# STATISTICAL ANALYSIS PLAN

**A Phase 2 Open Label Extension Study of Conatumumab**

**Protocol Number 20101116**

**Version: 1. 1**

**Date: 10 December 2010**

**Author:** [redacted]

NCT Number: NCT01327612
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

## TABLE OF CONTENTS

## List of Tables



## List of Appendices

## TABLE OF ABBREVIATIONS

| Abbreviation/ Acronym | Definition/Explanation |
|---|---|
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| BUN | blood urea nitrogen |
| CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| DMP | data management plan |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| INR | international normalization ratio |
| IP | investigational product (AMG 655 and/or AMG 479) |
| IPD | important protocol deviation |
| PD | progressive disease |
| PFS | progression-free survival |
| PLT | platelets |
| PTT | prothrombin time |
| SOC | standard of care |
| TLGs | tables, figures, and listings |
| WBC | white blood cell |

## 1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for Conatumumab Study 20101116 dated 07 September 2010. The scope of this plan includes the final analysis that is planned and will be executed by the Biostatistics department or designee.

## 2. OBJECTIVES

### 2.1 Primary

To provide ongoing treatment with conatumumab therapy, with or without chemotherapy (including bevacizumab) or with or without AMG 479, for subjects who are eligible, according to the parent study, to receive their next dose of conatumumab.

### 2.2 Secondary

To evaluate the safety profile of conatumumab, with or without chemotherapy (including bevacizumab) or AMG 479, including adverse events and serious adverse events.

## 3. STUDY OVERVIEW

### 3.1 Study Design

This is a Phase 2 multi-center, open-label study that permits subjects who have completed a separate Amgen conatumumab study to continue treatment with conatumumab, with or without chemotherapy or with or without AMG 479. Subjects who have not progressed on a separate Amgen protocol are eligible to participate in this trial.

This study will only be conducted in centers that treated subjects in previous conatumumab studies managed by Amgen Inc..

Subjects must have received conatumumab, with or without chemotherapy (including bevacizumab) or AMG 479, on the parent study.

In this extension study, conatumumab study drug will be administered at the same dose level and schedule that the subject received at the conclusion of the parent conatumumab study, accommodating any subjects who were maintained on a reduced dose level or different schedule of administration in their parent study. At the discretion of the investigator, subjects who were receiving conatumumab monotherapy on the

parent study may switch at the time of starting this study (and only at this time) to receive monotherapy at an extended dosing frequency, to a maximum of every 3 weeks, if the total weekly dose remains the same as for the parent study.
Subjects will be evaluated before every cycle of conatumumab therapy at the study clinic. These study visits will include a standard of care clinical assessment which includes collection of vital signs, adverse events, concomitant medications, and laboratory samples and results. Radiological assessments to evaluate disease extent (with change compared to nadir from the parent protocol) should be performed at regular intervals, at a minimum once every 12 weeks, per standard of care (SOC) at each facility.

Reasons for study discontinuation will include progressive disease, intolerance to investigational product(s), and/or need for additional systemic anticancer treatment. When a subject discontinues the study for any reason, a safety follow-up visit will be completed at least 30 (+3) days after the last dose of protocol-specified therapy. This visit will include a standard of care clinical assessment, vital sign measurements, laboratory tests for blood and urine, adverse event assessment, and concomitant medications assessment. Subjects will also be assessed for anti-conatumumab antibody (and anti-AMG 479 antibody, if the subject has received AMG 479) assessment 60 (±14) days after the last administration of protocol-specified therapy.
The overall study design is described by a study schema at the end of the protocol synopsis section.

### 3.2 Sample Size

The sample size for this study cannot be determined prospectively, as it is contingent on the number of subjects still receiving conatumumab on the parent studies. The sample size is estimated to be approximately 16 subjects.

