Official Title of Study:

A Phase I/IIa Study of BMS-986148, a Mesothelin Directed Antibody Drug Conjugate, in Subjects With Select Advanced Solid Tumors

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STATISTICAL ANALYSIS PLAN
FOR EARLY-PHASE ONCOLOGY STUDIES

ONCOLOGY PROTOTYPE

PROTOCOL(S) CA008002

VERSION # 1.0

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1 BACKGROUND AND RATIONALE

Research Hypothesis:

There is no formal primary research hypothesis for this study to be statistically tested. The purpose of this study is to evaluate the safety profile, tolerability, preliminary efficacy, pharmacokinetics and pharmacodynamics of BMS-986148 in subjects with select advanced solid tumors.

Schedule of Analyses:

Data emerging from each dose level or each part of the study will be examined prior to the formal locking of the study database for timely decisions about, but not limited to, dose selection, regimen selection and early termination of the study. No formal inferences requiring any adjustment to statistical significance level will be performed.

The final analysis will be performed following the database lock after all subjects have completed the study.

2 STUDY DESCRIPTION

2.1 Study Design

This is a phase I/IIa, open label study to characterize the safety and tolerability of BMS-986148 in subjects with select advanced solid tumors (pancreatic, ovarian, NSCLC, gastric, or mesothelioma). The study has two segments Part 1 (Phase I study - dose escalation) and Part 2 (Phase IIa - dose expansion) (see Figure 2.1.1-1). All subjects will complete up to four study periods (see Figure 2.1.1-2): Screening (up to 28 days), Treatment (21 days/cycle for Q3 weekly dosing and 28 days/cycle for Q weekly dosing), Follow-up (60 days), and Survival Follow-up (up to 1 year following the last dose of study drug). Part 1 is divided into two sections, i.e., Part 1A and Part 1B. BMS-986148 will be administrated every 3 weeks (Q3 week dosing, 21 day/cycle) in Part 1A, and weekly for 3 weeks with one week off in Part 1B. Part 2 includes five expansion cohorts restricted to these tumor types 1) mesothelioma 2) pancreatic 3) ovarian 4) NSCLC and 5) gastric cancer.

The duration of the study is anticipated to be approximately 5 years. The end of the study will occur when the last subject has the last survival follow-up visit.

Figure 2.1.1-1: Sequence of Study Phases

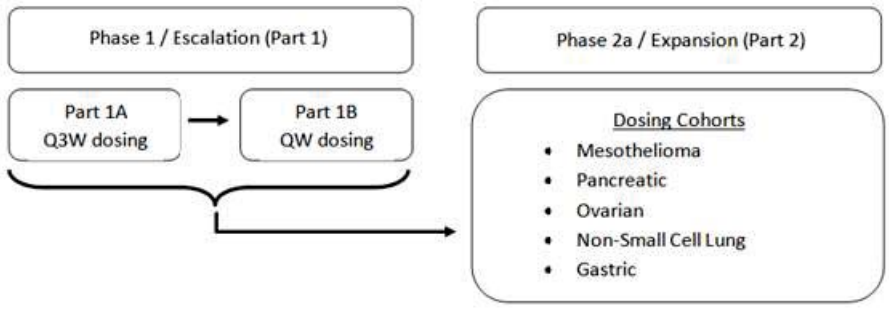
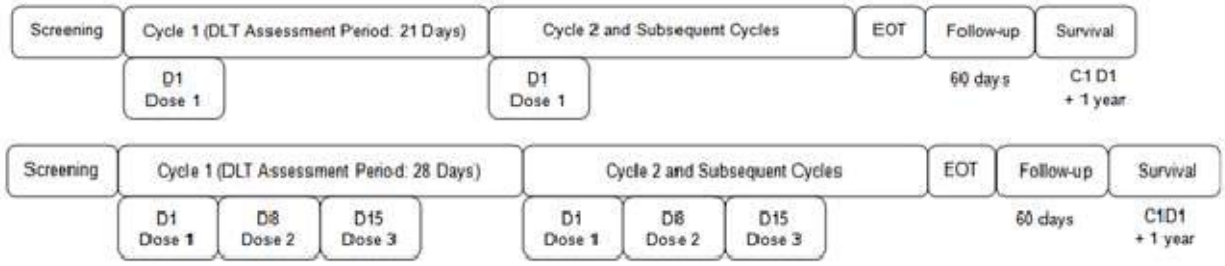


Figure 2.1.1-2: Dosing (Q3W and QW) and Study Periods



DLT: Dose limiting toxicity; EOT: End of Treatment; D: Day; C1D1: Cycle 1 Day 1 (first dose)

2.2 Treatment Assignment

All enrolled subjects who have signed informed consent, registered, and have eligibility for the study confirmed will be administered intravenous doses of BMS-986148 per the cohort assignment and the duration of treatment as indicated in the study design.

