR = PR confirmed

NB: Intermediate missing (NE) scan evaluations between the response scan and the confirmation scan are allowed, e.g. the sequences PR-NE-PR and PR-NE-NE-PR will be considered PR confirmed.

In all cases the scan that confirms the first scan with CR/PR must occur no sooner than 4 weeks after the first scan.

[redacted]

A subject with sequences that qualify both as PR confirmed and CR confirmed, e.g. PR-PR-CR-CR would be considered a CR confirmed.

If PR or CR are not confirmed, the response will be SD when on or after 35 days and NE when before 35 days. The 35 days takes into account the minimal 6-weeks duration +/- 1 week window.]

The following statistical hypotheses will be tested to address the primary efficacy objective:

$$H_0: \theta \leq 11\% \text{ vs. } H_A: \theta > 11\%$$

where θ is the ORR. The test will be performed as an exact test at a one-sided 2.5% alpha level.

In addition an exact 95% two-sided confidence interval for the ORR will be provided using the Clopper-Pearson method.

The analysis will be performed on the FAS with an ITT approach so that any subjects with missing information regarding response to treatment will be counted as non-responders. See section 4.8 for detailed information of handling of missing values.

Best overall response will be summarized descriptively. Subjects with no post-baseline data will be identified by NE for best response.

ORR including unconfirmed responders will also be analyzed as a supportive analysis.

In addition, confirmed ORR will be analyzed by subgroup (as described in section 4.4) using a forest plot.

Further confirmed ORR as well as confirmed and unconfirmed ORR, as assessed by the investigator, will be analyzed and summarized in the same way.

13.2 Secondary Efficacy Objectives

Evaluate tumor response durability and evaluate clinical response.

13.2.1 Duration of confirmed response

Duration of response (DOR) only applies to the subset of subjects in the FAS whose confirmed best overall response is CR or PR according to RECIST v1.1[2], based on tumor response data per IRC review. The start date is the date of first documented response of CR or PR (i.e. the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented disease progression verified by IRC or death.

Subjects continuing without disease progression or death will be censored and the censoring date will be the date of the last adequate tumor assessment prior to data cut-off/start of new anti-cancer therapy. In case of progression after ≥2 missed scans, censoring will be done at last adequate tumor assessment date prior to the missed scans. Reason of censoring will be summarized.

DOR (months) will be listed for all subjects in the FAS with confirmed best overall response of CR or PR, and presented graphically as well as summarized using survival analysis methods:

- Kaplan-Meier curves
- Kaplan-Meier estimate of the median time, the first and third quartiles, along with approximate 95% confidence interval of the median (the default conftype=loglog in SAS proc lifetest will be used), and the range.

Six months DOR rate (i.e. percentage of subjects with DOR ≥6 months) and 95% CI will also be summarized using Kaplan-Meier estimates.

13.2.2 Time to Confirmed Response

Time to response (TTR) is defined as the time (months) from the date of the first IMP administration to the first documented response of either CR or PR, which must be subsequently verified by the IRC (although date of initial response is used, not date of confirmation). CR and PR are based on tumor response data as per IRC review and according to RECIST v1.1[2].

TTR will be summarized in the FAS population restricted to subjects with a confirmed response using descriptive statistics.

13.2.3 Progression-Free Survival

Progression free survival (PFS) is defined as the time (months) from the date of the first IMP administration to the date of the first documented disease progression or death due to any cause. PFS will be assessed via IRC review according to RECIST v1.1[2].

PFS will be censored if no PFS event is observed before the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-cancer therapy is started. The censoring date will be the date of the last adequate tumor assessment prior to cut-off/start of new anti-cancer therapy. In case of progression after ≥2 missed scans, censoring will be done at last adequate tumor assessment date prior to the missed scans.

PFS will be analyzed in the FAS population and presented graphically as well as summarized using survival analysis methods:

- Kaplan-Meier curves
- Kaplan-Meier estimate of the median time, the first and third quartiles, along with approximate 95% confidence interval of the median (the default conftype=loglog in SAS proc lifetest will be used).

Three and 6 months PFS rates (i.e. percentage of subjects with PFS ≥3 months and ≥6 months respectively) and 95 %CI will also be summarized using Kaplan-Meier estimates.

13.2.4 Overall Survival

Overall survival (OS) is defined as the time (months) from the date of the first IMP administration to the date of death due to any cause.

If a subject is not known to have died, then OS will be censored and the censoring date will be the latest date the subject was known to be alive (on or before the cut-off date).

OS will be analyzed in the FAS population and presented graphically as well as summarized using survival analysis methods:

- Kaplan-Meier curves
- Kaplan-Meier estimates of the median time, the first and third quartiles, along with approximate 95% confidence interval of the median (the default conftype=loglog in SAS proc lifetest will be used).

Six and 12 months OS rates (i.e. percentage of subjects with OS ≥6 months and ≥12 months respectively) and 95% CI will also be summarized using Kaplan-Meier estimates.

13.3 Supportive Analyses of Secondary Efficacy Objectives

Investigator assessment of DOR, TTR and PFS, based upon RECIST v1.1[2], will be analyzed in the same way as the corresponding IRC review based endpoints (except Kaplan-Meier curves which will only be presented for IRC review).

Concordance between IRC review and Investigator assessment will be summarized at a patient level for confirmed ORR and confirmed BOR.