## 4. STUDY ENDPOINTS

The endpoints for this study include:

- Adverse events
- Serious adverse events
- Vital signs
- Clinical laboratory tests

- Tumor response
- Disease progressions and deaths

## 5. HYPOTHESES AND/OR ESTIMATION

The main purpose of this study is to provide a mechanism for subjects to continue to receive treatment with conatumumab and/or AMG 479.

## 6. DEFINITIONS

- Baseline (of parent protocol)

Baseline is defined as the last non-missing assessment prior to the first administration of protocol specified treatment in the parent study. Where baseline measurements are taken on the same day as the protocol specified treatment and no times are reported it will be assumed that these measurements are taken prior to the protocol specified treatment being administered.

- Cycle

A treatment cycle will be calculated as the time from the first administration of protocol specified treatment (in the extension study) for the given cycle to the day before the first administration of the subsequent cycle. Cycles are planned to include either a 14 day or 21 (±3) day period (as defined in the parent protocol) following the start of the treatment with investigational product (IP) in combination with chemotherapy plus additional time, as needed, for the resolution of protocol-specified therapy-related toxicities. If the investigator decides to change the cycle duration from 2 to 3 weeks at enrollment, then this must be recorded in the electronic case report form (eCRF). The new cycle duration should remain the same throughout the duration of the protocol (allowing time to recover from toxicity as required). For the last cycle, this includes the time from the first administration of protocol specified treatment in the extension study in the last cycle up to and inclusive of the date of the safety follow-up visit (or last contact date of no safety follow-up visit exists).

- Cycle Start Date

The cycle start date will be identified as follows: the earliest start date when a treatment component was administered in the extension study (ie, actual dose > 0) for the respective cycle.

- Day 60 Follow-up Visit

Immunogenicity follow-up visit 60 days (± 14 days) after the last dose of protocol-specified therapy in the extension study.

- Disease Progression (DP)

Assessments of progressive disease will be determined by the investigator as per standard of care (SOC) at each facility (includes both radiographic and clinical progressions).

- Last Contact Date

The latest date a subject is known to be alive will be based on the latest of the date variables included in all the raw datasets (with the exception of the comments datasets). For dates captured on the end of study, safety and day 60 follow-up pages, the date will only be used if the reason is not “lost to follow-up”.

- End of Study

The end of study for a subject is defined as the date the subject withdraws consent from this study, completes or has the opportunity to complete the Day 60 Follow-up visit or dies, whichever occurs first.

- Enrollment (into extension study)

Subject enrollment into the extension study occurs when the subject has signed the informed consent, eligibility criteria has been confirmed and the site has received confirmation of enrollment from the sponsor.

- Investigational Product/Protocol Specified Treatment

As per parent protocols, investigational product will include conatumumab and/or AMG 479. The term ‘Protocol Specified Treatment’ is used to reference the following treatments:

  - Conatumumab, AMG 479, bevacizumab, leucovorin, oxaliplatin, 5-FU bolus and 5-FU continuous IV infusion.

- On-Study Death

Any death that occurs after receiving protocol specified therapy through to 30 days after the last dose of protocol specified therapy or safety-follow up visit, whichever is later. The primary cause of any on-study death will be reported as a serious adverse event.

- Parent Study

Refers to protocols under which a subset of subjects received their initial treatment with conatumumab. Subjects who received conatumumab with or without chemotherapy or AMG479 and have not progressed on the Parent Study are eligible to participate in this trial.

- Randomization/enrollment date (in parent study)

The randomization date is defined as the date when the call is made to the IVRS vendor and a randomization number is assigned in the parent study. For parent studies that are open-label where there is no randomization, the enrollment date in parent study will be used instead. Prior to this call the subject must have signed an informed consent and all eligibility criteria should have been verified.

- Reporting of Adverse Events and Deaths

Adverse events will be collected at least throughout the period beginning with the signing of the informed consent for this study, until the safety follow-up visit or 30 days after the last administration of protocol specified treatment, whichever is the later. Treatment emergent adverse events from the parent study will be concatenated with adverse event data from this study and will be reported across both protocols.