2.3 Blinding and Unblinding

Not applicable.

2.4 Protocol Amendments

This SAP incorporates the following protocol amendments.

Table 1: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes

3 OBJECTIVES

3.1 Primary

To assess the safety and tolerability of BMS-986148 in subjects with select advanced solid tumors.

3.2 Secondary

- To assess the preliminary anti-tumor activity of BMS-986148 as measured by overall response rate (ORR), response duration, and progression free survival (PFS)
- To characterize the pharmacokinetics (PK) of the total antibody (unconjugated antibody + antibody conjugated to tubulysin or antibody conjugated to any tubulysin metabolites), active ADC (antibody conjugated to tubulysin), and unconjugated tubulysin
- To assess the effect of dosage regimen and exposure (active ADC and unconjugated tubulysin) on the QT interval
- To characterize the immunogenicity of BMS-986148

[redacted]

4 ENDPOINTS

4.1 Primary Endpoints

Incidence of adverse events (AEs) at its worst grade, serious adverse events (SAEs) at its worst grade, adverse events leading to discontinuations, deaths, frequency of laboratory test toxicity grade shifting from baseline. Safety will be evaluated from the time that the subject signs the informed consent, and for up to 60 days after the last dose of study drug.

AEs and Laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

4.2 Secondary Endpoints

4.2.1 Pharmacokinetics

The pharmacokinetics of total antibody, [redacted] active ADC, [redacted] and unconjugated tubulysin will be characterized using the following endpoints:

- Cmax: Maximum observed serum or plasma concentration
- Tmax: Time of maximum observed serum or plasma concentration
- AUC(0-t): Area under the concentration-time curve from time zero to time t
- AUC(TAU): Area under the concentration-time curve in one dosing interval
- Ctau: Concentration at the end of a dosing interval
- Ctrough: Trough observed serum or plasma concentration (includes pre-dose and Ctau concentrations)
- CLT: Total body clearance
- Vss: Apparent volume of distribution at steady state
- Vz: Volume of distribution of terminal phase

- AI_AUC: AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
- AI_Cmax: Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
- AI_Ctau: Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
- Cavg: average concentration over the dosing interval; AUC(TAU)/tau
- T-HALF: Terminal serum or plasma half life

4.2.2 Efficacy

Efficacy based on RECIST v1.1 or Modified RECIST for malignant pleural mesothelioma will be assessed using the following secondary endpoints:

- **Best overall response (BOR):** defined as the best response designation over the study as a whole, recorded between the dates of first dose until the last tumor assessment prior to subsequent therapy. CR or PR determinations included in the BOR assessment must be confirmed by a second scan performed no less than 4 weeks after the criteria for response are first met. For those subjects who have surgical resection, only pre-surgical tumor assessments will be considered in the determination of BOR.
- **Objective Response Rate (ORR):** defined as the total number of subjects whose best overall response (BOR) is either a CR or PR divided by the total number of subjects in the population of interest.
- **Duration of Response (DOR)**: defined as the time between the date of first response and the subsequent date of objectively documented disease progression or death, whichever occurs first. For those subjects who remain alive and have not progressed or received subsequent therapy, duration of response will be censored on the date of last tumor assessment.
- **Progression Free Survival (PFS)**: defined as the time from the first dose of study medication to the date of the first objective documentation of tumor progression or death due to any cause. Subjects who did not progress nor died will be censored on the date of their last tumor assessment. Subjects who did not have any on-study tumor assessments will be censored on the date of the first dose of study medication.
- **Progression Free Survival Rate (PFSR) at week 't'**: defined as the proportion of subjects who remain progression free and surviving at 't' weeks (t=12, 24, 36, etc). The proportion will be calculated by the product-limit method (Kaplan-Meier estimate) which takes into account censored data.

[redacted]

4.2.3 QTc

Change in QTcF, (ΔQTcF) from baseline, at selected times.

