STATISTICAL ANALYSIS PLAN

A Phase 1b Open-label Study Investigating the Safety and Pharmacokinetics of Administration of Subcutaneous Blinatumomab for the Treatment of Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma

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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	03May2017	
Amendment 1 (v2.0)	21May2019	1. SAP is updated as per protocol amendment 6. 2. Section 6 Definitions of Best Overall Response is updated for assessment timepoint during Safety Follow-up visit. 3. Section 6 DLT evaluable definition, Optional Cycle2 are updates as per protocol 4. Section 8.1.1.1 Dose Level Review Team and 8.1.1.2 Dose Limiting toxicity rules are updated as per protocol amendment 6 5. Section 10.5.1 ,Analysis for DRE included. 6. Section 10.6.1 Analyses of Secondary Efficacy Endpoints is updated. 7. Table 4, 5, and 6 Schedule of assessment for cycle 1 and cycle 2 are removed. 8. Appendix D updated to include PROC FREQ code for Clopper Pearson method to find 95 % CI. 9. Section 6 TEAE definition is updated to “A treatment emergent adverse event refers to the adverse event that starts on or after first dose of blinatumomab ~~through 30 days after the last dose of blinatumomab~~. 10. Section 10.5.1 Adverse Event is updated to include "Similar summaries will be repeated for EOIs. Time to onset and duration of selected EOIs (infection and neurologic events) may also be summarized.”

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
cIV	Continuous Intravenous
CR	Complete Response
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DLRT	Dose Level Review Team
DLT	Dose Limiting Toxicities
ECOG	Eastern Cooperative Oncology Group
EOS	End of Study
FAS	Full Analysis Set
FL	Follicular Lymphoma I, II, IIIA
ICH	International Conference on Harmonisation
IP	Investigational Product
IV	Intravenous
MCL	Mantle cell lymphoma
MTD	Maximum Tolerated Dose
NHL	Non-Hodgkin's Lymphoma
ORR	Overall response rate
PD	Pharmacodynamic
PK	Pharmacokinetic
PR	Partial Response
q12h	Every 12 hours
q24h	Every 24 hours
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	System Organ Class
WBC	White Blood Cells
WHO	World Health Organization

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 study 20140286 Blinatumomab, Superseding Amendment 6 V2 dated 25Feb2019. The scope of this plan includes the interim analysis and the final analysis that are planned and will be executed by the Biostatistics department or designee unless otherwise specified eg, pharmacokinetic (PK) analysis will be provided by Clinical Pharmacology, Modeling and Simulation (CPMS) department.

2. Objectives

2.1 Primary Objective

- To evaluate the safety and tolerability of subcutaneous (SC) blinatumomab dose administrations.

2.2 Secondary Objectives

- To determine pharmacokinetics (PK) with continuous intravenous (cIV) and SC administrations
- To estimate the maximum tolerated dose (MTD) tested for blinatumomab administered subcutaneously
- To determine the incidence of anti-blinatumomab antibody formation following SC administration
- To evaluate efficacy response following treatment with SC blinatumomab administration

2.3 Exploratory Objective

- To determine the pharmacodynamics (PD) time profiles for B- and T-lymphocytes as well as cytokine profiles during SC administration.
- To evaluate efficacy response following treatment with SC blinatumomab administration using Lugano criteria if positron emission tomography-computed tomography (PET/CT) is used for evaluation (Appendix B)

3. Study Overview

3.1 Study Design

This is a global multi-center, Phase 1b open-label study investigating the safety and PK of blinatumomab administered subcutaneously for the treatment of relapsed/refractory indolent NHL. The SC administration of blinatumomab will be tested for the first time in humans.

Period 1 of the study will focus on the determination of PK, bioavailability, and safety profile of blinatumomab SC administration. The PK and bioavailability data from Period 1 of the study will be used in conjunction with safety data (DLT) to determine the SC

MTD. The MTD or the maximum tested dose, if MTD is not reached, will be further tested in Period 2 in an expanded cohort. Efficacy of blinatumomab administered subcutaneously will also be investigated in each period of the study.