Safety Follow-up Visit (30 Day Safety Follow-up Visit)

The study visit at 30 days (+3 days) after the last dose of protocol-specified therapy.

- Screening Failures

A screen failure is defined as a subject who signs the informed consent for this study but does not enroll into the study because the subject did not meet the eligibility criteria as defined in Section 4.0 of the protocol.

- Study Day for Extension Study

This is the number of days from the date of the first administration of study specified treatment in the extension study, inclusive.

Study Day = (Date of Interest - Date of first dose in extension study) + 1

Study Day 1 is therefore the day that the first dose of study specified treatment is administered in the extension study. For dates that occur prior to study day 1, this will be calculated as:

Study Day = (Date of Interest – Date of first dose in extension study)

Therefore, the day prior to study day 1 is -1.

- Study Day for Parent Study

This is the number of days from the date of the first administration of study specified treatment in the parent study, inclusive.

Study Day = (Date of Interest - Date of first dose in parent study) + 1

Study Day 1 is therefore the day that the first dose of study specified treatment is administered in the parent study. For dates that occur prior to study day 1, this will be calculated as:

Study Day = (Date of Interest – Date of first dose in parent study)

- Time to Death

This is the time interval between the randomization/enrollment date in parent study and the date of death.

- Time to Disease Progression

This is the time interval between the randomization/enrollment date in parent study and the date of disease progression or death, whichever occurs first.

- Time from Randomization/Enrollment in Parent Study to End of Study

This is the time interval between the randomization/enrollment date in parent study and the end of study date for this extension study.

- Time to End of Study

The time to the end of study is defined as the time interval between the date the subject signs the informed consent for this study and the end of study date.

- Time to the End of Treatment for Each Component of Protocol Specified Treatment

The time to the end of treatment for each component of protocol specified treatment is defined as the time interval between the date of first dose with a component of treatment in the extension study and the date the decision was made to end the treatment component in the extension study.

- Treatment Emergent Adverse Event

A treatment emergent adverse event is defined as an adverse event that occurs or worsens on or after the date of the first administration of protocol specified treatment in the parent study through 30 days after the last administration of protocol specified treatment in the extension

study or the date of the safety follow-up visit (if this occurs more than 30 days after the last administration of protocol specified treatment).

- Treatment Phase (across parent and extension protocols)

The treatment phase begins on study day 1 for parent study and continues until the earlier of the date the decision to withdraw the subject from all study specified treatment, death, or completion of the safety-follow up visit in the extension study.

- Treatment Phase for Extension Study

The treatment phase begins on study day 1 for extension study and continues until the earlier of the date the decision to withdraw the subject from all study specified treatment, death, or completion of the safety-follow up visit (in the extension study).

- Tumor Response

Radiological assessments to evaluate disease extent (relative to the nadir from the parent protocol) will be performed at regular intervals, at a minimum once every 12 weeks, per SOC at each facility. The investigator reported response (complete response, partial response, stable disease, progressive disease, not evaluable, unknown or not done) collected on the eCRF will be used as tumor response data (no confirmation of response is required).

## 7. ANALYSIS SUBSETS

### 7.1 All Enrolled Analysis Set

The All Enrolled Analysis Set will include all subjects enrolled into this extension study.

### 7.2 Safety Analysis Set

The Safety Analysis Set will include all subjects that received at least one dose of conatumumab or AMG479.

### 7.3 Covariates

Due to the small sample size, the impact of baseline characteristics on study outcomes will not be explored, and no subgroup analyses will be performed.

## 8. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

No interim analysis is planned for this study.

# 9. DATA SCREENING AND ACCEPTANCE

## 9.1 General Principles

The objective of the data screening is to assess the quantity, quality and statistical characteristics of the data relative to the requirements of the planned analyses.

## 9.2 Data Handling and Electronic Transfer of Data

Amgen's Clinical Data Management department will provide all data to be used in the planned analyses. Clinical data from this study will be stored in a single electronic data capture (EDC) system, RAVE 5.6.1 or higher. The database will be subjected to edit checks outlined in the Clinical Data Management Plan (DMP).

