ABBREVIATED FINAL ANALYSIS STATISTICAL ANALYSIS PLAN

Aduro Biotech, Inc.

Protocol Number: ADU-CL-02

A Phase 1B Study to Evaluate the Safety and Induction of Immune Response of CRS-207 in Combination with Pemetrexed and Cisplatin as Front-line Therapy in Adults with Malignant Pleural Mesothelioma

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SAP Author:	[redacted]
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I confirm that I have reviewed this document and agree with the content.

Designation	Print Name	Signature	Date
SAP Author	[redacted]	[redacted]	21 May 2018
Reviewing Biostatistician	[redacted], PhD	[redacted]	18 MAY 018
Aduro Biotech Reviewer	[redacted], PhD	[redacted]	17 May 2018

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Events
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BMI	Body Mass Index
BSA	Body Surface Area
BV	Boost Vaccination
CFU	Colony-forming units
CI	Confidence Interval
CSR	Clinical Study Report
CR	Complete Response
CRF	Case Report Form
Cy	Cyclophosphamide
DCR	Disease control rate
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DPFU	Disease Progression Follow-Up Period
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISPOT	Enzyme-Linked Immunosorbent Spot
EOC	End of Course
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
HLA	Human leukocyte antigen
ICH	International Council on Harmonisation
IFN-γ	Interferon gamma
irRC	Immune-Related Response Criteria
iDAP	Immune Data Analysis Plan
MedDRA	Medical Dictionary for Regulatory Activities
MPM	Malignant Pleural Mesothelioma
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MV	Maintenance Vaccinations
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
OS	Overall Survival
PBMC	Peripheral blood mononuclear cell(s)
PD	Progressive Disease
PFS	Progression-free Survival
PFTs	Pulmonary Function Tests
PR	Partial Response
PT	Preferred Term

Abbreviation	Definition
PV	Prime Vaccination
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease, Standard Deviation
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Events
TTP	Time to Progression
ULN	Upper limit of normal
VC	Vital Capacity
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

ADU-CL-02 is a phase 1b, multicenter, open-label study in adults with malignant pleural mesothelioma (MPM) who are not eligible for curative surgery. The study consists of two cohorts which received CRS-207 in combination with pemetrexed and cisplatin chemotherapy (Cohort 1) or low-dose cyclophosphamide (Cy) prior to each CRS-207 infusion (Cohort 2). The study is intended to determine the safety of CRS-207 (with or without Cy) when administered in combination with pemetrexed and cisplatin and to evaluate the induction of immune response to mesothelin.

1.2. Objectives of the Abbreviated Statistical Analysis Plan (ASAP)

This is an abbreviated statistical analysis plan (ASAP) designed to outline the methods to be used in the analysis of study data for the abbreviated final analysis. The derivation and analysis of selected immunological / tumor marker endpoints will be discussed in another standalone document.

The statistical analyses and summary tabulations described in this ASAP will provide the basis for the abbreviated reporting of the final analysis results from this trial. Populations for analysis, data handling rules, statistical methods, changes from the study protocol, and formats for data presentation are provided.

2. STUDY OBJECTIVES

2.1. Primary Objectives

To determine the safety of CRS-207 (with or without low-dose cyclophosphamide [Cy] given one day prior to CRS-207) when administered in combination with pemetrexed and cisplatin and to evaluate the induction of immune response to mesothelin as measured by IFN-γ ELISPOT assay prior to treatment and at time points during and after treatment.

2.2. Secondary Objectives

The secondary objectives are to evaluate:

- Tumor response
- Progression free survival
- Time to progression
- Overall survival
- Predictive value of serum mesothelin for therapeutic response for each treatment regimen

2.3. Exploratory Objectives

The exploratory objectives are to:

- conduct immune subset analysis (e.g., CD4, CD8, T_{reg}) and gene expression profiling of tumor tissue pre- and post-vaccination;
- to assess induction of anti-mesothelin humoral immune response;
- to measure tumor marker kinetics as biomarkers of tumor response;
- evaluate the association between pulmonary function improvement and tumor response;
- evaluate the relationship of tumor response to overall survival.