4.2.4 Immunogenicity (Anti-Drug Antibodies)

The endpoints of immunogenicity of BMS-986148 include frequency of different subject immunogenicity status, e.g., subject positive ADA, persistent positive ADA and others. Definitions of all the immunogenicity endpoints are given below:

Sample ADA Status:

- Baseline ADA-positive sample: ADA is detected in the last sample before initiation of treatment
- Baseline ADA-negative sample: ADA is not detected in the last sample before initiation of treatment
- ADA-positive sample: After initiation of treatment, (1) an ADA detected (positive seroconversion) sample in a subject for whom ADA is not detected at baseline, or (2) an ADA detected sample with ADA titer to be at least 4-fold or greater (≥) than baseline positive titer
- ADA-negative sample: After initiation of treatment, ADA not positive sample relative to baseline

Subject ADA Status:

- Baseline ADA-positive subject: A subject with baseline ADA-positive sample
- ADA-positive subject: A subject with at least one ADA positive-sample relative to baseline at any time after initiation of treatment
  - Persistent Positive (PP): ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart
  - Not PP-Last Sample Positive: Not persistent positive with ADA-positive sample at the last sampling timepoint
  - Other Positive: Not persistent positive but some ADA-positive samples with the last sample being negative
- ADA-negative subject: A subject with no ADA-positive sample after the initiation of treatment

4.2.5 Biomarker

The biomarker endpoints are exploratory summaries for [redacted] CA125, and CA19-9.

[redacted]

5 SAMPLE SIZE AND POWER

Dose Escalation: In the dose escalation part of the study, i.e., both Part 1A and 1B, the sample size per dose level cannot be precisely determined but depends on the observed DLTs and the decision rules of mTPI. Between 2 and up to 13 DLT evaluable subjects may be enrolled to a given cohort. Treating additional subjects beyond the 13 would be unlikely to alter the decision specified by the mTPI algorithm.

Cohort Expansion: During this part of the study approximately 25 subjects with high expression of mesothelin are expected to be treated in each tumor cohort at the maximally administered dose or at a dose near the MTD (as determined from dose escalation). This number is based on achieving a reasonable precision of the objective response rate (ORR) and adequate control on the false negative rate (FNR) and false positive rate (FPR) (assuming a historic and target response rate). In a cohort of 25 marker positive subjects if 5 or 6 responses are observed (e.g. for gastric or pancreatic cohorts) then the ORR 90% CI are (8.2%, 37.5%) and (11%, 42%), respectively. If 7 responses are observed (e.g. NSCLC cohort), then the 90% CI is (14%, 46.2%), and if 8 or 9 responses are observed (e.g. mesothelioma or ovarian cohorts), then the 90% CI for ORR are: (17%, 50.4%) and (20%, 54.4%), respectively. These calculations are based on the Clopper- Pearson method for exact confidence intervals.

In addition, 25 subjects per cohort provide the following FNR and FPR under assumptions of expected true ORR. If the true objective response rate (ORR) is 40% (e.g. mesothelioma and ovarian cohorts), then with 25 subjects in a cohort there is 97% and 93% chance of observing at least 6 or 7 responses, respectively, and there is 7% chance of observing 6 or fewer responses (false negative rate). If the true ORR for these tumors is only 20% (rather than 40%), then there is 22% and 11% chance respectively of observing at least 7 and at least 8 responses among 25 subjects (false positive rate).

Similarly if the true ORR is 20% (e.g. gastric and pancreatic cohorts), then there is 97% and 90% probability of observing at least 2 or 3 responses respectively, among 25 subjects and 10% of observing 2 or fewer responses (false negative rate). If the true ORR for these tumors is 10% (rather than 20%) then there is 24% and 10% chance respectively, of observing at least 4 and at least 5 responses (FPR).

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

This study consists of four periods: Screening (up to 28 days), Treatment (21 days/cycle for Q3 weekly dosing and 28 days/cycle for Q weekly dosing), Follow-up (60 days), and Survival Follow-up (up to 1 year following the first dose of study drug).

6.2 Treatment Regimens

In escalation phase, the selection of doses for the two cohorts Part 1A and Part 1B will be based on a modified Fibonacci dose escalation and an mTPI design. BMS-986148 will be administrated

every 3 weeks in Part 1A and weekly for 3 weeks with one week off in Part 1B. In the expansion phase, the optimal regimen from Part 1A or 1B selected upon agreement between the Sponsor/Medical Monitor and Investigators will be adopted in the five cohorts corresponding to these tumor types: mesothelioma, pancreatic, ovarian, NSCLC, and gastric cancer.

The analysis and reporting of safety data will be performed on an as assigned basis at time of study therapy initiation unless otherwise specified. If a subject received the incorrect study medication for the entire period of treatment, the subject will be analyzed in the treatment group associated with the incorrect study medication.

6.3 Populations for Analyses

- All Enrolled Subjects: All subjects who signed an informed consent form
- All Treated Subjects: All subjects who received at least one dose of study medication
- Pharmacokinetic Subjects: All subjects who received at least one dose of BMS-986148 and have evaluable serum and plasma concentration data

[redacted]

- Immunogenicity (ADA) Subjects: All treated subjects who have baseline and at least one post baseline immunogenicity assessment
- ECG Evaluable Population: all treated subjects who had a baseline ECG and at least one on-study ECG.
- Response Evaluable Population: all treated subjects who had baseline tumor measurement and at least one other tumor measurement after treatment, clinical progression, or death prior to the first on-treatment tumor assessment.