At a minimum, the following items will be identified for further investigation and resolution by CDM:

- Missing disease response data
- Missing dates of disease progression and death
- Outlier lab data
- Missing key baseline data
- Dose administration
- Adverse Events

Any data inconsistencies or suspicious values will be reviewed and aimed to be resolved before the database is locked.

### 9.2.1 Laboratory Ranges

For the evaluation of abnormal laboratory values and toxicity grading of laboratory parameters, the normal ranges included within the database will be used. Textbook normal ranges will be used to calculate CTC-NCI grades for laboratory parameters, with the exception of amylase, lipase and creatine kinase which will be entered using local ranges. Additional details regarding these ranges are included within the DMP.

### 9.2.2 Data Extraction from the EDC System

The Biostatistics Infrastructure group will set up an automated job in the CDM2SAS interface to extract and download data from the EDC system. The infrastructure group will then provide the programming team with Study Data Tabulation Model (SDTM) datasets via the Amgen Submission Data File (SDF) system. SDTM generation will be performed when requested by the programming team.

### 9.3 Handling of Missing and Incomplete Data

Missing and incomplete data will be identified through programmatic checks and a review of the tables and listings created within Biostatistics. Missing and incomplete data will be identified for investigation, and possible resolution, by CDM and Clinical Research Management prior to database lock (or prior to a data snapshot).

In general, data will be analyzed as retrieved from the study database and no imputation for missing data will be performed.

#### 9.3.1 Missing data for Safety

With the exception of adverse event, concomitant medication and disease diagnosis dates, missing data for safety endpoints will not be imputed. Details regarding date imputations can be found in appendix A.

### 9.4 Outliers

Outliers will be identified via the use of descriptive statistics and the review of SDTM and tables, figures and listings (TFLs). Edit checks will be created to specifically look for outlier data as indicated in the DMP. All confirmed outlier data will be included in the analyses presented in this statistical analysis plan unless there is sufficient scientific rationale to exclude them.

### 9.5 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software, for example the SAS System.

## 10. STATISTICAL METHODS OF ANALYSIS

### 10.1 General Principles

The studies preceding this open label extension are sufficiently different to preclude pooling over the studies. Since the number of subjects enrolled per parent study will be low most of the data will be shown in listings. A limited number of summary tables will be produced when the number of subjects makes this sensible.

The final analysis of this study will be performed at the end of the study i.e. when all the

subjects have completed or had the opportunity to complete the Day 60 Follow-up visit. The data may be summarized and listed before the final analysis to support Regulatory filings.

Data from the extension study will be concatenated with data from the parent study for the following endpoints: treatment emergent adverse events, exposure to protocol-specified treatment, laboratory parameters and vital signs. Summaries and listings will be presented grouped by the parent study, unless otherwise stated.

### 10.2 Subject Accountability

The denominators for the percentages in the subject accountability summaries will be the total number of subjects enrolled from each parent study.

Subject disposition (number screened, enrolled into the study, receive study specified products, withdrawn from the study and reasons for subjects discontinuing study) will be summarized for all enrolled subjects.

Listings of subject accountability and of subjects who discontinued from the study with the reason and timing of discontinuation will be provided using the all enrolled analysis set.

### 10.3 Important Protocol Deviations

Important Protocol Deviation (IPD) categories will be defined by the study team before the first patient visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes and descriptions will be used during the course of the study. The final IPD list will be used to produce the List of Subjects with IPDs (see section 12.2).

### 10.4 Demographic and Baseline Characteristics

Demographics (age, sex, race, height, weight) and tumor type will be listed using the all enrolled analysis set.

A listing will be provided of new medical history (any new history of an abnormality, disease or surgery that was not collected in the parent protocol) using the all enrolled analysis set.

Further listings showing the demographic and baseline characteristics (including prior medical and surgical history, prior surgery, prior radiotherapy, prior anti-cancer medications/regimens, and other

regional therapies) as collected at baseline of the parent protocol will be presented for all enrolled subjects.