13.4 Anti-tumor Activity

Anti-tumor activity measured by tumor shrinkage (based on sum of the diameter(s) of all target lesions from the radiological scan evaluations) will be listed and summarized descriptively using individual subject plots:

- Waterfall plot and spider plot summarizing the percent change from baseline of the sum of diameter(s) of all target lesions (using response data as assessed by IRC).
- Swimlane plot showing the time to progression (or censoring) for each subject indicating also overall responses as well as withdrawal reason (using response data as assessed by IRC). Swimlane plot will be also repeated restricted to subjects with confirmed response.

13.5 Follow-up Time

The follow-up time (months) will be summarized using descriptive statistics.

14. Pharmacokinetics (PK)

The plasma concentrations will be summarized as described below.

Values below limit of quantification will be counted as having a value of half the lower limit of quantification. See section 4.8 for detailed information of handling of missing values.

Plasma concentrations (HuMax-TF, HuMax-TF-ADC and MMAE) data will be listed.

15. Safety Evaluation

15.1 Extent of Exposure

The duration of exposure to IMP (months), the number of doses received and the cumulative dose (mg/kg), as well as the actual and relative dose intensities will be summarized by means of descriptive statistics using the FAS.

The number of subjects with dose reductions will be summarized together with the reasons.

Details of the other reason category as well as all dosing data will be listed.

15.2 Secondary Safety Objectives

Assess safety and tolerability of tisotumab vedotin.

15.2.1 Adverse events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be graded according to the National Center Institute Common Terminology Criteria for AEs (NCI-CTCAE criteria [v5.0][3]).

Summary tables for AEs described below will only include AEs that are treatment-emergent, i.e. AEs that started or worsened (taking into account the dates of grade changes) during the on-treatment period.

Adverse events collected during the pre-treatment period will be tabulated together with the medical history (by SOC and PT) and will be included in the AE listings (marked with a flag). Adverse events collected during the post-treatment period will be tabulated separately from the treatment-emergent AEs and will be included in the AE listings (marked with a flag).

See section 4.1.1 for definition of pre-treatment, on-treatment and post-treatment periods.

Missing or partial AE start date will be estimated in order to include events in summary tables in case of doubt (see section 4.7 for more details).

A summary table will present the number and percentage of subjects with at least one:

- Adverse event (AE)
- AE related to tisotumab vedotin
- Grade ≥3 AE
- Grade ≥3 AE related to tisotumab vedotin
- Serious AE
- Serious AE related to tisotumab vedotin
- AE leading to drug withdrawal
- AE leading to drug interruption
- AE leading to dose reduction
- Fatal AE
- Fatal AE related to tisotumab vedotin

In addition, tabulations of the number of subjects who experienced AEs as well as severity grade of the events will be presented by preferred term (ordered by decreasing frequency). Subjects will only be counted once for each preferred term. In case a subject experienced the same event more than once, the worst severity grade will be presented.

The following tabulations will be presented:

- All AEs
- All AEs (Occurrence >=10%)
- AEs related to tisotumab vedotin
- AEs leading to drug withdrawal
- AE leading to drug interruption
- AE leading to dose reduction

All adverse events will also be summarized by severity grade, system organ class and preferred term (ordered by decreasing frequency of SOC and by decreasing frequency of preferred term within a SOC).

AE of special interest will be summarized grouped by AESI category (Ocular AE, Peripheral neuropathy, Bleeding event), preferred term and severity grade.

The AESI categories will be defined using MedDRA SMQ lists provided by sponsor at the time of the analysis programming. The AESI indicator per eCRF data will only be used as a data monitoring tool.

In addition, time to onset of first AESI event (for subjects with at least one event), total number of AESI events, total number and percentage of AESI events with outcome of resolution, and time to resolution of each AESI event (for events which are resolved) will be summarized by AESI category (Ocular AE, Ocular Surface Disease, Peripheral Neuropathy, Bleeding Event) using descriptive statistics. AESI events with partial start date will be imputed accordingly to the rules described in section 4.7.

Time to onset of first AESI event will also be presented graphically by AESI category (Ocular AE, Ocular Surface Disease, Peripheral Neuropathy, Bleeding Event) using Kaplan-Meier curves (one plot with one line for each AESI category); subjects with no AESI will be censored at the end of the treatment period.

Adverse events of special interest will also be presented graphically using lines plots. Plots will be performed individually for each subject and will show the reported AESI by category on a time-based x-axis (arrow will be used to show ongoing AEs). Plots will also include lines to show start date in the study (i.e. informed consent date) and last contact date of subject, as well as start and end dates of on-treatment period. Colors will be added for the grades (worst grade).

Lastly, the number of subjects who reported hypersensitivity, number of subjects who reported infusion related reactions and number of subjects who reported anaphylaxis will be summarized by ADA status (As per definition described in section 15.2.5.2).

Listings of all AEs (including those from the pre and post-treatment periods) will be provided including the subject identifier, verbatim, preferred term, system organ class, duration of the event, severity, action taken, outcome, causality, date of onset, days since the first dose, and days since the last dose. The AEs collected during the pre-treatment and post-treatment periods will be flagged.

15.2.2 Deaths and Serious Adverse Events

Serious adverse events (SAEs), SAEs (Occurrence >=2%), SAEs related to tisotumab vedotin, fatal AEs, Grade ≥3 AEs, and Grade ≥3 AEs related to tisotumab vedotin will be summarized grouped by severity grade (except fatal AEs and Grade ≥3 AEs) and preferred term (ordered by decreasing frequency). Serious adverse events will also be summarized by severity grade, system organ class and preferred term (ordered by decreasing frequency of SOC and by decreasing frequency of preferred term within a SOC).