This ASAP will not include the analysis of: immune response to mesothelin, predictive value of serum mesothelin; or any secondary and exploratory objectives. The analysis of mesothelin related objectives will be discussed in another standalone document.

3. STUDY DESIGN

3.1. Synopsis of Study Design

Up to 16 subjects were originally planned to be enrolled in this study. Up to an additional 44 subjects were then subsequently planned to be enrolled in this study (for a total of up to 60 subjects) to obtain additional safety, immune, and efficacy data. Subjects were enrolled into two mutually exclusive cohorts described below.

Cohort 1: A total of 38 subjects received 2 prime vaccinations (PV) of CRS-207 (1×10^9 colony-forming units (CFU) given intravenously (IV) over approximately 1 hour) 2 weeks apart, followed 2 weeks later by up to 6 cycles of pemetrexed and cisplatin 3 weeks apart. Three weeks after completion of chemotherapy, subjects received an additional 2 infusions (boost vaccinations; BV) of CRS-207 3 weeks apart. Subjects enrolled in Cohort 1 included the 16 subjects originally planned plus a minimum of the first 16 subjects additionally enrolled.

Cohort 2: The remaining subjects enrolled (22 total) received CRS-207 in combination with chemotherapy at the dose and schedule described above; however, these subjects also received low-dose Cy (200 mg/m^2) over 30 minutes 1 day prior to each CRS-207 infusion (i.e., prior to each PV and BV infusion).

All subjects were to return to the clinic 4 weeks after their 2nd boost vaccination for an End of Course (EOC) visit. Subjects then had follow-up visits 4 weeks after the EOC visit and every 8 weeks thereafter until treatment discontinuation. Subjects continued to receive maintenance vaccinations (MV) with (Cohort 1) or without Cy (Cohort 2) at each follow-up visit (following their original schedule) if they were clinically stable and continued to meet dosing eligibility. Subjects could continue on treatment with radiographic disease progression if clinically stable and the investigator believed the treatment may be providing benefit.

Subjects were to return to the clinic for follow-up approximately 4 weeks after their EOC visit and every 8 weeks thereafter until disease progression or the investigator determined the subject was no longer receiving benefit from treatment (if a subject continues treatment beyond progression). All subjects were to complete an End of Study (EOS) visit no more than 4 weeks following the final dose of study medication or prior to receipt of other cancer-related treatment.

Following participation in this study, subjects could consent to long-term follow-up in the ADU-CL-03 study, which would follow them every 3 months until death. Death was captured from public record for subjects who did not enroll in ADU-CL-03.

To monitor initial safety of the sequential vaccine regimen, no more than one subject was enrolled per week for the first six subjects. If at any point during the study more than 33% of subjects, cumulative, experienced a dose limiting toxicity (DLT), the dose would have been lowered from 1×10^9 CFU to 3×10^8 CFU for all subsequent dosing with CRS-207. Subjects already receiving treatment would have continued to receive CRS-207 dosing at the lower dose and all subsequent subjects would have received CRS-207 at the lower dose.

Subjects who withdrew consent or were removed from study medication before completing at least two cycles of chemotherapy were considered dropouts and replaced at the discretion of the lead investigator, sponsor, and medical monitor.

3.2. Randomization and Blinding

This is a non-randomized, open-label study. Subjects were assigned to each cohort sequentially.

3.3. Study Procedures

The schedule of assessments is outlined in Section 5.1 of the study protocol.

3.4. Study Endpoints

3.4.1. Primary Endpoints

The primary efficacy endpoint is the change in number of mesothelin-specific T cells producing interferon gamma (IFN-γ) by ELISPOT (enzyme-linked immunosorbent spot) assay from baseline to:

- immediately after CRS-207 (with or without Cy);
- after receiving chemotherapy;
- and after receiving two subsequent doses of CRS-207 (with or without Cy) following chemotherapy.