## 10.5 Analysis of Key Study Endpoints

### 10.5.1 Tumor Response, Disease Progressions and Deaths

Tumor response, disease progression and deaths will be recorded for all enrolled subjects. Since summaries are presented by parent study and the number of subjects enrolled per study will be low, listings will be provided for tumor response, disease progression and deaths. Time to disease progression or death (whichever occurs first) will be presented as well as time to death (refer to section 6 for the definitions).

Investigator assessed tumor response as per eCRF will be listed for the extension study only (ie the time interval between enrollment into extension study and end of study).

### 10.5.2 Safety Endpoints

Safety data will be presented for subjects in the safety analysis set.

#### 10.5.2.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 13.0 or later will be used to code all adverse events to a system organ class and a preferred term. The severity of adverse events will be assigned in accordance with the NCI CTCAE version 3.0 guidelines.

Treatment emergent adverse event data from the parent study will be concatenated with adverse event data from the extension study.

Treatment emergent adverse events (all, serious and related) will be listed by subject, system organ class, preferred term, and severity. Further listings will show treatment emergent adverse events with a CTCAE $\geq 3$ by system organ class and preferred term, on-study deaths, serious adverse events, and adverse events leading to premature discontinuation from protocol specified therapy and/or study. Sponsor defined adverse events of interest will be flagged in the listings.

Adverse events will be reported up to 30 days after last dose of protocol specified therapy or safety-follow up visit, whichever is later.

#### 10.5.2.2 Laboratory Test Results

Listings will be provided for hematology, chemistry, and urinalysis parameters.

Table 10.1 lists the laboratory parameters measured during the study. Laboratory test results in the parent study will be concatenated with the results in the extension study for the parameters listed in table 10.1.

Table 10.1 Laboratory Parameters Measured During the Study

| Chemistry | Coagulation | Urinalysis | Hematology | Other Labs |
|---|---|---|---|---|
| Sodium | INR | Specific gravity | RBC | Anti-conatumumab antibodies |
| Potassium | PTT | pH | Hemoglobin | Pregnancy test |
| Chloride | | Blood | Platelets | Anti-AMG479 antibodies |
| Albumin | | Protein | WBC | HgbA1c* |
| Calcium | | Glucose | ANC | |
| Magnesium | | | Differentials | |
| Phosphorus | | | • Neutrophils | |
| Glucose | | | • Lymphocytes | |
| BUN | | | • Monocytes | |
| Creatinine | | | • Eosinophils | |
| Uric acid | | | • Basophils | |
| Creatine Kinase | | | | |
| Total bilirubin | | | | |
| Alk phosphatase | | | | |
| AST (SGOT) | | | | |
| ALT (SGPT) | | | | |
| Amylase | | | | |
| Lipase | | | | |

* HgbA1c required for subjects with diabetes (Type 1 or Type 2) receiving AMG 479

Textbook ranges will be used to calculate CTC-NCI grades for laboratory parameters, with the exception of amylase, lipase and creatine kinase which will be entered using local ranges. Where normal ranges are available, values outside of the range will be flagged. Severity grades for laboratory values will be derived programmatically based on NCI-CTC version 3.0.

Listings will be provided for baseline measurement in the parent study and all post-baseline measurements until the end of study. Further listings will show hematology and clinical chemistry assessments with grade 3 and 4 toxicities.

#### 10.5.2.3 Vital Signs

Vital sign parameter measurements in the parent study will be concatenated with the vital

sign parameter measurements in the extension study. Listings for each vital sign parameter will be provided for baseline measurement in parent study and all post-baseline measurements until end of study.

### 10.6 Protocol-specified Treatment Administration

Protocol-specified treatment administration data from parent protocol will be concatenated with data from the extension study.

Listings will be presented using the safety analysis set.