In addition, listings of serious AEs and fatal AEs will be provided similarly to the listing of all AEs.

All deaths (on-treatment and post-treatment) will be listed together with the primary reason of death.

15.2.3 Clinical Laboratory Data

The following laboratory parameters are measured:

- Hematology parameters: Platelets, red blood cell count (including RBC indices, i.e. Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and % reticulocytes), hemoglobin, hematocrit, white blood cell count with differential (i.e. Neutrophils, lymphocytes, monocytes, eosinophils and basophils)

- Coagulation factors: prothrombin time, international normalized ratio and activated partial thromboplastin time.
- Biochemistry parameters: Sodium, potassium, magnesium, creatinine (GFR calculation), calcium, blood urea nitrogen, AST, ALT, alkaline phosphatase, albumin, glucose, total bilirubin, direct bilirubin, lactate dehydrogenase, uric acid, C-reactive protein, s-Ferritin and total creatinine kinase.

Grading of laboratory values (hematology and biochemistry) will be assigned programmatically as per the NCI-CTCAE criteria [v5.0][3]. The calculations of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. CTCAE grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by the CTCAE, results will be categorized as low/normal/high based on laboratory normal ranges.

All laboratory assessments will be converted to the corresponding international system of unit.

All summaries described below will be generated separately for hematology, coagulation and biochemistry tests.

For continuous laboratory tests, box plots will be presented for actual values and for changes from baseline by visit for each parameter.

For all laboratory tests where grades are defined by the CTCAE grading, shift tables from the baseline CTCAE grade to the highest post-baseline CTCAE grade (during on-treatment period) will be produced.

For the calculation of the maximum CTCAE grade, both scheduled and unscheduled values available post-baseline (during on-treatment period) will be used.

Shift tables will be produced based on normal ranges (Low/Normal/High) for all laboratory tests (even the ones defined in the NCI-CTCAE grading guidelines). These tables will summarize the number of subjects with each baseline category (Low/Normal/High) and changes to the worst high and worst low category (Low/Normal/High). Both scheduled and unscheduled values available post-baseline (during the on-treatment period) will be used.

The following subject data listings will be produced for all laboratory parameters where CTCAE grades are defined:

- Listing of subjects with laboratory abnormalities of CTCAE grade 3 or 4.
- Listing of all laboratory data including CTCAE grades (if applicable) as well as classifications relative to laboratory normal ranges.

All other laboratory parameters will be listed by laboratory parameter and subject including the classifications relative to the laboratory normal ranges.

In addition, the frequency of subjects with incidence of drug induced liver laboratory abnormalities (defined as subjects meeting or exceeding the following predefined limits: ALT > 3xULN and Total Bilirubin > 2xULN, AST > 3xULN and Total Bilirubin > 2xULN, AST and/or ALT > 3xULN and Total Bilirubin > 2xULN, AST and/or ALT > 3xULN and Total Bilirubin > 2xULN and ALP < 1.5xULN) will be summarized descriptively and listed. Total bilirubin and/or ALP measurements concurrent or within 21 days subsequent to ALT/AST elevation will be included for the assessment of the incidence.

15.2.4 Ophthalmology results

Eye examination results (Normal / Abnormal / Not done) will be tabulated over time for visual inspection of eye orbit, eye movement and conjunctiva. In addition, frequency of subjects going from normal result at baseline to abnormal result at any post-baseline visits (all together) and at treatment discontinuation visit and safety follow-up (individually) will also be summarized.

The frequency of subjects with normal or abnormal findings at the baseline ophthalmological evaluation will be summarized separately for subjects with and without a reported treatment-emergent ocular AE (MedDRA SMQ lists to be defined by sponsor). The baseline ophthalmological evaluation is considered abnormal if one of the ophthalmological tests included (i.e. Visual acuity, Schrimer's tear test, SLIT lamp, IOC pressure, fundoscopy) is recorded as abnormal in either of the eyes. In addition, the frequency of subjects with an abnormal finding at the baseline evaluation will be summarized for each ophthalmological test separately (Pooling results from both eyes, i.e. abnormal if abnormal in one of the eyes).

Lastly, ophthalmological results will be summarized for the FAS restricted to subjects with a reported treatment-emergent ocular AE as a shift table from baseline to any post-baseline visit (for overall ophthalmological evaluation and for each test separately).

All results from the ophthalmological tests will also be listed for subjects with at least one abnormal finding. A flag for subjects who develop a treatment emergent ocular AE will be added in the listing.

15.2.5 Other Safety Data

15.2.5.1 ECG

ECG interpretation (Normal / Abnormal) and ECG measurements (HR, RR, QT, QTcF, PR and QRS) will be tabulated/summarized by visit and ECG time point (Before IMP administration and End of IMP administration (+15 min)). The three 12-lead ECG performed at each visit/time point will be combined as one measurement using the average of the three results (for ECG measurements), and the worst outcome of the three results for ECG interpretation.

Categorical analysis of QT and QTcF interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT and QTcF intervals (>450 ms or >480 ms or >500 ms) or changes from baseline (change of >30 ms or >60 ms) will be presented at baseline and at any post-baseline visit.

Additionally, categorical analysis of PR interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute PR (>200 ms or >220 ms) or changes from baseline (change of >25%) will also be presented at baseline and at any post-baseline visit.