Safety will be assessed by evaluation of the following:

- Adverse events (AEs)
- Deaths
- Vital signs
- Physical examination findings
- Clinical chemistry and hematology laboratory findings

3.4.2. Secondary Endpoints

The following secondary endpoints will be used to assess efficacy:

- Objective tumor response
- Progression free survival (PFS)
- Time to progression (TTP)
- Overall survival (OS)
- Measure of serum mesothelin to assess predictive value for therapeutic response

Tumor response and progression will be assessed using modified Response Evaluation Criteria in Solid Tumors (mRECIST)[3] for assessment of response in MPM and irRC[4].

This ASAP will not include the analysis of primary or secondary efficacy endpoints. Tumor and overall response data, based on mRECIST only, will be listed (irRC based

outcomes will not be provided); the handling of the primary endpoint will be as described in Section 2 and Section 3.4.3.

3.4.3. Exploratory Endpoints

The exploratory endpoints described in this analysis plan are:

- Pulmonary function tests (PFTs) measured by forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and vital capacity (VC) [for Cohort 2 only]

Additional endpoints, corresponding to exploratory objectives, will be evaluated based on a separate, standalone document.

This ASAP will not include the analysis of the exploratory endpoints. PFTs will be listed as described in Section 5.11.2. The analysis of the other exploratory objectives will be discussed in another standalone document.

4. SUBJECT POPULATIONS

4.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Full Analysis Set (FAS): All enrolled subjects who received at least one dose of study treatment. The FAS will be used for all analyses of efficacy and safety.

The final SAP version 1.0 used FAS as the analysis dataset. This definition is the same as the definition of the Safety Analysis Set. The FAS now is replaced by the Safety Analysis Set.

4.2. Protocol Deviations / Violations

Protocol deviations will be identified and classified as major (violations) before the database is locked. Major protocol deviations may include but are not limited to:

- Received the wrong study medication
- Dose not properly administered, including
    - Administrations in which Cy was not administered within 24 hours of CRS-207
    - Administrations in which protocol required pre-medications were not given
- Did not complete at least 2 chemotherapy cycles
- Received prohibited concomitant medications
- Violation of inclusion or exclusion criteria, including
    - Misdiagnosis

5. STATISTICAL METHODS

5.1. Sample Size Justification

Up to 60 subjects in total could be enrolled, based on the original planned cohort of 16 subjects and the study was then expanded to enroll up to an additional 44 subjects. A total of 32 subjects were planned for Cohort 1 (CRS-207 in combination with chemotherapy) (Cohort 1), and up to 28 subjects were planned for Cohort 2 (Cy 1 day prior to each CRS-207 administration combined with chemotherapy). Ultimately, a total of 38 subjects were in Cohort 1, and 22 subjects were in Cohort 2 (for a total of 60 subjects).

The originally planned sample size calculation was based on the primary endpoint of mesothelin-specific T cell responses as measured by ELISPOT (enzyme-linked immunosorbent spot) assay. With one primary parameter (ELISPOT) to be measured with respect to a change from baseline at three post-baseline time points, the sample size was selected to allow each test to be performed using a 0.017 two-tailed significance level, in order to allow the overall set of three tests to be very conservatively performed as if at an overall 0.05 level using a Bonferroni adjustment. Assuming 14 subjects with complete measurements of the main parameter at baseline and the three subsequent time points, there would be 80% power to detect a change from baseline to each time point equal to 1.0 standard deviations of the change (1.0 effect size) using a two-tailed 0.017 level paired t-test. This stringent multiplicity adjustment is for power computation only. In practice, for analysis purposes, instead of requiring that each test achieve a 0.017 level in order to be declared significant, a less overly stringent Hochberg adjustment will be used. In order to allow for a small number of non-evaluable subjects, up to 16 subjects could be enrolled.

The planned expanded cohort of up to 44 additional subjects (Cohort 2) was intended to obtain additional safety, immune, and efficacy data for future study planning. The

sample size was based on practical rather than statistical considerations.

