STATISTICAL ANALYSIS PLAN

Protocol Number:	SGN33A-003
Version:	Amendment 3; 15-Mar-2017
Protocol Title:	A Phase 1/2 study of vadastuximab talirine administered in sequence with allogeneic hematopoietic stem cell transplant in patients with relapsed or refractory acute myeloid leukemia (AML)
Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

APPROVAL SIGNATURES

Product:	SGN-CD33A
Protocol Number/Amendment:	SGN33A-03 / Amendment 3
SAP Version:	2
Version Date:	30-Aug-2017

The individuals signing below have reviewed and approve this statistical analysis plan.

[redacted] _____ [redacted]
Date

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Date

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Date

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LIST OF ABBREVIATIONS

ADC	antibody-drug conjugate
AE	adverse event
alloSCT	allogeneic stem cell transplant
AML	acute myeloid leukemia
ATA	antitherapeutic antibodies
AUC	area under the concentration-time curve
CR	complete remission
CRi	complete remission with incomplete blood count recovery
CBC	complete blood count
CRF	case report form
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EOT	end of treatment
GCP	good clinical practice
GVHD	graft-versus-host disease
ICH	International Conference on Harmonization
IND	Investigational New Drug
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NCI	National Cancer Institute
CTCAE	Common Terminology Criteria for adverse events
OS	overall survival
RIC	reduced intensity chemotherapy
SAE	serious adverse event
SAP	statistical analysis plan
SMC	safety monitoring committee
ULN	upper limit of normal
VOD	veno-occlusive disease

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGN33A-003, entitled "A Phase 1/2 study of vadastuximab talirine administered in sequence with allogeneic hematopoietic stem cell transplant in patients with relapsed or refractory acute myeloid leukemia (AML)". Results of the proposed analyses will become the basis of the clinical study report for this protocol.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. All planned analyses specified in this document will be performed. Any changes to this plan, in the form of "post hoc" or "data driven" analyses will be identified as such in the final clinical study report. Any changes will either be reflected in amendments to this plan before the database lock or specifically documented in the clinical study report.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- Phase 1
  - To assess the safety and tolerability of vadastuximab talirine
  - To determine the recommended dosing levels of vadastuximab talirine pre- and post-allogeneic hematopoietic stem cell transplant (alloSCT)
- Phase 2
  - To assess the 1-year survival rates of patients treated with vadastuximab talirine at the recommended doses pre- and post-alloSCT
  - To assess the rate of MRD negativity at Day –1 pre-transplant and Day 30 post-transplant in the pre-transplant portion of the study (Part A only).
  - To assess the safety and tolerability of vadastuximab talirine at the recommended dosing levels

2.2 Secondary Objectives

- To assess the best response on study treatment (Part A only)
- To assess the duration of response (Part A only)
- To assess overall survival (OS)

2.3 Additional Objectives

- To assess the pharmacokinetics, antitherapeutic antibodies (ATA), and pharmacodynamics of vadastuximab talirine
- To assess event-free survival (EFS)
- To assess the rate of MRD negativity
- To assess lymphocyte subset recovery after alloSCT

- To assess CD33 expression levels and post-treatment target (CD33) saturation
- To assess biomarkers of biological activity, resistance, and outcome

3 STUDY ENDPOINTS

3.1 Safety Endpoints

- Type, incidence, severity, seriousness, and relatedness of adverse events (AEs)
- Type, incidence, and severity of laboratory abnormalities
- Incidence of dose-limiting toxicity (DLT)

3.2 Efficacy Endpoints

- One-year survival
- Day –1 and Day 30 rates of MRD negativity (Part A only)
- Complete remission rate (Part A only)
- Best response (Part A only)
- Duration of response (Part A only)
- Overall survival

3.3 Additional Endpoints

- MRD – negativity
- Event-free survival
- PK parameters for SGN-CD33A, and released SGD-1882
- Incidence of ATA
- Biomarkers of vadastuximab talirine activity
- Quantification of T-, B-, and NK-cell lymphocyte subsets post-transplant

4 STUDY DESIGN

This is a 2-part study to evaluate the safety and efficacy of vadastuximab talirine in patients with relapsed chemo-resistant AML: Part A will examine vadastuximab talirine in cytoreduction pre-conditioning and Part B will examine vadastuximab talirine in post-alloSCT maintenance. Each study part will consist of a Phase 1 safety evaluation followed by a Phase 2 expansion for efficacy. Parts A and B will enroll concurrently. Phase 2 will be initiated following dose level recommendation by the Safety Monitoring Committee (SMC) with the determination of the MTD or recommended Phase 2 doses for Parts A and B, and an evaluation of the overall safety profile. At the discretion of the SMC, dose levels may be

expanded in Phase 1. All patients will be followed for survival status until 5 years after the last patient is enrolled, or until study closure, whichever occurs first.