Lastly, categorical analysis of QRS interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QRS (>110 ms or >120 ms) or changes from baseline (change of >25%) will also be presented at baseline and at any post-baseline visit.

A listing of these subjects will be produced.

QTcF will also be presented graphically using a mean-SE plot for change from baseline values.

15.2.5.2 Immunogenicity (anti-drug antibodies) of tisotumab vedotin

Data on immunogenicity (anti-drug antibodies) of tisotumab vedotin will be summarized as described below.

Titers of tisotumab vedotin will be listed.

Positive/negative host immune response to tisotumab vedotin will be tabulated at baseline and at any post-baseline visit. For post-baseline results, a subject will be considered positive if negative at baseline and at least one positive post-baseline result, or positive at baseline and at least one positive post-baseline result with a titer higher than baseline. Of note, subjects with no post-baseline ADA assessment will have a missing ADA status.

All details will be listed.

Of note, ADA positivity requires confirmation in 2 assay steps. First step has many false positive; the second assay step (confirmation) ensures specificity of the assay. Only confirmed ADA positivity results will be considered as positive. The others will be negative.

Presence of neutralizing antibodies (positive/negative) will be presented in the listing.

For ADA-positive subjects, all ADA assessments should be listed together with their PK value.

The effect of immunogenicity will be assessed for efficacy through a swimlane plot for NAb positive subjects. The plot will examine timing, frequency and nature of ADA occurrence (i.e. the plot will summarize titer values, ADA and NAb status over time as well as progression free survival and best overall response, individually for each subject).

In addition, information from NAb positive subjects will be detailed in individual case narratives. This will include but not limited to ADA test results, ADA titer, and key safety and efficacy data by date or study day.

15.2.6 Pregnancy Test

All positive pregnancy test data will be listed.

16. Exploratory Objectives

Asses biomarkers related to clinical response, assess potential pharmacodynamic biomarkers, and assess Health Related Quality of Life (HRQL).

16.1 TF expression

TF expression (membrane H-score, membrane total % TF expression, cytoplasmic H-score and cytoplasmic total % TF expression) at baseline will be summarized for all subjects using descriptive statistics.

Median TF expression will be presented for each best clinical response category (SD, PR, CR, PD), and also for subjects who derived clinical benefit (SD, PR, CR) versus those with progressive disease (PD).

In addition, TF expression will also be summarized by confirmed BOR first using descriptive statistics, and then graphically using box plots of actual values.

All analyses based on responses in this section will be duplicated using first response data as assessed by investigator and then using response data as assessed IRC.

Additional evaluations of TF expression with other trial data may be performed for exploratory purposes.

[redacted]

Confidential

[redacted]

16.2 Circulating TF

Circulating TF (cTF) will be measured from whole blood samples. [redacted]

Actual values and percent change from baseline of cTF will be graphed per visit using mean-SE plots, overall and by confirmed BOR (one line per response and one line for all).

Actual values and percent change in cTF will be calculated and summarized per visit using descriptive statistics, overall and by confirmed BOR.

Median percent change in cTF will be presented per visit for those subjects with clinical benefit (SD, PR, CR) and compared to those subjects with progressive disease (PD).

All analyses based on responses in this section will be duplicated using first response data as assessed by investigator and then using response data as assessed IRC.

16.3 Health Related Quality of Life (HRQL)

The analysis of health related quality of life will be assessed through EORTC-QLQ-C30 questionnaire together with the EORTC-QLQ-CX24 questionnaire (additional module for subjects treated for cervical cancer).

16.3.1EORTC-QLQ-C30

The EORTC-QLQ-C30 questionnaire consists of both multi-item scales and single items measures. These include 5 functional scales, 3 symptom scales, a global health status/QoL scale, and 6 single items. Each of the multi-item scales includes a different set of items (i.e. no item occurs in more than one scale).

The questionnaire is composed of 30 questions for which the answers ranges either from 1 (Not at all) to 4 (Very much) for items 1 to 28, or from 1 (Very poor) to 7 (Excellent) for items 29 to 30.

All of the scales and single-item measures range in score from 0 to 100, with a high scale score representing a higher response level (e.g. a high level of functioning, a high QoL, or a high level of symptomatology/problems).

The principle for scoring the scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the raw score

[redacted]

2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worst") level of symptoms.

Table 1 Scoring the EORTC-QLQ-C30

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

Table 1 summarizes the different scales and component items.

For all scales, the *RawScore (RS)* is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$$

and for **Symptoms scales/items** and **Global health status/QoL**:

$$Score = \{(RS-1)/range\} \times 100$$

See section 4.8 for detailed information of handling of missing values.

[redacted]

The 15 scores computed from EORTC-QLQ-C30 questionnaire will be summarized using descriptive statistics (n, mean and SD) at baseline, and at each scheduled visit for actual values and changes from baseline.

In addition, compliance and completeness to the questionnaire, as defined below, will also be summarized. Compliance will be presented overall and by visit, while completeness will only be presented by visit.

Compliance (percentage) will be computed on a subject level as the number of visits for which the subject filled in the questionnaire (at least one item answered) divided by the number of visits scheduled for HRQL data taking into account which visit the subject reached. Of note, all screening visits have been pooled as one visit.

Compliance will also be computed on a visit level as how many subjects filled in the questionnaire (at least one item answered) divided by the total number of subjects who reached that visit.

Completeness will be computed on a visit level as how many subjects filled in the questionnaire (at least one item answered) divided by the total number of subjects in the FAS population, regardless of subject drop-outs.