7 STATISTICAL ANALYSES

All analyses will be performed in SAS using version 9.2 or higher. Some figures may be generated using S-Plus.

7.1 General Methods

Continuous variables will be summarized using descriptive statistics, ie, medians, minimums, maximums, and means with standard deviations/standard errors of the mean. Categorical variables will be summarized by frequencies and percentages. Percentages will be rounded and may not always add up to 100.

7.2 Grouping Scheme

Individual subject's data will be listed in the order of subject ID and collection time.

Throughout this analysis plan, a cohort is defined a unique group of subjects identified by study phase (escalation, expansion), dose, dose regimen (Q3W or QW for 3 weeks followed by one week off), and tumor type (if in expansion phase). Summary analyses in this study will be performed with various grouping schemes: cohort, dose+dose regimen, expansion cohorts only, and overall, as shown in Table 2. The scheme of dose + dose regimen consists of groups decided

by the unique combination of dose and dose regimen, regardless of tumor type and study phase. The scheme of expansion cohorts only has the five groups of subjects with different tumor types enrolled into the expansion cohorts.

Grouping for efficacy analyses are further divided by different endpoints as in Table 2, where analyses of BOR and ORR will be done by cohort, and other endpoints will be summarized for expansion cohorts only by tumor type.

Safety analyses will be conducted using data from all cohorts by dose, dose regimen and overall. If appropriate, certain safety endpoints may be summarized with further grouping of tumor type.

Table 2: Grouping Scheme for Analyses

Analyses	Dose+Dose Regimen	Cohort	Expansion Cohorts Only	Overall
Subject Disposition		X		X
Demographics and Baseline Characteristics		X		X
Extent of Exposure		X		X
BOR, ORR		X		X
PFSR, [redacted] PFS, DOR			X	
Safety	X			X
Immunogenicity	X			X
PK	X			
[redacted]				

[redacted]

7.2.1 Study Information

Listing:

- Batch number of study drug

7.2.2 Accrual

The following will be presented on the All Enrolled Subjects.

Summary:

- Number (%) of subjects accrued by country and investigational site: Include country, site number, Principal Investigator's name, number of subjects enrolled, and number of subjects treated

Listing:

- Subjects accrued by country and investigational site

7.2.3 Relevant Protocol Deviations

Relevant Protocol Deviation is a deviation that could potentially affect the interpretability of the study results. Any change to the SAP that involves analysis/reporting of Relevant Protocol Deviations should be made prior to breaking the blind (or prior to the database lock for open-label study.

Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) will be reported through [redacted] listings. The following programmable deviations from inclusion and exclusion criteria will be considered as relevant protocol deviations and a listing will be provided, subject to data availability and applicability.

Inclusion Criteria

1) Only subjects with high expression of mesothelin in the tumor tissue will be enrolled in the expansion phase
2) All subjects must have at least one measurable lesion at baseline by CT or MRI as per RECIST v1.1 or Modified RECIST criteria for malignant pleural mesothelioma
3) ECOG performance status score 0-1

Exclusion Criteria

4) Grade 2 or higher eye disorders (inclusive of all NCI CTCAE v4.03 criteria). Mild eye symptoms such as blurry vision, either age-related or due to ocular or systemic disorder (e.g. diabetes, dry eyes, cataracts, uncorrected refraction abnormality) may be allowed at the discretion of the ophthalmologist if deemed as not constituting a predisposition to drug-induced corneal deposits and blurry vision.
5) Physical and Laboratory Test Findings
   a) Inadequate bone marrow function defined as:
      i) Absolute neutrophil count (ANC) < 1,500 cells/mm^3 ;
      ii) Platelet count < 100,000 cells/mm^3;
      iii) Hemoglobin < 9.0 g/dL
   b) Subjects with a stable chronic transfusion requirement (e.g. due to cumulative toxicity from previous therapy) of no more than once per month will be allowed if the trough hemoglobin is > 8.0 g/dL.
   c) Inadequate hepatic function defined as:
      i) Total bilirubin > 1.5 times the institutional ULN (except known Gilbert's syndrome);
      ii) Alanine transaminase (ALT) or aspartate transaminase (AST) > 3 times the institutional ULN.
   d) Inadequate renal function defined as:
      i) Blood creatinine > 1.5 times the institutional ULN
   e) Any of the following on 12-lead electrocardiogram (ECG) prior to study drug administration, confirmed by repeat.