In part A, one dose of vadastuximab talirine will be administered intravenously on Day −14 for patients in the cytoreduction pre-conditioning part followed by reduced intensity chemotherapy (RIC) of melphalan and fludarabine on Days −5 to −2. AlloSCT will be performed on Day 0. Patients will be evaluated for response at Day 30, and every 3 months from transplant for 1 year and then every 6 months until 3 years post-transplant. Part A Phase 1 of the study will be conducted using a standard 3+3 design starting from Dose Level 1. Dose cohorts are specified in the following Table 1. Dose de-escalation from Dose Level 1 is permitted based on SMC recommendation.

Table 1: Part A dose levels

Dose Level for Part A	Part A Dose of Vadastuximab Talirine (mcg/kg)
−1	30
1	40
2	60
3	80
4	100

In Part B, patients will enter the study between 42 and 100 days after the alloSCT and will receive vadastuximab talirine on Day 1 of 42-day cycles for up to 8 cycles. Response assessments will be every 3 months after the first dose of study drug for 2 years (every other cycle during treatment), and then every 6 months until 3 years post-transplant. Patients in Part B who discontinue study treatment prior to relapse will be evaluated for response until progression or initiation of new anticancer treatment, whichever comes first. Part B Phase 1 of the study will treat 6 patients at Dose Level 1 (10 mcg/kg). Once these 6 patients have completed the DLT period, the sponsor, in consultation with the SMC, may decide to explore safety and activity in an additional 6 patients. In the event of DLT occurring in 2 or more patients in either the first or the second 6-patient cohort, the sponsore, in consultation with the SMC, may choose to modify the schedule or dose level for further investigation. If fewer than 2 DLTs occur in either the first or second 6-patient cohorts, the sponsor will determine, in consultation with the SMC, the day when therapy may start and recommended dose for further evaluation. The planned doses for Part B are summarized in Table 2.

Table 2: Part B dose levels

Dose Level for Part B	Part B Dose of Vadastuximab Talirine (mcg/kg)
–1	5
1	10

5 ANALYSIS SETS

This section defines each of the analysis sets that will be utilized. The use of each analysis set will be discussed in Section 7.

5.1 All Treated Patients Analysis Set

The All Treated Patients analysis set includes all patients who receive any positive amount of vadastuximab talirine.

5.2 DLT Evaluable (DE) Set

The DLT-evaluable (DE) analysis set includes all treated patients in Phase 1 who received vadastuximab talirine and either experienced a DLT or were followed for the full DLT evaluation period.

6 STATISTICAL CONSIDERATIONS

6.1 General Principles

This is a Phase 1/2 study including dose-escalation. All analyses will be descriptive; however, confidence intervals may be presented to describe precision of estimates. Part A and Part B will be summarized separately. Patients will be grouped by dose level across Phase 1 and Phase 2 within study part.

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be used to summarize continuous variables. Frequencies and percentages will be used to summarize categorical variables. Median of a time-to-event endpoint will be estimated by the Kaplan-Meier method. Analyses will be presented by dose level.

Any analysis not described in this plan will be considered exploratory, and will be documented in the clinical study report (CSR) as a post hoc analysis or a change to the planned analysis.

To comply with regulatory electronic submission guidelines, listings of all clinical data will be submitted as electronic data sets. To facilitate data review for the study report, only pertinent data listings will be created and attached to the appendix of the CSR. All statistical output will be produced using SAS®, version 9.3 or more recent. Other statistical software, if used, will be described in the clinical study report.

6.2 Determination of Sample Size

[redacted]

6.3 Randomization and Blinding

Not applicable.

6.4 Data Transformations and Derivations

Age in years will be calculated with the SAS INTCK function (with method specified as "continuous") using informed consent date and birth date.

Time variables based on two dates (e.g., Start Date and End Date), will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified in the planned analysis section.