All details including answers to individual questions will be listed.

16.3.2 EORTC-QLQ-CX24

The cervical cancer module is meant for use among cervical cancer subjects varying in disease stage and treatment modality. It should always be complemented by the QLQ-C30.

The EORTC-QLQ-CX24 is composed of 24 questions for which the answers range from 1 (Not at all) to 4 (Very much).

Table 2 Scoring the EORTC-QLQ-CX24

	Scale name	Number of items	Item range	QLQ-CX24 item numbers
Functional scales				
Body image	CXBI	3	3	15 – 17
Sexual activity	CXSXA	1	3	19
Sexual enjoyment	CXSXE	1	3	24
Sexual/vaginal functioning	CXSV	4	3	20 – 23
Symptom scales				
Symptom experience	CXSE	11	3	1 – 7,9,11 – 13
Lymphoedema	CXLY	1	3	8
Peripheral neuropathy	CXPN	1	3	10
Menopausal symptoms	CXMS	1	3	14
Sexual worry	CXSW	1	3	18

Table 2 summarizes the different scales and component items.

The scoring system is similar to the one for EORTC-QLQ-C30 and fully described in the previous section 16.3.1. See section 4.8 for detailed information of handling of missing values.

As for the EORTC-QLQ-C30, the 9 scores computed from EORTC-QLQ-CX24 questionnaire will be summarized using descriptive statistics at baseline, and at each scheduled visit for

actual values and changes from baseline. In addition, compliance and completeness to the questionnaire will also be summarized as described in the previous section 16.3.1.

All details including answers to individual questions will be listed.

17. References

1. http://www.consort-statement.org/
2. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer (Oxford, England: 1990). 2009;45(2):228-247.
3. CTCAE 5.0. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. Published: November 27, 2017. U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES. National Institutes of Health. National Cancer Institute. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf
4. EORTC-QLQ-C30 Scoring Manual. https://www.eortc.be/qol/files/SCManualQLQ-C30.pdf
5. EORTC-QLQ-CX24 Scoring Manual. http://www.eortc.be/qol/files/ScoringInstructions/CX24_summary.pdf

18. List of Tables/Graphs/Listings

18.1 List of Statistical Tables

General
Table 14.01.01: Subject Treatment Disposition
Table 14.01.02: Subject Study Disposition
Table 14.01.03: Important Protocol Deviations
Table 14.01.04: Demographic and Baseline Disease Characteristics
Table 14.01.05: Baseline Biopsy Information
Table 14.01.06.01: Medical History and Pre-Treatment Adverse Events – Resolved prior to C1D1 – By SOC and PT
Table 14.01.06.02: Medical History and Pre-Treatment Adverse Events – Ongoing – By SOC and PT
Table 14.01.06.03: Surgical History – By SOC and PT
Table 14.01.07.01: Prior Systemic Regimen in Extra-pelvic Metastatic or Recurrent Setting
Table 14.01.07.02: Prior Anti-Cancer Therapies – By ATC level 3 and Active Ingredient
Table 14.01.07.03: Prior Cancer Radiations– By Setting and PT
Table 14.01.07.04: Prior Cancer Surgeries – By SOC and PT
Table 14.01.08.01: Anti-Cancer Therapies after Tisotumab Vedotin Treatment
Table 14.01.08.02: Anti-Cancer Therapies after Tisotumab Vedotin Treatment – By ATC level 3 and Active Ingredient
Table 14.01.09: Concomitant Medications – By ATC level 3 and Active Ingredient
Efficacy Evaluation
Table 14.02.01.01: Confirmed Objective Response Rate (Assessed by IRC and Investigator)
Table 14.02.01.02: Objective Response Rate including Unconfirmed Response (Assessed by IRC and Investigator)
Table 14.02.02: Duration of and Time to Confirmed Response (Assessed by IRC and Investigator)
Table 14.02.03: Progression-Free Survival (Assessed by IRC and Investigator)
Table 14.02.04: Overall Survival
Table 14.02.05: Concordance/Discordance of Confirmed Response Assessment per IRC vs Investigator
Table 14.02.06: Follow-up Time
Safety Evaluation
Table 14.03.01: Extent of exposure to Tisotumab Vedotin
Table 14.03.02: Summary of Treatment-Emergent Adverse Events
Table 14.03.03.01: Treatment-Emergent Adverse Events - By PT, and Maximum Severity Grade
Table 14.03.03.02: Treatment-Emergent Adverse Events - By SOC, PT, and Maximum Severity Grade
Table 14.03.03.03: Treatment-Emergent Adverse Events (Occurrence >=10%) - By PT, and Maximum Severity Grade
Table 14.03.04: Treatment-Emergent Adverse Events Related to Tisotumab Vedotin - By PT, and Maximum Severity Grade
Table 14.03.05.01: Treatment-Emergent Adverse Events of Special Interest – By AESI category, PT, and Maximum Severity Grade
Table 14.03.05.02.01: Treatment-Emergent Adverse Events of Special Interest - Ocular Adverse Event: Time to Onset and Time to Resolution
Table 14.03.05.02.02: Treatment-Emergent Adverse Events of Special Interest - Ocular Surface Disease: Time to Onset and Time to Resolution
Table 14.03.05.02.03: Treatment-Emergent Adverse Events of Special Interest - Peripheral Neuropathy: Time to Onset and Time to Resolution
Table 14.03.05.02.04: Treatment-Emergent Adverse Events of Special Interest - Bleeding Event: Time to Onset and Time to Resolution
Table 14.03.06: Grade >=3 Treatment-Emergent Adverse Events – By PT
Table 14.03.07: Grade >=3 Treatment-Emergent Adverse Events Related to Tisotumab Vedotin – By PT
Table 14.03.08.01: Serious Treatment-Emergent Adverse Events – By PT, and Maximum Severity Grade
Table 14.03.08.02: Serious Treatment-Emergent Adverse Events – By SOC, PT, and Maximum Severity Grade
Table 14.03.08.03: Serious Treatment-Emergent Adverse Events (Occurrence >=2%) – By PT, and Maximum Severity Grade
Table 14.03.09: Serious Treatment-Emergent Adverse Events Related to Tisotumab Vedotin – By PT, and Maximum Severity Grade
Table 14.03.10: Treatment-Emergent Adverse Events Leading to Drug Withdrawal – By PT, and Maximum Severity Grade
Table 14.03.11: Treatment-Emergent Adverse Events Leading to Drug Interruption – By PT, and Maximum Severity Grade