3.1.1 Cycle 1/Period 1

In Period 1, 3 or more separate dose cohorts of up to 6 DLT evaluable subjects each will be enrolled and undergo treatment as follows:

- Subjects will undergo an initial cIV blinatumomab run-in period (weeks 1 to 3) followed by a 12-hour treatment free period.
- Subjects will then receive SC administration (week 4) followed by a treatment free period of 2 to not more than 3 days.
- After the SC administration period, subjects should return to receive cIV treatment to complete 6 weeks of therapy (weeks 5 to 6).

For all cohorts, the initial cIV dose of blinatumomab will be 9 µg/day for the first 7 days (to mitigate for potential cytokine release syndrome [CRS] and neurologic events associated with introduction to blinatumomab) which then will be escalated (dose-step) to 28 µg/day starting on day 8 through day 14 (week 2), and to 112 µg/day starting on day 15 until day 21 (week 3).

After stopping cIV blinatumomab, there is a 12-hour treatment free period before starting SC blinatumomab. SC blinatumomab starts after the 12-hour treatment free period and will be administered (week 4) as the following dose-cohort levels:

- Dose Cohort 1: 112 µg q12h × 5 days for a total of 9 doses (n= 6)
- Dose Cohort 2: 225 µg q12h × 5 days for a total of 9 doses (n = 6)

(Note: A total of 9 SC doses will be given for the q12h dosing, so intensive PK samples can be obtained on day shift to reduce errors).

- Dose Cohort 3: 450 µg q24h × 5 days for a total of 5 doses (n = 6)
- Additional Dose Cohorts: Dose level and dosing frequency to be determined as described below

One or more dosing regimens (refer to Dosing Schema Figure 1 in protocol) may be selected based on clinical findings including safety, tolerability, and PK results from previous cohorts; and after Dose Level Review Team (DLRT) review and make recommendations for the next SC cohort dose and frequency. The dose may be increased (by 1 dose level or between the dose of the previous cohort and the next higher dosing level in Figure 1 schema in protocol), kept at the same dose level or decreased by 1 or more dose levels. The dose frequency chosen (q12h, q24h, q48h,

q72h, q96h, or q7days) will be decided by the DLRT and will be based on the previous cohort PK data.

Once the SC dosing is complete, a treatment free period of 2 to not more than 3 days between stopping SC and restarting cIV will be observed. Then the cIV blinatumomab dosing will resume at 112 µg/day (weeks 5 to 6) to complete 6 weeks of treatment.

For each SC dose cohort, if ≤ 1 of the 6 DLT evaluable subjects experience a DLT during the SC administration DLT evaluation period then the dose will be determined to be tolerable and the DLRT will decide the next dose level to be initiated and the frequency of administration for the next cohort; see Section 6.2.1.2.2 in protocol for definition of the DLT evaluation period.

For each SC dose cohort, if ≥ 2 of the 6 DLT evaluable subjects experience a DLT during the SC administration then dosing will stop for individual subjects who experience a DLT, a DLRT meeting will be conducted, and further steps will be determined, such as dose de-escalation or increasing dosing interval (Figure 1 in protocol). In addition, if subjects on this cohort have not reached the SC dosing, they will be allowed to stay on study but will finish cycle 1/period 1 as cIV.

MTD will be defined as the highest dose level at which ≤ 1 of 6 subjects experience a DLT.If no subject experiences a DLT, the MTD will be defined as the maximal dose tested.

For further details, see Section 6.2.1.2.1 and Section 6.2.1.2.3 of protocol.

3.1.2 Cycle 1/Period 2

The aim of Period 2 will be to assess the MTD as derived from Period 1, or the maximum tested dose, if MTD has not been reached, for additional safety and preliminary efficacy data in an expanded cohort of up to 15 evaluable subjects receiving SC treatment only (no cIV run-in).