i) QRS ≥ 120 msec, except right bundle branch block
ii) QTcF ≥ 450 msec for males, ≥ 470 msec for females, except right bundle branch block

7.3 Study Population

7.3.1 Subject Disposition

Summary:

- Pre-treatment period: The number (%) of subjects of the following will be summarized on the All Enrolled Subjects.
  - All enrolled into the study
  - Entering the treatment period
  - Enrolled but not entering the treatment period together with the reasons
- End of treatment period and of study: The number (%) of subjects of the following will be summarized by cohort and overall, based on the All Treated Subjects.
  - All treated subjects
  - Subject completing the treatment period
  - Reasons for not completing the treatment period
  - Subjects continuing in the study
  - Subjects not continuing in the study
  - Reasons for not continuing in the study
- All related data will be listed

7.3.2 Demographics and Other Baseline Characteristics

Summary:

Descriptive statistics will be summarized for the following baseline characteristics for all treated subjects by cohort and overall.

- Age (in years) ; age category (<65, ≥65)
- Gender
- Race
- Ethnicity (if applicable)
- Height
- Weight
- BMI
- ECOG performance status
- Baseline mesothelin expression
- Disease characteristics such as stage and factors that might affect response to therapy and possibly relevant variables (eg, smoking)
- Prior cancer therapy

Listing:

- All relevant data, generally variables listed above by cohort.

7.4 Extent of Exposure

The extent of exposure will be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed. Analyses in this section will be performed on the All Treated Subjects.

7.4.1 Study Therapy

Summary:

Descriptive statistics will be provided by cohort for the following.

- Number of doses, if appropriate
- Duration of therapy (weeks) = (last dose date - first dose date + 7)/7 for Q weekly dosing cohort(s) and (last dose date - first dose date + 21)/7 for Q3 weekly dosing cohort(s)
- Cumulative dose = the sum of all actual doses that a subject received
- Dose intensity = Cumulative dose/Duration of therapy.
- Relative dose intensity (%) = (dose intensity / planned dose intensity)*100
  - Categories: <50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%

Listing:

- Drug administration of BMS-986148
- Duration of therapy, cumulative dose, dose intensity and relative dose intensity

7.4.2 Modification of Study Therapy

Summary:

The following will be provided by cohort.

- Number (%) of subjects with dose delay, omission and discontinuation along with the reason
- Number (%) of subjects with dose reduction along with the reason
- Infusion interruptions
  - Number (%) of subjects with at least one infusion interruption along with the reason
  - Number of infusion interruptions per subject
  - Number (%) of subjects with at least one IV infusion rate reduction along with the reason

Listing:

- All relevant information on dose modification listed above

7.4.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary. Concomitant medications are defined as medications other than study medications which are taken at any time on-treatment.

Listing:

- All prior and concomitant medications

7.5 Efficacy

In general, efficacy analyses will be performed for All Treated Subjects unless otherwise specified. Limited efficacy analyses may be performed on the Response-evaluable Subjects (e.g., ORR summary).

Time to event distribution (e.g. progression free survival, overall survival, and duration of response) will be estimated using Kaplan-Meier (K-M) method. When appropriate, the median along with 95% CI will be provided using Brookmeyer and Crowley methodology[1]. Available medians and confidence intervals will also be presented in K-M plots. Rates at fixed time points (e.g. PFSR at 12, 24, 36 weeks) will be derived from the K-M estimates and corresponding confidence intervals will be derived based on Greenwood formula.

Summary:

- BOR and ORR outcomes (confidence interval will be calculated by the Clopper-Pearson method) will be tabulated by cohort
- The duration of response (with median [95% CI] and range [min, max]), PFS will be estimated by Kaplan-Meier (K-M) methodology by tumor type for the expansion cohorts only. PFSR (e.g., at 12, 24, 36 weeks) will be similarly estimated based on the Kaplan-Meier methodology

[redacted]

Figure:

- Percent change from baseline in target lesions (aka spider plot) by tumor type
- Maximum reduction in baseline target lesions (aka waterfall plot) by tumor type
- Swimmer plot of time to response, duration of response by tumor type

[redacted]

Listing:

- Sum of target lesions at each visit, along with corresponding percent change from baseline, percent increase from nadir, and other lesion information will be provided in the order of cohort, subject ID, and assessment study day
- Subject level BOR, duration of response, and PFS will be provided using RECIST v1.1 criteria or Modified RECIST for malignant pleural mesothelioma

[redacted]

7.6 Safety

Analysis of safety will be based on All Treated Subjects and presented by dose, dose regimen, and overall (if appropriate).