[redacted]

Confidential

Table 14.03.12: Treatment-Emergent Adverse Events Leading to Dose Reduction – By PT, and Maximum Severity Grade
Table 14.03.13: Fatal Treatment-Emergent Adverse Events – By PT
Table 14.03.14: Post-treatment Adverse Events – By PT, and Maximum Severity Grade
Table 14.03.15: Incidence of Hypersensitivity and Infusion reactions by ADA status
Table 14.03.16: Hematology Laboratory Results – Shift table from Baseline CTCAE grade to Highest Post-Baseline CTCAE grade
Table 14.03.17.01: Hematology Laboratory Results – Shift Table Baseline vs Worst Highest Post-Baseline Abnormality
Table 14.03.17.02: Hematology Laboratory Results – Shift Table Baseline vs Worst Lowest Post-Baseline Abnormality
Table 14.03.18: Biochemistry Laboratory Results – Shift table from Baseline CTCAE grade to Highest Post-Baseline CTCAE grade
Table 14.03.19.01: Biochemistry Laboratory Results – Shift Table Baseline vs Worst Highest Post-Baseline Abnormality
Table 14.03.19.02: Biochemistry Laboratory Results – Shift Table Baseline vs Worst Lowest Post-Baseline Abnormality
Table 14.03.20: Coagulation Laboratory Results (Local) – Shift table from Baseline CTCAE grade to Highest Post-Baseline CTCAE grade
Table 14.03.21.01: Coagulation Laboratory Results (Local) – Shift Table Baseline vs Worst Highest Post-Baseline Abnormality
Table 14.03.21.02: Coagulation Laboratory Results (Local) – Shift Table Baseline vs Worst Lowest Post-Baseline Abnormality
Table 14.03.22: Subject Incidence of Drug Induced Liver Laboratory Abnormalities
Table 14.03.23: Eye Examination over Time
Table 14.03.24: Eye Examination - Shift table from Baseline to any Post-Baseline visits
Table 14.03.25: Ophthalmological Evaluation at Baseline
Table 14.03.26: Ophthalmological Evaluation – Shift table from Baseline to any Post-Baseline visits – For subjects with a reported treatment emergent ocular AE
Table 14.03.27: ECG over Time
Table 14.03.28: ECG Categorical Analysis
Table 14.03.29: Tisotumab Vedotin Immunogenicity
Exploratory Evaluation
Table 14.04.01.01: Biomarkers – TF expression (Response Data as Assessed by Investigator)
Table 14.04.01.02: Biomarkers – TF expression (Response Data as Assessed by IRC)
Table 14.04.02.01: Biomarkers – Circulating TF (Response Data as Assessed by Investigator)
Table 14.04.02.02: Biomarkers – Circulating TF (Response Data as Assessed by IRC)
Table 14.04.03.01: Health Related Quality of Life – EORTC-QLQ-C30
Table 14.04.03.02: Health Related Quality of Life – EORTC-QLQ-C30: Compliance and Completeness
Table 14.03.04.01: Health Related Quality of Life – EORTC-QLQ-CX24
Table 14.03.04.02: Health Related Quality of Life – EORTC-QLQ-CX24: Compliance and Completeness

[redacted]

Confidential

18.2 List of Graphs

[redacted]