Doses for Cycle 1/Period 2 will be derived based on PK, bioavailability, and safety data collected in Cycle 1/Period 1 and DLRT review and recommendations. Subjects will receive sequentially the estimated SC doses equivalent to the 9 µg/day cIV in week 1, SC doses equivalent to the 28 µg/day cIV starting in week 1 and continuing into week 2, and then the SC doses of the selected maximal dose and dosing interval from Cycle 1/Period 1 starting in week 2 (day 12) and continuing to complete a total of 6 weeks of blinatumomab (see Section 6.2.1.2.2 in protocol for definition of the DLT evaluation period for Period 2).

3.1.3 Safety Monitoring

Safety monitoring will be implemented using continuous toxicity monitoring for early termination of the trial in Cycle 1/Period 2. Termination of study Cycle 1/Period 2 will occur if the posterior probability that the DLT rate is greater than 25%, given the cumulative data thus far, is at least 80%. Starting with the fifth subject treated in Cycle 1/Period 2, stopping may occur at any time.

The stopping boundaries assume a prior beta distribution of (0.50, 1.50) and a batch size of 1 (starting with the fifth subject treated) are presented in Table 1 and the operating characteristics are given in Table 2. The operating characteristics in Table 2 provide the probability of stopping the trial early for given hypothetical true DLT (please see section 6 for more details) rates whereas the stopping criteria in Table 1 are based on situations where the empirical evidence would result in a posterior probability ≥ 80% that the true DLT rate is ≥ 25% (Thall et al, 1995).

Table 1. Cycle 1/Period 2 Stopping Boundaries

Cumulative Number of Subjects	Stop Study if This Many Subjects Have a Dose-limiting Toxicity
5 - 6	≥ 3
7 - 10	≥ 4
11 - 13	≥ 5
14	≥ 6
15	Study Period 2 is complete at 15

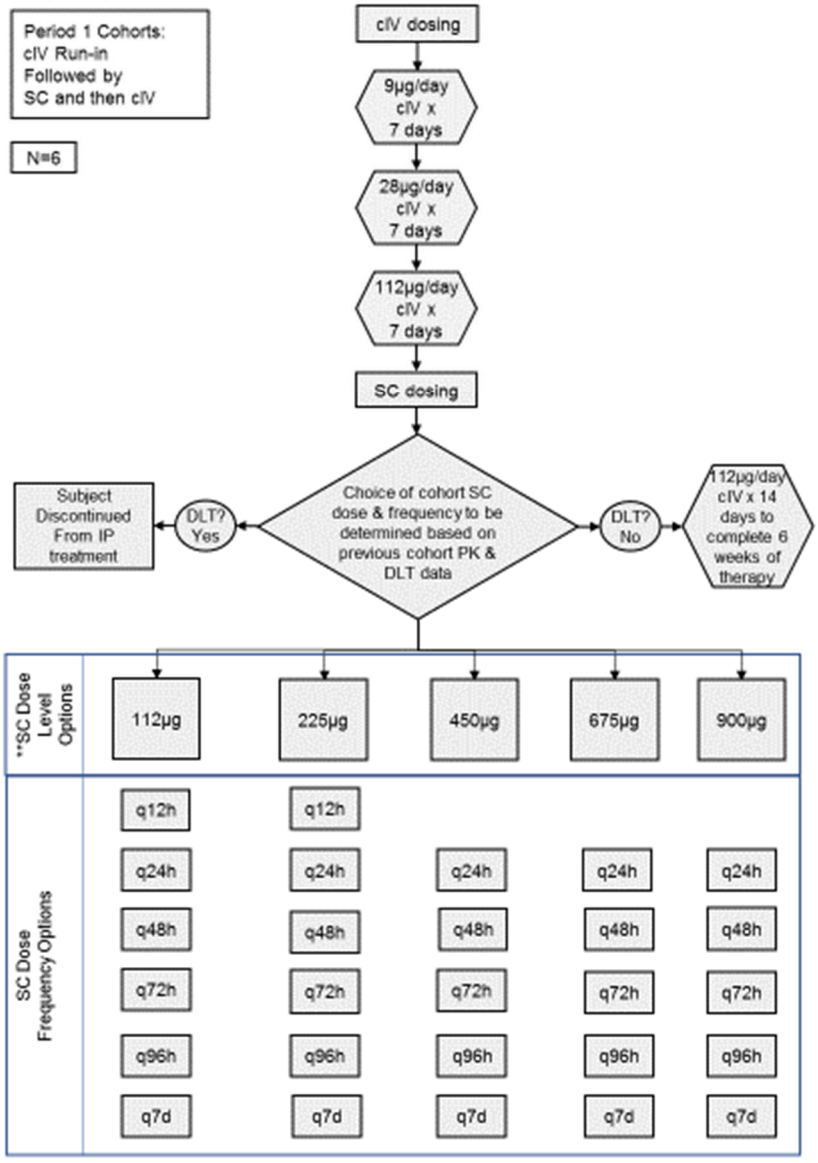
Note: Study may stop with fewer than 5 subjects if 3 or more subjects with DLTs have been observed