For both Part A and Part B, Study Day will be calculated as Date–First Dose Date+1 for dates on or after the first dose date. For dates prior to the first dose date, Study Day will be calculated as Date–First Dose Date.

The following unit conversion will be implemented unless otherwise specified:

- Months = Days / 30.4375
- Years =Days / 365.25

Unless otherwise specified, baseline values used in all statistical analyses will be the most recent non-missing measurement prior to the first dose of vadastuximab talirine.

The end-of-treatment (EOT) date will be the date the EOT visit is performed; if an EOT visit is not performed then the EOT date will be either the end-of-study (EOS) date or 30 days for Part A and 42 days for Part B after the last dose of any study drug, whichever is earlier.

For efficacy assessments, the date of the response assessment will be the bone marrow exam date or local lab CBC date (if applicable) at the corresponding visit. If the response is determined to be anything except 'Relapse from CR/CRi', the latest date of the bone marrow exam or the local lab CBC exam will be the response assessment date. For the response 'Relapse from CR/CRi', the earliest date of the bone marrow exam or the local lab CBC exam will be the response assessment date.

6.5 Handling of Dropouts and Missing Data

In general, missing data will not be imputed. But missing AE dates will be imputed while calculating duration of events and treatment-emergent status (see Appendix A for imputation details and Appendix B for the treatment-emergent definition).

The algorithm below will be used to impute the start date of subsequent anti-cancer treatment when only the day part is missing.

- If the month and year of the new anti-cancer treatment start date are the same as the month and year of the documented relapse date, the new anti-cancer treatment will be assumed to start on the same day as relapse.
- Otherwise, the new anti-cancer treatment will be assumed to start on the first day of that month.

Censoring rules for the time-to-event endpoints will be described in Section 7 with each planned analysis, as applicable.

6.6 Multicenter Studies

There are multiple centers in this study; however, it is not anticipated that any center will accrue enough patients to warrant an analysis by center.

6.7 Multiple Comparison/Multiplicity

No multiple comparisons are planned and no alpha adjustment is needed in this Phase 1/2 study.

6.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Subgroups may include but are not limited to the following:

- Age (≤65, and >65)
- Age (≤50, and >50)
- Current disease status (relapsed and refractory, Part A only)
- HCT comorbidity index (low (0), intermediate (1 to 2), and high (≥3) , Part A only)
- Cytogenetic risk category (favorable, intermediate and adverse)
- Number of prior AML systemic therapies (1, 2, and ≥3)
- Bone marrow blast prior to alloSCT (<25%, and ≥25%, Part A only)

6.9 Covariates

Covariates are not considered for adjustment in the analyses.

6.10 Timing of Analyses

Each part of the study will be conducted separately. Section 8 will provide details of the timing.

7 PLANNED ANALYSES

7.1 Disposition

An accounting of study patients by disposition will be tabulated by cohort and total using All Enrolled Patients analysis set. Reasons for discontinuation of treatment and study will be summarized by cohort and total. The number and percentage of patients who signed informed consent forms and the number of patients in each analysis set will be summarized for all patients by cohort and total.

7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age, gender, ethnicity, race, baseline height, weight, and ECOG score will be listed and summarized; summaries will be presented for each cohort and total using the All Treated Patients analysis set. Disease specific characteristics, including time from diagnosis, current disease status, baseline HCT

comorbidity index, cytogenetic risk, and previous cancer-related treatments will be listed and summarized for each cohort and the total using the All Treated Patients analysis set.

7.3 Protocol Deviations

Important protocol deviations (defined as protocol violations by Seattle Genetics) are those that represent a divergence from the protocol that could have a significant effect on the integrity of the study data, or on the subject's rights, safety, or welfare. Important protocol deviations also include exemptions to the study inclusion/exclusion criteria and will be summarized by category. A list of patients with important protocol deviations will be presented.

7.4 Treatment Administration

7.4.1 Vadastuximab Talirine

Treatment administration will be summarized by cohort using the All Treated Patients analysis set. For Part B, summary statistics for treatment period (weeks) and the number of cycles per patient will be presented, as well as the number and percentage of patients who were treated at each cycle. Cumulative dose, absolute dose intensity (ADI), and relative dose intensity (RDI) will be summarized with descriptive statistics. The number and percentage of patients whose dose was ever modified will be summarized in tables by modification type, cycle, and overall (i.e. over all drug administrations for a patient); listings may be presented as well.