Adverse events (AEs) will be coded according to the most current version of MedDRA and be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Drug-related AEs are those events with relationship to study drug "Related" as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related.

Listing of adverse events will include all enrolled subjects as SAEs and deaths are collected pretreatment. Summaries of adverse events will include (1) events occurring from the first dose date to 60 days (inclusive) after the last dose of BMS-986148 for subjects who are off study treatment and (2) all events occurring from first dose date for subjects who are still on study medication.

When reporting adverse events by CTC grade, summary tables will be provided based on the event with worst CTC grade (independent of relationship to study medication). Subjects will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total subject' row at their worst CTC grade, regardless of SOC or PT.

The analysis of laboratory results will be based on All Treated Subjects. Laboratory results will be categorized according to NCI CTCAE (version 4.03) grade. Baseline is defined as the last non-missing measurement prior to the first dosing date and time. Summaries of laboratory results include baseline and (1) post-baseline results up to 60 days (inclusive) after the last dose of BMS-986148 for subjects who are off study treatment and (2) all available post-baseline results for subjects who are still on study medication.

7.6.1 Overall Adverse Events

Summary:

AEs and drug-related AEs will be tabulated by descending frequency of SOC and descending frequency of PT within each SOC, unless specified otherwise.

- Overall summary of any AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of any non-serious AEs presented by PT. This table will be restricted to events with an incidence greater or equal to 5% in any dose+dose regimen group for all treated subjects (total).

Listing:

All recorded Adverse Events occurring in the pre-treatment, on-treatment, and post treatment period will be listed.

7.6.2 Deaths

Summary:

All deaths during the study within 60 days after the last dose of BMS-986148 will be summarized for cause of deaths by treatment.

Listing:
All recorded deaths for All Enrolled subjects will be listed.

7.6.3 Other Serious Adverse Events

Summary:

- Summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT.
- Summary of drug-related SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

Listing:
By-subject SAE listing will be provided for the All Enrolled Subjects.

7.6.4 Adverse Events Leading to Discontinuation of Study Therapy

Adverse events leading to study drug discontinuation are AEs with action taken = "Drug was discontinued".

Summary:

- Overall summary of AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT.
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

Listing:
By-subject AEs leading to discontinuation listing will be provided.

7.6.5 Multiple Events

Analyses that take into account the multiple occurrences of a given adverse event will be conducted. In order to prepare these analyses, the CRF data will be processed according to standard BMS algorithms[2] in order to collapse adverse event records into unique records based on the preferred term. This data will be presented as the rate per 100 patient-years of exposure. This analysis will take into account all on-treatment events (allowing more than 1 event per subject) and the total duration of exposure. The patient-years exposure will be computed as the sum over the subjects' exposure expressed in years where the duration of exposure is defined as

- Date of last dose of study treatment - date of first dose of study treatment + 7 (for QW dosing regimen) or + 21 (for Q3W dosing regimen) days, for subject who are off study treatment and were followed at least 60 days after last dose of study medication.
- Last known date alive- date of first dose of study medication +1, for subjects who are still on-treatment or who are off study treatment and were followed less than 60 days after last dose of study medication.

Summary:

The following summary tables will be provided:

- Total number and rate (exposure adjusted) of occurrences for all AEs occurring in at least 5% of the subjects treated in any dose + dose regimen group.

Listing:

- Unique instances of all AEs, ie, after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (ie, same PT) have been collapsed.

7.6.6 Adverse Events of Special Interest

Not applicable at the time of the development of this statistical analysis plan.

7.6.7 Clinical Laboratory Evaluations

Clinical laboratory data will be first analyzed using International System of Units (SI). Analyses will be repeated using US conventional units.

Summary:

The number (%) of subjects with the following will be summarized by treatment and overall, if appropriate, using the worst CTC grade on-treatment per subject.

- Post-baseline grade
- Grade change from baseline
- Descriptive statistics of laboratory test result and their changes from baseline by treatment and study day

Listing:

A by-subject listing of these laboratory parameters will be provided. Laboratory abnormality criteria and laboratory results outside of normal range will be listed.

7.6.7.1 Abnormal Hepatic Test

Summary:

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by dose and dose regimen:

- ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN
- Total bilirubin > 2 x ULN
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN

Figure:

- Scatter plot of Total bilirubin peak vs AST peak
- Scatter plot of Total bilirubin peak vs ALT peak

On-treatment peak total bilirubin and on-treatment peak AST/ALT needs to happen on the same day of liver testing.

Listing:

A by-subject listing of these specific abnormalities will be provided.

7.6.7.2 Other Labs of Interest

A by-subject listing of these specific labs of interest, e.g. related to neotropenia (neutrophil count) and thrombocytopenia (platelet count) will be provided with flags for abnormal value.