Table 2. Operating Characteristics

True Rate of Dose-Limiting Toxicities	Probability of Stopping Early	Average Sample Size
20%	17%	13.7
25%	30%	12.7
30%	45%	11.6
40%	72%	9.3
50%	90%	7.3
60%	98%	6.1

3.1.4 Study Schema

Figure 1. Study Schema for Cycle 1/Period 1: cIV Run-in and SC Dose

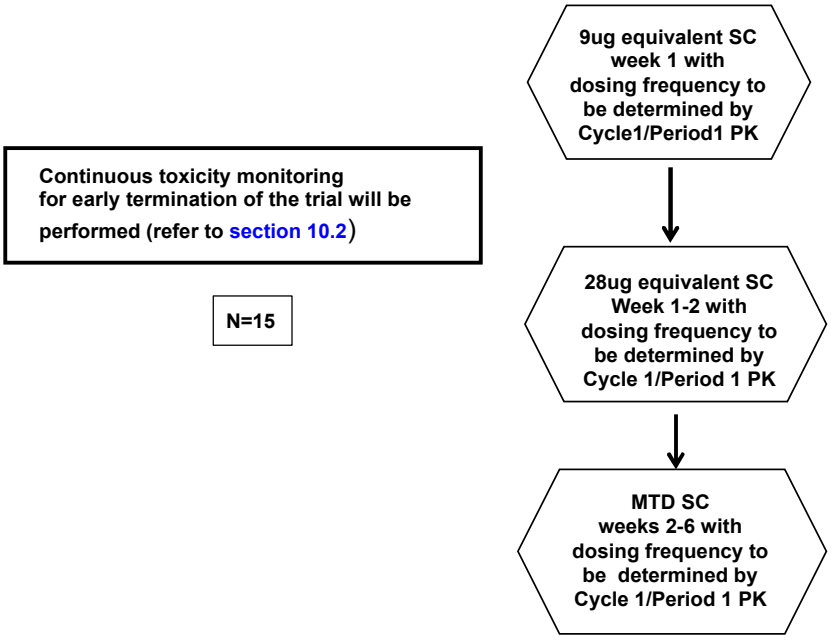


Abbreviations: cIV = continuous intravenous; DLRT = Dose Level Review Team; DLT = dose limiting toxicities; IP = investigational product; PK = pharmacokinetic; SC = subcutaneous; q12h = every 12 hours; q24h = every 24 hours, q48h = every 48 hours, q72h = every 72 hours, q96h = every 96 hours, q7d = every 7 days

**SC dose may be increased (by 1 dose level or between the dose of previous cohort and next higher dosing level), kept at the same dose level or decreased by 1 or more dose levels, and the dose frequency chosen (q12h, q24h, q48h, q72h, q96h, or q7days) will be decided by the DLRT and will be based on the previous cohort PK data.