5.2. Statistical Methods

5.2.1. General Methods

- All statistical analysis and data summarization will be generated using SAS version 9.3 or later.
- Unless otherwise stated, summary tables will be presented by treatment regimen (cohort) and overall.
- No formal comparisons across treatment regimen (Cohort 1 vs. Cohort 2) will be performed.
- Confidence intervals (CIs) will be presented at the 95% significance level
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, first quartile, third quartile, and maximum.

- Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects (percentages will not be shown when cell count is zero).
- AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0.
- Concomitant medications will be coded using World Health Organization (WHO) Drug Version 1Q 2012.

5.2.2. Definitions

- Age: (Informed Consent Date – Date of Birth)/365.25, rounded down to the nearest integer
- First Dose Date: Date of first exposure to any study medication (CRS-207, Cy, or chemotherapy)
- Last Dose Date: The last date which the subject was exposed to any study medication as recorded on the case report form (CRF)
- Study Day: Elapsed time from First Dose Date measured in days and defined as:
    - Study Day = Event Date – First Dose Date + 1, for events occurring on or after the First Dose Date
    - Study Day = Event Date – First Dose Date, for events occurring before the First Dose Date
- Baseline: Last observation prior to first dose of study medication
- Treatment Course 1: Treatment Course 1 is defined as the sequence of two CRS-207 prime vaccinations (with or without low-dose Cy); chemotherapy treatments (up to six cycles); two post-chemotherapy boost vaccinations; EOC follow-up
- End of Course: End of the treatment course for subjects that do not receive MV; for subjects that receive MV, the visit following the last administration of MV
- End of Study: May occur when a subject discontinues the study. The EOS visit is to take place 28 days (4 weeks) after last dose of study medication.
- Study Periods:
    - Treatment Period: The Treatment Period includes the time from first dose through the EOS safety visit occurring 28 days after the final study medication dose.
- Duration of Treatment Exposure: Latest of (Date of EOS visit, Last Dose Date + 28) – First Dose Date + 1. It is assumed that EOS visit occurs approximately 28 days after the final dose of study medication; the EOS visit represents the latest date for which a new AE can be observed/recorded for a subject.

- Percentage Change from Baseline in Tumor Thickness per mRECIST: (total tumor thickness at post-baseline visit – baseline total tumor thickness) / (baseline total tumor thickness)

5.2.3. Adjustments for Covariates

Not applicable.

5.2.4. Multiplicity

Not applicable.

5.2.5. Subgroup Analyses

Subgroup analyses are not planned to be performed for the final analysis.

5.2.6. Interim Analyses

No formal interim analyses are planned. Safety data are reviewed on an ongoing basis.

5.2.7. Missing, Unused and Incomplete Data

All AEs with partial/missing onset dates will be considered treatment-emergent adverse events (TEAEs) unless a partial date clearly indicates that it occurred prior to first dose of study treatment or more than 28 days after the last dose of study treatment.

Start dates with a missing day but which have month and year populated will be imputed such that:

- If the provided month and year match the month and year for that subject's first dose date, then the first dose date will be used.
- In all other cases, the 1st of the month will be used with the provided month and year.

Start dates with a missing day and month but which have year populated will be imputed such that:

- If the provided year matches the year for that subject's first dose date, then the first dose date will be used.
- In all other cases the 1st of January will be used with the provided year.

If the start date is completely missing then the date will be assumed as the subject's first dose date and the event will be considered as treatment emergent, unless the stop date indicates that the event ended prior to first dose date. No imputation will be performed for subjects who did not receive study treatment. In those cases, the start date will be counted as missing.

Stop dates will be imputed as follows:

- Missing day with a provided year and month will use the last day of the month.
- Missing day and month with provided year will use December 31.

- Completely missing stop dates will be treated as missing and no imputation will be done.

If the imputed stop date is greater than the last known date for the subject (e.g., date of last contact, date of death) then the imputed date will be replaced with the last known date.