Treatment period is defined as time from the first vadatuximab talirine dose to 44 days for Part A, and 42 days after the last study dose for Part B, or death, whichever occurs earlier:

- Part A: minimum of (death date – first dose date + 1, 44)
- Part B: minimum of (death date – first dose date + 1, last dose date – first dose date + 42).

Intended Dose Intensity (IDI) is defined as the intended dose of drug (mcg/kg) per week. For example, the IDI for the 40 mcg/kg cohort in Part A is 40/(44/7) = 6.36 mcg/kg/wk. The IDI for the 10 mcg/kg cohort in Part B is 10/(42/7) = 1.67 mcg/kg/wk.

Absolute Dose Intensity (ADI) is defined as the actual dose (mcg/kg) per week that the patient received over the entire treatment period.

Relative dose intensity (RDI) is defined as the absolute dose intensity as a percentage of the intended dose intensity.

RDI = ADI/IDI * 100.

7.4.2 Reduced Intensity Chemotherapy (Part A Only)

Dose administration of each of the two RIC therapies (fludarabine and melphalan) will be listed using the All Treated Patients analysis set.

7.4.3 GVHD Prophylaxis (Part A Only)

Dose administration of each of the two GVHD prophylaxes (tacrolimus and methotrexate) will be listed using the All Treated Patients analysis set.

7.5 Efficacy Analyses

All efficacy analyses will be presented using the All Treated Patients analysis set. Analyses may also be performed using the subgroups listed in Section 6.8. Efficacy endpoints for each patient will be presented in listings.

7.5.1 One-year Survival

One year survival rate is the percentage of patients in the study who are still alive for one year after their alloSCT. The one-year survival rate will be summarized by cohorts using Kaplan Meier method. The associated two sided 95% CIs will be calculated using complementary log-log transformation method.

7.5.2 Day -1 and Day 30 MRD (Minimal Residual Disease) Negativity (Part A only)

MRD detected in bone marrow will be listed at Day -1 and Day 30.

7.5.3 Best Response (Part A only)

The best response is defined as the best disease response determined by the investigator based on the response criteria for AML (Cheson 2003) during the study before other anticancer treatment. The response categories are CR, CRi, mLFS, PR, and SD. The patients' best response will be listed.

7.5.4 Duration of Response (Part A only)

Duration of response is defined as the time from the start of the first documented CR/CRi to the first documentation of relapse or death due to any cause, whichever comes first. Duration of response information will be listed.

7.5.5 Overall Survival (OS) from alloSCT

Overall survival (OS) is defined as the time from the date of alloSCT to date of death due to any cause. Specifically,

OS = date of death – date of alloSCT + 1.

OS information will be listed.

7.6 Safety Analyses

The All Treated Patients analysis set will be used to summarize all safety endpoints.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 18.0 or higher).

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

Concomitant medications will be coded using WHO Drug (version: June 2015 or more recent).

7.6.1 Adverse Events

Adverse events will be summarized by MedDRA preferred term in descending frequency of occurrence by cohort and total, and separately for Part A and Part B unless otherwise specified. For incidence reporting, if a patient reports more than one AE that was coded to the same system organ class or preferred term, the patient will be counted only once for that specific system organ class or preferred term.

A treatment-emergent AE is defined as a newly occurring or worsening AE after the first dose of study drug. See Appendix B for details regarding treatment-emergent classification. Summaries of AEs will be provided by dose cohort and total within study part for the following:

- Treatment-emergent Adverse Events by preferred term
- Treatment-emergent AEs by system organ class and preferred term
- AEs related to vadastuximab talirine by preferred term
- AEs related to reduced intensity chemotherapy (RIC) by preferred term (Part A only)
- AEs related to GVHD by preferred term
- Serious Adverse Events (SAEs) by preferred term
- SAEs related to vadastuximab talirine by preferred term
- SAEs related to RIC by preferred term (Part A only)
- SAEs related to GVHD by preferred term
- AEs leading to dose delay of vadastuximab talirine by preferred term (Part B only)
- AEs leading to treatment discontinuation by preferred term (Part B only)
- AEs leading to treatment discontinuation related to vadastuximab talirine by preferred term (Part B only)
- Infusion related reactions by preferred term
- DLTs by preferred term
- Treatment-emergent AEs by system organ class, preferred term and maximum grade. At each system organ class or preferred term, multiple occurrences of events within a patient are counted only once at the highest grade

- Grade 3 - 5 treatment-emergent AEs by preferred term

All adverse events, Treatment-emergent adverse events, serious adverse events, adverse events leading to treatment discontinuation, adverse events as the primary cause of death, and adverse events of special interest (including pulmonary event, renal event, severe hepatic dysfunction, cardiac death, and sepsis) will be listed.