Listings will be provided for each protocol-specified treatment administration for each subject (the total dose administered/infused, dose modifications, if applicable (including dose reductions, dose delays, or doses withheld) and the reasons for dose modifications.

In addition, a listing of subject box and lot numbers will be provided by parent study.

### 10.7 Exposure to Concomitant Medication

Use of concomitant medications will be grouped by medication class and active ingredient according to the most up to date version of the World Health Organization Drug (WHODRUG) dictionary implemented by Amgen. Concomitant medications include those that started on or after the day of the first dose of protocol specified treatment (or planned start of treatment in the case of subjects who have their first dose delayed for any reason), through 30 days after the last administration of protocol specified treatment or safety follow-up visit, which ever comes earlier.

Listings of all concomitant medications by subject will also be provided by parent study. In addition, listing of concomitant medications that were continuing at the end of the parent study will be provided.

### 10.8 Physical Examination/Physical Measurements

Listing of weight will be provided for baseline measurement, minimum observed on-study measurement, maximum observed on-study measurement and last observed on-study measurement, including change from study day -1 in extension study to each of those on-study measurements.

Listing of physical examination at baseline and at follow-up visit will be provided.

## 11. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

There are no changes to the protocol-specified analyses.

## 12. LIST OF PLANNED TABLES, FIGURES AND LISTINGS [TFLs]

Amgen's Department of Biostatistics standard macros and programs will be used wherever possible to create the planned tables, figures and listings.

For the final analysis, the following TFLs will be provided.

Table, listing and figure shells will be created and agreed to by the team prior to the final analysis. Standard tables and listings will be used whenever possible.

Since the number of subjects enrolled per parent study will be low most of the data will be shown in listings.

### 12.1 Planned Tables

| Category | Title | Description |
|---|---|---|
| Disposition | Subject Disposition - All Enrolled Subjects | Tabulates the disposition of all enrolled subjects, including the number of subjects screened, the number of subjects enrolled, the number of subjects who received or did not receive investigational product by parent study. The reason for investigational product discontinuation and the reason for study discontinuation will also be summarized by parent study.<br>*[The footnote for the disposition table should include the dates for study initiation, early study termination (if applicable), and study completion, as required for the title page of the CSR.]* |

### 12.2 Planned Listings

| Title | Description |
|---|---|
| Study Accounting | Listing of the subjects together with the number of doses received, time and reason for ending study, reason for ending any protocol-specified treatment, time and dates for terminations, and completion of safety-follow up, grouped by parent study. |

| Title | Description |
|---|---|
| Screen Failures | Listing of subject screen failures and the reason for screen failure grouped by parent study. |
| Medical History | Listing of subjects with any new medical history not recorded in parent protocol grouped by parent study. |
| Subject Listing of Important Protocol Deviations | Listing of the Important Protocol Deviations with category and sub-category codes, and descriptions for each subject, grouped by parent study. |
| Listing of Unique Manufacturing Lot Numbers | Listing of the unique Manufacturing Lot Numbers used in the study, grouped by parent study (investigational product name and concentration). |
| Subject Listing of Manufacturing Lot Numbers | Listing of the subjects administered each Manufacturing Lot Number grouped by parent study (investigational product name and concentration). |
| Demographics (at enrollment) | Listing of the subjects together with age, sex, race, height, weight and tumor type grouped by parent study. |
| Baseline Demographics | Listing demographic and baseline characteristics as collected at baseline of parent study grouped by parent study |
| Prior Medical history | Listing of prior medical and surgical history, prior surgery, prior radiotherapy, prior anti-cancer medications/regimens, and other regional therapies as collected at baseline of parent protocol grouped by parent study. |
| Tumor Response | Listing of tumor response (CR, PR, SD, PD) for each subject grouped by parent study. |
| Time to Disease Progression and Time to Death | Listing of time to disease progression or death (whichever occurs first) and time to death grouped by parent study. |
| All Adverse Events | Listing of treatment-emergent adverse events (verbatim and preferred terms, start and stop dates, duration, severity, relation and action taken), grouped by parent study, subject ID. |
| Serious Adverse Events | Listing of serious treatment-emergent adverse events (verbatim and preferred terms, start and stop dates, duration, severity, relation and action taken), grouped by |