Similar rules will be used for prior/concomitant medications with incomplete or missing start or stop dates.

In order to calculate time from diagnosis, partial dates will be imputed. Missing months will be assumed as July. Missing days will be assumed as the 1st of the month. If the entire diagnosis date is missing, then no imputation will be performed.

No additional imputation for other missing data is planned. Missing values will be listed as represented in the clinical database (e.g. 'NR' (not reported), blanks).

5.3. Timing of Analyses

On 12 December 2017, Aduro decided to cease development activities of CRS-207 and close out ongoing studies. As of 19 January 2018 every subject had completed their end of treatment visit except for 3 subjects who will have the option to continue study-drug treatment based on agreement between the Investigator and patient. All data through 19 January 2018 will be cleaned and soft-locked for CSR synopsis reporting. Additional data collection will be ongoing for these 3 subjects through to the date of database soft-lock. Additional data following database lock will be captured in an amendment to the final CSR synopsis once the 3 subjects have completed their end of study follow-up. This ASAP details the analysis plans for the CSR synopsis.

5.4. Subject Disposition

Subject disposition will be presented by overall and cohort (Cohort 1 and Cohort 2). The number of subjects in Safety Analysis set; number who completed Treatment Course 1; number who received MV; number who discontinued Course 1 and the Treatment Period; and reasons for Course 1 and Treatment Period discontinuation will be summarized using frequency counts and percentages. Time on study (first dose to EOS visit) and duration on treatment will be summarized.

5.5. Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized by cohort and overall based on the Safety Analysis set.

Age, sex, ethnicity, race, and baseline weight, height, body mass index (BMI), and body surface area (BSA) will be summarized using descriptive statistics. Summaries will be produced for the FAS. The following formulas will be used for derivation and/or data conversion:

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

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

$BSA(m^2) = \sqrt{[(height(cm)*weight(kg))/3600]}$

Disease characteristics at baseline will be summarized. Time from diagnosis of primary tumor will be summarized using descriptive statistics methods. Time from the date of diagnosis of primary tumor to consent date (inclusive) will be displayed in months Primary site of cancer, histology, TNM classification at diagnosis and study entry, stage at diagnosis and study entry, extent of disease, baseline tumor measurements (sum of longest diameter in target lesions per RECIST 1.1, total tumor thickness measurements, and total sum of assessments per modified RECIST for MPM), number and percentage of subjects with prior radiation and prior surgery, screening PFTs, and baseline ECOG will be summarized. Additional diagnosis data will be listed.

5.6. Prior Anti-Cancer Therapies

Prior cancer-related treatment (surgery and radiotherapy) will be listed.

5.7. Medical History

Medical history data will not be summarized but will be included in the data listings.

5.8. Concomitant Medications

Medications are collected throughout the study. Medications will be categorized as a prior or concomitant. If a medication was taken and stopped prior to the first dose date, it will be categorized as a prior medication. Otherwise, a medication identified to have been taken post-dose will be considered concomitant medication. Medications with missing or partial dates will be considered concomitant unless the partial date indicates that the medication ended prior to the first dose date or started after the last dose date.

All medications and coded terms will be provided in a by-subject data listing.

5.9. Other Assessments

Coagulation data, urinalysis data, creatinine clearance, virology data, and human leukocyte antigen (HLA) typing will be provided in by-subject data listings only.

5.10. Treatment Exposure

Exposure to study treatment will be summarized overall and by cohort. Treatment duration summaries will be provided separately for CRS-207, Cy, and chemotherapy.

The following study medication administrations will be summarized using descriptive statistics as well as categorical based on the number of administrations received (categories will be 1-2 infusions, 3-4 infusions, 5-6 infusions, and > 6 infusions in the applicable summaries):

- Number of total CRS-207 doses received
- Number of Cy administrations (for Cohort 2 only)
- Number of pemetrexed doses administered (complete or partial)
- Number of cisplatin, carboplatin, and total cisplatin/carboplatin doses administered (complete or partial)
    - The number of subjects who switched between cisplatin/carboplatin

Chemotherapy will also be presented categorically by 1- 2 cycles, 3 - 4 cycles, 5 - 6 cycles. The average volume of CRS-207 administered per subject will be summarized using descriptive statistics. The average will be calculated for each subject across all infusions then summarized overall and by cohort.