- If ≥ 2/6 DLT, then an immediate DLRT review will be conducted to determine next steps
- If ≤ 1/6 DLT, then DLRT will be convened and next dose will be tested in a new cohort of subjects as outlined in the protocol

Figure 2. Study Schema for Cycle 1/Period 2



Abbreviations: MTD =maximum tolerated dose; PK = pharmacokinetic; SC = subcutaneous

3.2 Sample Size

Approximately 54 subjects will be enrolled in this study in order to ensure approximately 30 evaluable subjects in Period 1 and up to 15 evaluable subjects in Period 2 are treated with blinatumomab.Subjects may be replaced (replacement rules outlined in protocol Section 3.4). This sample size is based on practical considerations and is consistent with conventional phase 1 oncology studies. If the true DLT rate is 10%, there is a 89% probability of observing ≤ 1 DLT and 11% probability of observing 2 or more DLT in 6 subjects. If the true DLT rate is 30%, the probability of observing ≤ 1 DLT decreases to 42% and probability of observing 2 or more DLT increases to 58%.

Up to 15 evaluable subjects will be enrolled into Cycle1/Period 2 with the planned target treatment dose being the highest tolerable dose regimen or highest tested dose regimen based on the DLRT's recommendations. There will be interim look at the cumulative data in this period and based on the toxicity observed, early termination of the trial in Cycle 1/Period 2 will occur. For example, with 14 subjects receiving AMG 103 SC doses in Cycle 1/Period 1, there is a 17% chance of early termination if the true DLT rate is

20% and with a true DLT rate of 30% increases the chance of early termination to 45% when the sample size is 12. Early termination rules are detailed in section Table 2.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoint

- Subject grade, incidence, and severity of dose limiting toxicities (DLTs) and adverse events

4.1.2 Secondary Endpoints

- Blinatumomab PK parameters under cIV and SC administrations
- MTD
- Incidence of anti-blinatumomab antibodies
- Overall response rate (ORR) (complete response [CR] + partial response [PR]) as determined by best overall response ORR using Cheson criteria (see Appendix B)

4.1.3 Exploratory Endpoint

- PD parameters of B- and T-lymphocytes and cytokines following administration of SC blinatumomab
- ORR (CR + PR) as determined by best overall response using Lugano criteria (see Appendix C)

4.2 Planned Covariates

The relationship of the certain baseline covariates to endpoints will be explored if appropriate. Biomarker data may be incorporated in additional exploratory subgroup or multivariate analyses. The analyses of biomarkers may be performed after collection of all samples during the conduct of the study and therefore may be reported after the final analysis.

5. Hypotheses and/or Estimations

No formal statistical hypothesis will be tested.

The clinical hypothesis is that blinatumomab administered through the SC route will demonstrate a tolerable safety-profile with serum concentrations comparable to those for which efficacy was shown with cIV administration in subjects with indolent relapsed/refractory Non-Hodgkin's Lymphoma (NHL).

6. Definitions

Age at Enrollment

Subject age at enrollment will be collected in years in the clinical database.

Baseline

For the analysis of all endpoints, baseline will be defined as the value measured on day 1 of the first cycle of blinatumomab.. If a day 1 value is not available, the most recent value before the day of the start of any protocol-specified therapy may be used.

Best Overall Response

Best overall response for a subject is determined as ORR (CR+PR) using Cheson (Appendix B) and Lugano criteria (Appendix C) during the Safety Follow-up visit (2 to 4 weeks after the end of therapy for cycle 1). In the case where a second cycle is administered, the assessment has to be done prior to the start of the next cycle to assess the evolution of disease (as close to 2 weeks after the last dose of IP cycle 1, but before starting cycle 2).

Change From Baseline

Change from Baseline is the arithmetic difference between post-Baseline and Baseline values.

Disease Related Events

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease eg, disease progression (Table 3). Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition.

Disease Related Events that do not qualify as Adverse Events or Serious Adverse Events:

- An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a Disease Related Event.
- Death due to the disease under study is to be recorded on the event CRF.

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the IP(s)/study treatment protocol required therapies and disease worsening, this must be reported as an adverse event or a serious adverse event. Table 3 outlines the expected Disease-Related Events by System Organ Class (SOC).