7.6.2 Clinical Laboratory Parameters

Laboratory values (e.g., chemistry, hematology, urinalysis, and pulmonary function tests) may be presented graphically for each lab test by scheduled visit, dose cohort and total within study part. Summary statistics may be tabulated where appropriate. Shift tables for the laboratory parameters with CTCAE grade may also be provided. Laboratory values will be listed with NCI CTCAE v4.03 grades and out-of-normal range flags.

7.6.3 ECOG Performance Status

ECOG performance status will be listed by patient.

7.6.4 Concomitant Medications

Concomitant medications will be listed by patient.

7.6.5 Deaths

The number of total deaths, deaths that occur within 30 days and 60 days of first study treatment, deaths that occur within 30 days of last study treatment, and deaths that occur more than 30 days after last study treatment, as well as the relationship to disease, will be summarized separately for Part A and B. In addition, cause of death will be identified by descending MedDRA preferred term (unless otherwise specified) and listed by patient.

7.6.6 GVHD Assessments

GVHD assessment will be listed for each scheduled assessment.

7.6.7 Allogeneic Stem Cell Transplant

The number and percentage of patients who received reduced intensity conditioning regimen, the time from transplant to first dose of SGN-CD33A (Part B), the time from last dose of SGN-CD33A to transplant (Part A), and SOS/VOD rate will be summarized.

Part A patients' post-alloSCT VOD assessment information will be listed using all treated patients set.

7.7 Additional Analyses

7.7.1 MRD - negativity

MRD detected in bone marrow will be listed at each bone marrow exam. The MRD negativity rate is defined as the proportion of patients with MRD negativity. The MRD negativity rate at each bone marrow exam will also be summarized.

7.7.2 Event-free Survival (EFS)

Event-free survival is defined as the time from the day of alloSCT to the first documentation of treatment failure (defined below). EFS information will be listed.

- **Part A**

  Treatment failure is defined as failure to achieve CR/CRi by Day 30, relapse from CR/CRi, or death, due to any cause, whichever comes first. Treated patients who die or withdraw from study before receiving alloSCT will be excluded from the analysis.

- **Part B**

  Treatment failure is defined as relapse of AML or death due to any cause, whichever comes first.

7.7.3 Pharmacokinetics

The observed plasma vadatuximab talirine ADC and SGD-1882 (if measurable) will be summarized with descriptive statistics at each PK sampling time point using the All Treated Patients analysis set. PK/PD analyses will be performed outside of Biometrics and may be presented in a separate PK report.

7.7.4 Antitherapeutic Antibody (ATA) Incidence Rate

The antitherapeutic antibody (ATA) incidence rate is defined as the proportion of patients who develop ATA at any time during the study.

ATA incidence rate may be summarized by cohort and total within study part for all treated patients. An exact two-sided 95% confidence interval using the Clopper-Pearson method (Clopper 1934) may be calculated.

7.7.5 Biomarker Analysis

Biomarker assessments may be summarized using descriptive statistics. Biomarker assessments may include the following: CD33 expression level and saturation by vadastuximab talirine on CD33+ cells, cytogenetic abnormalities and/or mutation of genes with known prognostic significance for AML, soluble CD33, lymphocyte subset recovery post-transplant, and evaluation of MRD at protocol specified time points.

7.7.6 Quantification of T-, B-, and NK-cell Lymphocyte Subsets Post-transplant

Recovery of T-, B- and NK-cell lymphocyte subsets post-transplant may be monitored in peripheral blood by the local laboratory according to institutional standard. In Part A, whether actual values for each post baseline test are in normal range or not may be summarized by cohort and total. In Part B, the changes from baseline (within 3 days prior to first dose of vadastuximab talirine) test may be summarized for each post baseline test by cohort and total.

8 INTERIM ANALYSIS

No formal interim analyses are planned.