Dose interruptions, incomplete administrations, and missed administrations will be included in the by-subject data listings.

5.11. Efficacy Evaluation

5.11.1. Tumor Evaluations and Overall Tumor Response

Tumor evaluations and overall tumor response data, based on mRECIST, will be listed by date of assessment.

5.11.2. Exploratory Endpoints

Pulmonary Function Tests FVC, FEV1, and VC will be listed by cohort and subject. All parameters collected will be based on the percent predicted values.

5.12. Safety Analyses

Safety analyses will be conducted using the Safety Analysis set and will be reported by cohort and overall.

The safety parameters collected and monitored during this study include AEs and deaths, hematology, serum chemistry, concomitant medications, physical examinations, vital signs and weight, ECOG performance, and 12-lead electrocardiograms (ECGs).

5.12.1. Adverse Events

Adverse events are assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) 4.03. An AE is any reaction, side effect, or other untoward event, regardless of relationship to study drug, that occurs any time during the study. Adverse events occurring at any time from the beginning of any study dosing until 28 days after the final dose of any study treatment are considered TEAEs.

If the start date is the same as the date of the first dose of study drug and there is no indication that the AE began before dosing, the event will be considered treatment emergent. Partial start and stop dates will be imputed as described in the section for missing data. If start and stop dates are missing and/or partial date(s) are insufficient to determine treatment emergence, then the AE will be considered treatment-emergent.

Verbatim adverse events will be mapped to preferred term (PT) and system organ class (SOC) using MedDRA version 15.0. In incidence summary displays, AEs will be counted only once per subject within MedDRA category (e.g., overall, SOC, and PT), by the worst CTCAE grade, and/or the strongest relationship to study drug (not related, unlikely related, possibly related, probably related, definitely related). Any relationship summaries will be produced for CRS-207 and cyclophosphamide in combination (for any relationship to either study drug).

The frequency and percentage of subjects with TEAEs will be tabulated by MedDRA SOC and PT. Tabulations will be prepared by SOC and PT within SOC and will include:

- All TEAEs
- Related TEAEs
- Serious TEAEs
- Related Serious TEAEs
- CTCAE Grade 3 or higher TEAEs
- CTCAE Grade 3 or higher related TEAEs
- TEAEs with frequency in any cohort >=5%

To account for potential differences in the extent of exposure between the treatment categories, a subject-year adjusted rate will also be presented. The rate is calculated as the number of subjects with an event divided by the total subject-years of exposure, where subject-years of exposure for each subject is defined as Duration of Treatment Exposure in days divided by 365.25. Duration of Treatment Exposure for all subjects is defined per total treatment duration in Section 5.2.2.

A comprehensive listing of all AEs (including those which are not treatment-emergent) will be provided in a by-subject data listing. In addition, the following listings will be provided:

- SAEs
- TEAEs leading to death
- TEAEs leading to treatment discontinuation

Adverse events specifically recorded as CRS-207 infusion-related reactions will be tabulated by frequency (count and percent) using MedDRA SOC and PT.

5.12.2. Deaths

The number and percent of subjects who died along with primary cause of death will be summarized overall (including the post-study survival surveillance period) and within 28 days of last dose of study drug. All death data will be listed.

5.12.3. CRS-207 Infusion-related Reactions

CRS-207 infusion-related reactions (fever, chills, rigors, nausea, vomiting, hypotension) that occurred within 2 days of the infusion will be summarized based on data recorded on applicable CRF pages. These AEs will be graded and coded in the same manner as general AEs.