Additional plots may be provided to explore potential effects of changes over time in these lab parameters.

7.6.8 ECG

Summary

- ECG measures
  - The frequency distribution of subjects' maximum recorded post-dose QTcF, PR, QRS and ΔQTcF will be tabulated by treatment and summarized for the following ranges:
    - For QTcF: QTcF ≤ 450 msec, 450 msec < QTcF ≤ 480 msec, 480 msec < QTcF ≤ 500 msec, QTcF > 500 msec
    - For PR: PR ≤ 200 msec, PR > 200 msec
    - For QRS: QRS ≤ 120 msec, QRS > 120 msec
    - For ΔQTcF: ΔQTcF ≤ 30 msec, 30 msec < ΔQTcF ≤ 60 msec, ΔQTcF > 60 msec

Figure:

- ECG measures
  - Scatterplot and regression of ΔQTcF on active ADC, [redacted] and unconjugated tubulysins concentrations, respectively.

Listing:

- ECG measures
  - Individual QTcF, PR, QRS or ΔQTcF values will be listed.
- ECG abnormalities

7.6.9 Vital Signs and Other Safety Evaluation

Summary:

- Vital signs

Listing:

- Vital signs
- Diagnostic procedures
- Medical treatment procedures

7.6.10 Immunogenicity

Summary:

The number (%) of subjects with the following anti-drug responses will be reported by dose, if applicable, and overall.

- Baseline ADA Positive
- ADA Positive
  - Persistent Positive
  - Only the Last Sample Positive

  - Other Positive
- ADA Negative

Listing:

- All collected immunogenicity will be listed with flags indicating baseline positive sample, ADA positive sample or ADA negative sample, and information regarding specificity to the antibody or unconjugated tubulysin if such data are available.

7.7 Pharmacokinetics

PK parameters for the total antibody, [redacted] active ADC, [redacted] and unconjugated tubulysin will be calculated using noncompartmental analysis. All available plasma/serum concentration-time data from subjects who receive BMS-986148 will be reported. All available derived PK parameter values will be included in the PK dataset and reported, but only subjects with adequate PK profiles will be included in summary statistics and statistical analysis.

PK analysis will be provided separately for each of the above analytes. In general, summary statistics will be tabulated for the pharmacokinetics parameters by dose, dose regimen, and study day for each select analyte. To assess the attainment of steady state geometric mean Ctrough values will be plotted versus study day by dose and dose regimen.

Exploratory assessment of dose proportionality for total antibody, [redacted] and unconjugated tubulysin will be performed based on the power model described by Gough et al. [3]

$$\text{PK Parameter} = \text{A} * \text{Dose}^{\beta},$$

which be estimated by the simple linear regression of the natural log of the PK Parameter (Cmax, AUC(TAU)) on the natural log of Dose:

$$\text{E}[\log(\text{PK Parameter})|\text{Dose}] = \alpha + \beta * \log(\text{Dose}).$$

A slope (β) equal to 1 would indicate perfect dose proportionality. For each PK parameters (Cmax, AUC(TAU)), the point estimates and 90% CI of the slopes will be provided. Note that dose proportionality analysis may not be performed if there are two few different doses under some dose regimen, e.g., for the QW dosing for three weeks with one week off.

[redacted]

A population pharmacokinetic analysis may be conducted, which would be presented in a separate report.

Summary:

Summary statistics will be provided for the following all listed parameters in Section 4.2.1 by dose, dose regimen, study day and time.

Geometric means and coefficients of variation will be presented for all parameters after the first dose except Tmax and T_HALF. Median, minimum, and maximum will be presented for Tmax, T_HALF.

Figure:

- Plot of individual Ctrough and their geometric mean at each cycle for each dose + dose regimen group.
- Scatter plot of AUC(TAU) vs dose in log-log scale by regimen and superposed with the regression line from the power model. Regression line's mathematical equation is also shown in the figure.
- Scatter plot of Cmax vs dose in log-log scale by regimen and superposed with the regression line from the power model. Regression line's mathematical equation shown in the figure.

Listing:

- All individual PK parameters will be listed including any exclusions and reasons for exclusion from summaries

7.8 Biomarker Analyses

Due to the exploratory nature of this study, analyses listed below may or may not be performed depending on data availability (some exploratory measurements in the study may be subject to change as technologies and assay methods evolve). Additional types of analyses may be conducted on a post-hoc basis pending review of data. Not all exploratory analyses will be included in the Clinical Study Report (CSR) unless they represent meaningful findings or are relevant to subject management.