18.3 List of Derived Data Listings

General
Listing 16.02.01.01: Screening Failures
Listing 16.02.01.02: Subject Disposition
Listing 16.02.01.03: Protocol Deviations
Listing 16.02.01.04: In- and Exclusion Criteria not met
Listing 16.02.01.05: Demographic Characteristics
Listing 16.02.01.06: Baseline Disease Characteristics
Listing 16.02.01.07: Medical and Surgical History
Listing 16.02.01.08.01: Prior Anti-Cancer Therapies
Listing 16.02.01.08.02: Anti-Cancer Therapies after Tisotumab Vedotin Treatment
Listing 16.02.01.09: Prior Cancer Radiations
Listing 16.02.01.10: Prior Cancer Surgeries
Listing 16.02.01.11: Procedures
Listing 16.02.01.12.01: Prior Medications
Listing 16.02.01.12.02: Concomitant Medications
Efficacy Evaluation
Listing 16.02.02.01.01: Target, non-target and new lesions information – Assessed by IRC
Listing 16.02.02.01.02: Target, non-target and new lesions information – Assessed by Investigator
Listing 16.02.02.02.01: Efficacy (Response data) – Assessed by IRC
Listing 16.02.02.02.02: Efficacy (Response data) – Assessed by Investigator
Listing 16.02.02.03.01: Efficacy (DOR, TTR, PFS, OS) – Assessed by IRC
Listing 16.02.02.03.02: Efficacy (DOR, TTR, PFS, OS) – Assessed by Investigator
Safety Evaluation
Listing 16.02.03.01:Tisotumab Vedotin Exposure Data
Listing 16.02.03.02: Adverse Events
Listing 16.02.03.03: Serious Adverse Events
Listing 16.02.03.04: Fatal Adverse Events
Listing 16.02.03.05: Deaths
Listing 16.02.03.06: Laboratory Results
Listing 16.02.03.07: NCI CTCAE Grade >=3 Laboratory Results
Listing 16.02.03.08: Incidence of Drug Induced Liver Laboratory Abnormalities
Listing 16.02.03.09: Eye examination results – by Investigator
Listing 16.02.03.10: Ophthalmology Examination Results (For subjects with at least one abnormal finding at any evaluation) – by Ophthalmologist
Listing 16.02.03.11.01: ECG
Listing 16.02.03.11.02: QT/QTcF, PR and QRS (For subjects meeting or exceeding the predefined limits)
Listing 16.02.03.12.01: Plasma Concentrations and Tisotumab Vedotin Immunogenicity
Listing 16.02.03.12.02: Plasma Concentrations and Tisotumab Vedotin Immunogenicity – ADA-positive subjects
Listing 16.02.03.13: Tisotumab Vedotin Immunogenicity – Case Narratives (For Nab positive subjects)
Listing 16.02.03.14: Positive Pregnancy Test
Exploratory Evaluation
Listing 16.02.04.01: Biomarkers –Circulating TF
Listing 16.02.04.02: Biomarkers – TF expression
Listing 16.02.04.03: Health Related Quality of Life

19. Version history

Version of the SAP and date	Changes
Final version 1.0, MAY2018	NA. First final version.
Final version 3.0, JAN2019 [Of note, final version 2.0 does not exist in the Vault due to wrong manipulation during the approval process.]	Major changes are described below, section by section. Additional minor updates were done for clarification or typos. **Section 4.1.2 Visit windows:** A paragraph was added to define visit windows for the radiological assessments. This will be used for all corresponding outputs presented by time points. **Section 4.4 Subgroup definitions:** Subgroup analysis by TF membrane H-score (TF+ or TF-) was removed as considered out of scope of this SAP based on data from GEN701. ROC analysis planned to define TF+ vs TF- was then also removed from section 13.1.1. **Section 4.9 Changes to protocol:** Section was updated to reflect the changes compared to the most up-to-date version of the protocol (Version 6.0). **Section 9 Prior cancer therapies:** Additional analyses were added to describe more in details the prior systemic treatments received. **Section 10 New cancer therapies:** Listing of new cancer therapies has been added. **Section 11 Procedures:** New section added to describe the analyses to be performed on the procedures data. **Section 12 Prior and concomitant medications:** Prior and concomitant medications were divided into three exclusive categories: prior (when they start and end before start of treatment), prior and ongoing (when they start before start of treatment and stop or continue after start of treatment) and concomitant (when they start on or after start of treatment). In addition, tables will be presented by active ingredient instead of generic term since the latter one will not be collected. **Section 13.1.1 Confirmed ORR:** Overall response at each time points and best overall response will also be summarized descriptively. **Section 13.2.2 Time to response:**

[redacted]

	A sentence was added to specify that Kaplan-Meier curves for TTR will be presented from bottom-left corner to top-right corner. **Section 13.4 Anti-Tumor Activity:** Wording was updated to make it clear that tumor shrinkage tables will be repeated by ADA status but corresponding graphs will only be presented overall. In addition, clear definition of ADA status was added. **Section 14.2.1 Adverse events:** Additional analyses were added for the AESI: time to first AESI, duration of first AESI, total duration of AESI (per patient), and duration of AESI (per event) will be summarized using Kaplan-Meier methods, for all AESI and for Grade 3 of higher AESI. Corresponding conventions were also added. Individual lines plots were also added for AESI. In addition, additional analyses were also added for hypersensitivity and infusion reaction events, overall and by ADA status. **Section 14.2.5.1 ECG:** A graph was added to visually describe QTcF. **Section 14.2.5.2 Weight and Vital signs:** A categorical analysis of the vital signs was added to better summarize the clinically notable values. **Section 14.2.5.3 Immunogenicity:** The wording of the paragraph was updated to better describe all analyses planned for the immunogenicity data as the section wasn't initially very much detailed. **Section 14.2.7 Pharmacokinetics:** Graphs planned for the PK data were updated from individual patient profile plots to a mean concentration plot. **Section 14.3: Exploratory objectives:** Some analyses were added for the exploratory objectives: sections were added for biomarkers (TF expression and circulating TF) and for the HRQL. A subsection describing conventions for handling missing biomarkers data was also added in section 4.8.
Final version 4.0, SEP2019	Major changes are described below, section by section. Additional minor updates were done for clarification or typos. **Section 4 General Analysis Definition:** 25th and 75th percentiles were removed from the descriptive statistics for continuous data. **Section 4.1.2 Visit Windows:**