A SMC consisting of all principal investigators, and the sponsor's medical monitor will monitor the trial for safety and DLTs. Each Phase 1 dose cohort will be evaluated for DLTs prior to enrolling the subsequent cohort. The SMC will also review aggregate safety data and efficacy data from Phase 2 in a regular basis. The process for dose escalation decisions and the roles and responsibilities of the SMC is documented in the SMC Charter.

In addition, interim data from the study may be presented at scientific meetings such as the American Society of Hematology (ASH) or the American Society of Clinical Oncology (ASCO).

The final analysis for this study will occur after all patients have completed treatment and the follow-up period, or after study termination by the sponsor.

9 CHANGES FROM PLANNED ANALYSES

9.1 Changes from the Original Protocol

There is one change from original protocol: the study stopping criteria is added.

9.2 Changes from the Original SAP

The sponsor decided to terminate the study earlier.There are some changes from the original SAP: 1) the study stopping criteria is added; 2) New algorithm for missing data imputation is added; and 3) GVHD and allogeneic stem cell transplant are included; 4) Summary of AE outputs are modified.

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APPENDIX A: IMPUTATION OF PARTIALLY UNKNOWN ADVERSE EVENT DATES

The algorithm below should be used to impute pre-existing condition and adverse event (AE) start dates for which only partial information is known. For ease of reading, both pre-existing conditions and AEs will be referred to as AE for the remainder of this document. The algorithm should be applied to every AE record on a record by record basis. AE start dates should be imputed before imputation of AE condition end date in all cases. The AE condition end date should only be used in the imputation of the AE start date if it is a complete, known date.

AE day and month are missing

- If the year is the same as the year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was pre-dose:
  AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of investigational agent)
- If the year is the same as the year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was post-dose:
  AE start date will be imputed as the minimum of (AE condition end date*, first dose date of investigational agent)
- If the year is before the year of first dose of investigational agent:
  AE start date will be imputed as the minimum of (AE condition end date*, December 31st see example 2 below)
- If the year is after the year of first dose of investigational agent:
  AE start date will be imputed as the minimum of (AE condition end date*, January 31st see example 2 below)

AE month only is missing

- Treat day as missing and replace both month and day according to the above procedure

AE day only is missing

- If the month/year is the same as the month/year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was pre-dose:

  AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of investigational agent)

- If the month/year is the same as the month/year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was post-dose:

  AE start date will be imputed as the minimum of (AE condition end date*, first dose date of investigational agent)

- If the month/year is before the month/year of first dose of investigational agent:

AE start date will be imputed as the minimum of (AE condition end date*, last day of the month)

- If the month/year is after the month/year of first dose of investigational agent:

  AE start date will be imputed as the minimum of (AE condition end date*, last day of the month)

* only use condition end date if known and complete end date is available.

The following algorithm should be used to impute AE condition end dates. The AE records for a condition/event should be sorted by the imputed start dates then record position (order of entry into the eCRF). After sorting, if any condition end date month/year is greater than any subsequent record end date month/year, then change the imputed start day only to end of month. Repeat as necessary.

After sorting the AE records, apply the following rules to partial or missing AE condition end dates:

For all records excluding the last chronological record for a condition/event

- AE condition end date will be imputed as the start date of the subsequent record

For the last chronological record for a condition/event

- If outcome is "recovered/resolved"," recovered/resolved with sequelae", or "fatal" apply the following:
  - If only year is provided for the end date and year is equal to the year of the last dose date:
    - AE condition end date will be imputed as the minimum of (last dose date + 30, death date, data extraction date, December 31st of the end date year)
  - If only year is provided for the end date and year is not equal to the year of the last dose date:
    - AE condition end date will be imputed as the minimum of (death date, data extraction date, December 31st of the end date year)
  - If month and year are provided for the end date:
    - AE condition end date will be imputed as the minimum of (death date, data extraction date, last day of the end date month/year)

- If outcome is "recovering/resolving", "not recovered/resolved","unknown", or blank:

  AE condition end date will not be imputed.