Summary:

- Summary statistics (e.g., mean, median, minimum value, maximum value, standard deviation) will be provided for: (1) [redacted] CA125 and CA19-9; (2) change and percent change from baseline in [redacted] CA125 and CA19-9. Those analyses will primarily grouped by dose and dose regimen. When applicable, similar analyses will be conducted by cohort.

Figure:

- Subject level longitudinal trend plot by cohort for [redacted] CA 125 and CA19-9.

[redacted]

- Individual subject percent change from baseline over time for [redacted] CA125 and C19-9 respectively.

[redacted]

8 CONVENTIONS

In general, EmBARC standard time windowing, imputation rules, and counting rules will be applied.

8.1 Decimal Places

The number of decimal places displayed in all listings will be determined by the number of decimal places in the raw data.

Unless otherwise specified, minimum and maximum will be reported to the precision as the data collected, one more decimal place for the mean and median, and two more decimal places for the standard deviation. The adjusted geometric mean, geometric mean ratio and the lower and upper limits of confidence interval will be displayed to three decimal places.

8.2 Pharmacokinetic Summaries

8.2.1 In-text Tables

For in-text pharmacokinetic tables, coefficient of variation (%CV) will be reported as integers. For other statistics except for standard deviations, values of 100 or higher will be presented as integers, values of 10 - <100 will be displayed to one decimal place, and values of 1 - < 10 will be displayed to two decimal places. Values less than 1 will be displayed to three decimal places. Ratios will also be displayed to three decimal places. Standard deviations will be reported to a precision of 1 decimal place more than the mean.

8.2.2 Handling of Non-Quantifiable Concentrations[4]

For the summaries of serum concentration-time data, concentrations that are less than the lower limit of quantification (LLOQ) should be displayed as "< LLOQ" in the listings and be treated as missing in summary tables and plots. For the purpose of calculating PK parameters, other than Ctrough, pre-dose concentrations that are less than LLOQ and concentrations prior to the first quantifiable concentration that are less than LLOQ will be set to zero, and all other concentrations less than LLOQ will be set to missing.

Summary statistics for Ctrough concentrations, analyses of PD-concentrations and ECG-concentration relationships will be calculated by imputing values less than LLOQ as ½ * LLOQ. This imputation is done for Ctrough concentrations because it is treated like a PK parameter; the imputation is not done for Day 1 pre-dose concentrations. Individual Ctrough listings will display these concentrations as "< LLOQ."

All available serum concentration-time data and derived pharmacokinetic parameter values will be included in the PK data set and listed accordingly.

8.2.3 Treatment of Outliers

Individual serum concentrations, if deemed to be anomalous, may be excluded from the analysis following a review of available documentation (e.g., bioanalytical report, clinical data). Any such exclusion will be clearly listed in the study report along with justification for exclusion.

Entire serum concentration-time profiles for a subject may be excluded following review of available documentation (e.g., bioanalytical report, clinical data). However, results of analysis with and without the excluded profiles may be presented in the study report. Any such exclusion will be clearly listed in the study report along with justification for exclusion.

8.2.4 PK Exclusions[4]

PK Analysis, Reporting, and Exclusion criteria should following the BMS PK Harmonization document Version 2.0. Specific guideline for exclusionary criteria for half-life and how other PK parameters are affected for exclusion is under section 9.2 of the BMS PK Harmonization document.

Exclusion of one or more parameters or the entire dataset may be considered due to incomplete profile such as AUC(TAU) or when T-HALF cannot be reliably calculated, or there is no sample around the suspected Cmax. In addition, subjects may be excluded from the analysis if they missed doses, had diarrhea, or vomited at or before a time equal to twice the median Tmax for immediate-release products, or vomited at any time during sampling after the administration of modified-release formulations.

9 CONTENT OF REPORTS

The complete list of analyses contributing to the clinical study report is given in the Data Presentation Plan.

10 DOCUMENT HISTORY

Version Number	Author(s)	Description
1.0	[redacted]	Initial version

11 REFERENCES

1 Brookmeyer R. and Crowley J. A confidence interval for the median survival time. Biometrics 38:29-41, 1982.

2 Global Biometric Sciences, SAS Analysis Dataset Specification, Adverse event. Version 1.0, January 10, 2011.

3 Gough, K., Hutchison, M., Keene, O., Byrom, B., Ellis, S., Lacey, L., & McKellar, J. (1995). Assessment of dose proportionality: report from the statisticians in the pharmaceutical

industry/pharmacokinetics UK joint working party. Drug Information Journal, 29(3), 1039-1048.

[4] PK Harmonization Document, Clinical Pharmacology and Pharmacometrics, Version 2.0, Bristol-Myers Squibb Research and Development, 2013.