	"Section 4.1.2.1 Radiological assessment" was removed as no efficacy output is presented by visit anymore. **Section 4.2 Planned Analysis:** The cut off of the primary reporting of the trial has been aligned to the most up-to-date version of the protocol (Version 7.0). **Section 4.4 Subgroup Definitions:** Some subgroups have been slightly updated either for combination of subcategories (Histology), or for a better specification of the subgroup itself (For the subgroups related to prior cancer therapies). Some new subgroups were added (ECOG and Age). **Section 4.7 Partial/Missing Dates:** Rules for derivation of partial/missing dates were updated for prior/concomitant medications and adverse events to better describe all possible cases. **Section 4.8 Methods to Be Used for Handling Missing Data:** Sections were added with methods for Biomarkers and Health Related Quality of Life missing data. **Section 4.9 Changes to protocol:** Section was updated to reflect the changes compared to the most up-to-date version of the protocol (Version 7.0). **Section 5.1 Disposition of Subjects:** Descriptive analyses for disposition were updated to better describe the treatment and study dispositions of subjects. **Section 6 Demographic Characteristics/Section 7 Baseline Disease Characteristics:** Selection of variables to be presented for demographic and baseline disease characteristics data was updated. Presentation of the subgroup variables was also added and described in the section. **Section 8 Medical and Surgical History:** Adverse events collected during pre-treatment period was added to the section as they will be combined within the medical history summary. **Section 9 Prior Anti-cancer therapies:** For tabulations summarized by anatomical therapeutic chemical (ATC) code, use of ATC level 2 has been changed to ATC level 3. The summary of the prior cancer radiation therapies has been updated to present data by setting rather than by system organ class. The analyses related to the prior systemic treatments were updated to better describe treatment regimens received by the subjects.

[redacted]

Confidential

	Section 10 Subsequent Anti-cancer Therapy: For tabulations summarized by anatomical therapeutic chemical (ATC) code, use of ATC level 2 has been changed to ATC level 3. In addition, a new analysis was added to present the subsequent anti-cancer therapies by combination of drugs as planned for the prior anti-cancer therapies. **Section 11 Procedures:** Tabulation of procedures was removed. **Section 12 Prior and Concomitant Medications:** Definition of prior versus concomitant medications was updated into two categories instead of three ("Prior and Ongoing" was removed). Tabulations of prior medications were removed. For tabulations summarized by anatomical therapeutic chemical (ATC) code, use of ATC level 2 has been changed to ATC level 3. Listing was updated to be produced separately for prior and concomitant medications. **Section 13.1 Primary Objective:** Summary of overall response by visit has been removed. Subgroups analyses have been limited to confirmed objective response rate and done using a forest plot rather than tabulations. **Section 13.2 Secondary Efficacy Objectives:** Computation of 6 months rate using Kaplan-Meier estimates has been added for duration of response. Time to response endpoint has been updated to be produced only for responders. Corresponding analyses were updated to simple descriptive statistics rather than Kaplan-Meier analyses. Computations of 6 and 12 months rates for progression-free survival using Kaplan-Meier estimates have been updated to 3 and 6 months. A new analysis has been added for the concordance between IRC review and Investigator assessment. **Section 13.4 Anti-tumor Activity:** Tabulations of tumor shrinkage by time point and corresponding mean-SE plots over time have been removed. Spider plots were added for tumor shrinkage data. **Section 13.5 ECOG Performance status:** The section was deleted as analysis of ECOG post-baseline data was removed. **Section 15.2 Secondary Safety Objectives:**

	Tabulations of adverse events collected during pre-treatment period was removed as they will be combined within the medical history summary. Content of summary table of TEAEs was slightly updated. Tabulations for TEAEs have been updated to be presented by PT rather than by SOC and PT. Tabulations for non-serious TEAEs was removed while tabulations for TEAEs with occurrence >=10%, TEAEs leading to drug interruption, TEAEs leading to drug reduction, and serious TEAEs with occurrence >=2% were added. The additional analyses for AESIs was limited to time to onset of first event (for subjects with at least one event) and time to resolution of each event (for events which are resolved) using descriptive analyses. The number of subjects who reported anaphylaxis was added to the hypersensitivity and infusion related reaction incidence table. The separate tabulation for deaths was removed to avoid duplication of the information. Descriptive statistics summary tables of laboratory data over time were removed. A new tabulation of drug induced liver abnormalities incidence and the corresponding listing have been added. The ophthalmology analyses were slightly updated to better describe the available data. A convention for pooling information from both eyes has been added. A convention for the handling of triplicates ECG measurements has been added. ECG categorical analyses were extended to PR and QRS in addition to QT/QTcF. All analyses for weight and vital signs have been removed. Definition of ADA status was updated for consistency throughout the document. Graphical analyses of association between ADA status and PK concentrations were removed. Listing of physical examination results was removed as no data collected as such. **Section 15.3 Exploratory Objectives:** Analyses planned for TF expression and circulating TF were updated to better describe the data. Analyses presented by quartiles were updated to by BOR. A convention for the selection of the baseline tumor biopsy when there are multiple records was added. New analyses for compliance and completeness of the HRQL data were added.
Final version 5.0, OCT2019	Major changes are described below, section by section. Additional minor updates were done for clarification or typos.

[redacted]

	Section 4.6 Calculated Variables: The definitions of dose intensity and relative dose intensity were slightly updated. **Section 15.2.1 Adverse events:** The following wording was removed: Those numbers will include preferred terms such as infusion-related reaction, hypersensitivity, and anaphylaxis regardless of causality within 48 hours of infusion throughout the treatment duration. **Section 15.3 Exploratory Objectives:** Section numbering was updated to Section 16.