| Title | Description |
|---|---|
| | parent study, subject ID. |
| On-study Deaths | Listing of dates of deaths and last administrations and primary cause of deaths, and overall survival grouped by parent study, subject ID. |
| Treatment Emergent Adverse events with a CTCAE $\geq 3$ | Listing of treatment emergent adverse events with a CTCAE $\geq 3$ by system organ class and preferred term grouped by parent study. |
| Discontinuations Due to Adverse Events | Listing of discontinuations due to adverse events, grouped by parent study, subject ID. |
| Clinical laboratory | Listing of laboratory parameters (including NTC-NCI grades) measured at baseline and all post-baseline visits, grouped by parent study, subject ID. |
| Grade 3 or higher Hematology Toxicities | Listing of hematology assessments with grade 3 and 4 toxicities grouped by parent study. |
| Grade 3 or higher Clinical Chemistry Toxicities | Listing of clinical chemistry assessments with grade 3 and 4 toxicities grouped by parent study. |
| Vital Signs | Listing of vital sign parameters measured at baseline, and all post-baseline visits grouped by parent study, subject ID. |
| Protocol specified Treatment Administration | Listing of dates, times, days and doses of treatments administered and reasons for dose changes, grouped by parent study, subject ID. |
| Concomitant Medication | Listing of concomitant medications (including start and stop dates, indication, dose, route, frequency) grouped by parent study, subject ID. |
| Concomitant Medications continuing from Parent Study | Listing of concomitant medications continuing at the end of parent study (including start and stop dates, indication, dose, route, frequency) grouped by parent study, subject ID. |
| Physical Measurement | Listing of weight measured at baseline, minimum and maximum observed on-study measurement and last observed measurement, including change from study day -1 for extension study grouped by parent study, subject ID. |

| Title | Description |
|---|---|
| Physical Examination | Listing of physical examination at baseline and follow-up visit for each subject, grouped by parent study. |

## 13. LITERATURE CITATIONS / REFERENCES

Cox, D. R. and D. Oakes. 1984. Analysis of Survival Data. Chapman and Hall, London.

## 14. APPENDICES

## Appendix A. Handling of Dates, Incomplete Dates for Adverse Events and Concomitant Medications

Imputation Rules for Partial or Missing Start Dates

| Start Date | | Stop Date | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Complete: *yyyymmdd*** | | **Partial: *yyyymm*** | | **Partial: *yyyy*** | | **missing** |
| | | < 1st dose | ≥ 1st dose | < 1st dose *yyyymm* | ≥ 1st dose *yyyymm* | < 1st dose *yyyy* | ≥ 1st dose *yyyy* | |
| **Partial: *yyyymm*** | = 1st dose *yyyymm* | 2 | 1 | 2 | 1 | n/a | 1 | 1 |
| | ≠ 1st dose *yyyymm* | | 2 | | 2 | 2 | 2 | 2 |
| **Partial: *yyyy*** | = 1st dose *yyyy* | 3 | 1 | 3 | 1 | n/a | 1 | 1 |
| | ≠ 1st dose *yyyy* | | 3 | | 3 | 3 | 3 | 3 |
| **Missing** | | 4 | 1 | 4 | 1 | 4 | 1 | 1 |

1 = Impute the date of first dose
2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year

Imputation Rules for Partial or Missing Stop Dates

- If the month and year are present, impute the last day of that month but do not exceed the subject's last contact date or final analysis cutoff date.
- If only the year is present, impute December 31 of that year but do not exceed the subject's last contact date or final analysis cutoff date.
- If the stop date is entirely missing, assume the event or medication is ongoing

If a partial or complete stop date is present and the 'on-going' or 'continuing' box is checked, then it will be assumed that the adverse event or concomitant medication stopped and the stop date will be imputed if partial.