The tabulation will include a count of the number of subjects with infusions, incidences of maximum grades for infusion-related reactions, as well as numerical summaries of the number of infusions and infusion-related reactions for subjects. An incidence table for infusion-related reactions similar to those specified for general AEs, by PT in decreasing order of overall frequency, will be presented. Denominators for percentages include subjects with 1 or more CRS-207 infusions.

A comprehensive by-subject data listing of all CRS-207 infusion-related reactions will be provided.

5.12.4. Dose Limiting Toxicities

If data allows, CRS-207 DLTs will be presented in a data listing. As defined in Section 3.6 of the study protocol, DLTs are events determined by the investigator as related to CRS-207 that meet one of the following criteria:

- A fever of >40°C that lasts for greater than 24 hours and does not respond to antipyretics
- Clinically significant hypotension unresponsive to intravenous fluids (e.g., systolic blood pressure <90 mmHg or mean arterial pressure <55 mmHg as measured on two separate occasions at least 10 minutes apart)
- Grade 3 or greater decreases in leukocytes, absolute neutrophil count (ANC), or platelets that persist for more than 4 days
- Hemoglobin ≤7.0 g/dL
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase elevations >5 times the upper limit of normal (ULN) (Grade 3) that persist for more than 7 days
- Initiation of antibiotic therapy, coincident with simultaneous isolation of CRS-207 from a normally sterile body site, other than blood (e.g., cerebrospinal fluid, joint fluid)
- Unexpected Grade 3 laboratory abnormalities lasting >48 hours
- Grade 3 or greater hypophosphatemia or lymphopenia that persist for more than 7 days
- Any other Grade 3 or greater event according to National Cancer Institute's CTCAE Version 4.03

5.12.5. Laboratory Data

Hematology and serum chemistry parameters will be converted according to the International System of Units (SI) and will be listed by cohort and subject.

Shift tables displaying the shift from baseline to the worst value by NCI CTCAE grade will be presented for the Treatment Period. The worst value is defined as the maximum NCI CTCAE grade based upon the worst observation post-baseline while on study. "Worst" can be defined as "high/hyper" or "low/hypo" (or bilaterally) and will be specified within the parameter being summarized. Separate shift tables will be prepared for shifts to the worst low toxicity and to the worst high toxicity for lab parameters with bi-directional toxicity grading.

5.12.6. Vital Signs and Physical Examinations

Physical examination data will be provided in a by-subject data listing.

Vital signs data will be provided in a by-subject data listing.

5.12.7. Electrocardiogram

Resting 12-lead ECG data will summarized by a shift table of baseline to worst result during the Treatment Period with the categories of ‘normal,’ ‘abnormal, not clinically significant,’ and ‘abnormal, clinically significant.’

5.12.8. ECOG Performance Status

ECOG data will be provided in a by-subject data listing.

6. CHANGES TO PLANNED ANALYSES

Changes to the protocol-specified statistical analyses are as follows:

- Primary and secondary efficacy endpoints will not be evaluated; tumor and overall response data, based on mRECIST alone, will be listed. Analysis of immune response to mesothelin, the predictive value of serum mesothelin, and all exploratory endpoints corresponding to exploratory objectives identified in Section 2.3, with exception of that corresponding to pulmonary function, will be discussed in a standalone document.
- The per protocol population will no longer be evaluated.
- Data are no longer planned to be summarized or evaluated by study phase.
- In regard to safety analysis only relevant safety data will be summarized and all will be listed.

7. REFERENCES

1. ICH-E9 Statistical Principals for Clinical Trials, September 1998

2. ICH-E3 Structure and Content of Clinical Study Report, July 1996

3. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO 2004;15:257-60

4. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clinical cancer research : an official journal of the American Association for Cancer Research 2009;15:7412-20

8. LIST OF TABLES, FIGURES AND LISTINGS FOR FINAL ANALYSIS

All tables, listings and figures will be numbered according to the ICH-E3 Guideline[2].

The complete table of contents of data tables, figures and listings can be found in the mock tables, figures, and listings document.