Example 1

AESPID 1: Condition/Event HEADACHE
First dose date 01JAN2012

Prior to imputation

Start date	Condition end date	Severity	Outcome	Onset
UNUNK2011	15APR2012	1	not recovered/resolved	pre-ICF
15APR2012	UNMAY2012	2	recovering/resolving	post 1st dose
UNMAY2012	UNJUN2012	1	not recovered/resolved	post 1st dose
UNJUN2012	UNJUN2012	3	recovering/resolving	post 1st dose
UNJUN2012	10JUL2012	2	recovering/resolving	post 1st dose
10JUL2012	--	1	not recovered/resolved	post 1st dose

Post imputation

Start date	Condition end date	Severity	Outcome
31DEC2011	15APR2012	1	not recovered/resolved
15APR2012	31MAY2012	2	recovering/resolving
31MAY2012	30JUN2012	1	not recovered/resolved
30JUN2012	30JUN2012	3	recovering/resolving
30JUN2012	10JUL2012	2	recovering/resolving
10JUL2012	--	1	not recovered/resolved

Example 2 (highlights choice of last day of the month as opposed to the 1st or the 15th)

AESPID 4: Condition/Event NAUSEA
First dose date 01APR2012

Prior to imputation

Start date	Condition end date	Severity	Outcome	Onset
UNUNK2011	25APR2012	1	not recovered/resolved	pre-ICF
25APR2012	UNAPR2012	2	recovering/resolving	post 1st dose
UNAPR2012	04MAY2012	1	recovered/resolved	post 1st dose

Post imputation

Start date	Condition end date	Severity	Outcome
31DEC2011	25APR2012	1	not recovered/resolved
25APR2012	31APR2012	2	recovering/resolving
31APR2012	04MAY2012	1	recovered/resolved

APPENDIX B: DEFINITION OF THE TERM "TREATMENT-EMERGENT" WITH RESPECT TO AE CLASSIFICATION

The algorithm below should be used to determine whether an adverse event (AE) is classified as a treatment-emergent adverse event (TEAE). A TEAE is defined as any AE which is newly occurring or worsening in severity, where newly occurring means that the AE was not present at baseline. For ease of reading, both pre-existing conditions and AEs will be referred to as AEs for the remainder of this document. AE dates should be imputed in accordance with the algorithm detailed in Appendix A prior to determination of TEAE classification. Details of the TEAE classification are as follows:

1) Determine the first dose date of study treatment
2) **Baseline AEs:** classify an AE as a baseline AE if it satisfies both of criteria a and b below:
    a) The onset period field is: "started before the signing of informed consent"; or "started after consent but before the first dose of any study treatment"; or, the onset period field is missing and the AE start date is prior to the first dose date of any study drug (step 1, above).
    b) The stop date satisfies either of i or ii below:
        i) The stop date is the same as or a later date than the first dose date of study treatment
        ii) The stop date is missing with outcome equal to:
            - recovering/resolving (this outcome may or may not be associated with a date), or
            - not recovered/not resolved, or
            - unknown
            - Note: if the AE has no outcome or stop date provided, the CRF data should be queried.
    c) Note: If the event ended on the date of first dose of study drug, it will be considered a baseline event.
3) **Post-baseline AEs:** classify an AE as post-baseline if it meets either of criteria a or b below:
    a) The onset period of the AE is "started after the first dose of any study treatment"
    b) The onset period of the AE is missing and the AE start date is the same as or a later date than the first dose date of study treatment

4) Compare post-baseline AEs to baseline AEs using the lower level term (LLT) and determine classification. **Note that classification may not be possible and the TEAE variable will be missing**:

   a) Classify all baseline AEs as not treatment emergent (not TEAEs).

   b) If a baseline and post-baseline AE have the same LLT but the post-baseline AE has a greater CTC grade then classify the post-baseline AE as a TEAE. If the post-baseline grade is less than or equal to the baseline grade then the post-baseline AE is not a TEAE.

   c) If there are no baseline AEs with a matching LLT for the post-baseline AE, then classify the post-baseline AE as a TEAE.

   d) If the post-baseline AE is uncoded, then classify the post-baseline AE as a TEAE.

NOTE: for summaries which include only treatment emergent AEs include all AEs which are classified as TEAEs as well as those AEs for which TEAE status could not be determined (e.g., the value of the TEAE variable may be missing if the event cannot be identified as baseline or post-baseline – missing information on the AE CRF should be queried). Only exclude those AEs which were determined to not be treatment emergent; events that have an end date prior to the first dose date (these should not be entered with the exception of protocol procedure related events) should be classified as not treatment emergent (not TEAEs).