Table 3. Disease-related Adverse Events by System Organ Class

System Organ Class (SOC)	Preferred Terms
Blood and lymphatic system disorders	Lymphadenopathy
General disorders and administration site conditions	Disease progression Fatigue
Investigations	Weight decreased
Skin and subcutaneous tissue disorder	Night sweats

Disease Related Events that would qualify as an Adverse Event or Serious Adverse Event:

- An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an Adverse Event or Serious Adverse Event.

DLT Evaluable

Period 1:

To be evaluable for DLT, subjects must meet one of the following criteria:

- Cohort I and II: received treatment for or at least 8 of the 9 doses or experienced a DLT at any time while receiving blinatumomab.
- Cohort III: treated at least 4 of the 5 doses or experienced a DLT at any time while receiving the target dose of blinatumomab.

If a subject does not experience a DLT during the DLT evaluation period and does not receive all doses (q48h, q72h, q96h, or q7d dosing), at least 4 of the 5 doses (q24h dosing) or at least 8 of the 9 doses (q12h dosing) of subcutaneous Blinatumomab and taken off study for reasons other than toxicity the subject will not be considered DLT-evaluable and will be replaced as described in Protocol Section 3.4.1.

Period 2:

To be evaluable for DLT, subjects must meet one of the following criteria:

- If only cycle 1 is given : experienced a DLT during the entire duration of the SC administrations and 30 days after the last SC dose or treated with blinatumomab targeted dose for 5 days.
- If cycle 2 is given: experienced a DLT during the entire duration of the SC administrations and 16 days following the last SC dose or until the start of cycle 2 (whichever is longer), up to 30 days after the last SC dose or treated with blinatumomab at 112 µg/day cIV for 42 days.

Dose Limiting Toxicity (DLT)

The occurrence of any of the toxicities mentioned in the section 6.2.1.2.3 of the protocol will be considered a DLT, if judged by the investigator to be related to administration of blinatumomab.

ECOG Performance Status Assessment

ECOG performance status assessment will be performed using the ECOG score. For more details please refer appendix C in Protocol.

End of Study for Individual Subject

End of IP Administration for subjects who had blinatumomab is defined as the date the decision was made to end IP as recorded on the End of IP CRF page.

End of Treatment

Defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject.

End of Follow-up

Defined as the date that the last subject completes the last protocol-specified assessment in the study.

Enrollment Date

Enrollment Date is defined as the date of enrollment collected on the CRF.

Subject Level End of Study (EOS) Date

End of study for each subject is defined as the date the subject last completed a protocol-specified procedure. The date will be recorded on the End of Study CRF page.

Investigational Product

The term ‘investigational product’ is used in reference to blinatumomab.

Last Dose Date of Investigational Product

This is the stop date of the last dose of blinatumomab administration reported on the Investigational Product Administration CRF.

Maximum Tolerated Dose (MTD)

MTD will be defined as the highest dose level at which ≤ 1 of 6 subjects experience a DLT. If no subject experiences a DLT, the MTD will be defined as the maximal dose tested.

Optional Cycle 2

A subject may receive a second cycle of blinatumomab administered SC if the subject derived clinical benefit (demonstrated on staging scans) from Cycle 1/Period 2 treatment. If no clinical benefit occurred with SC in Cycle 1/Period 2 then an optional Cycle 2/Period 2 may still be given but will administered as a cIV infusion instead of SC. If blinatumomab is administered as a cIV infusion it will be dosed at 9 µg/day cIV for 7 days for days 1 through day 7, next the dose will be escalated (dose step) to 28 µg/day cIV for 7 days starting on day 8 through day 14, and then advanced to 112 µg/day cIV for 28 days starting on day 15 through day 42.

Percent Change From Baseline

Percent change from Baseline is the arithmetic difference between post-Baseline and Baseline divided by Baseline values times 100.

Screened

A subject is considered in screening once a consent form has been signed.

Study Day 1

Study day 1 is defined as the first day of administration of the investigational product after enrollment. The day prior to Study Day 1 is considered Day -1.

Study Day

Post study day 1: study day= (date - date of Study Day 1) + 1

Pre study day 1: study day= (date – date of Study Day 1)

Study Duration

For an individual subject, the length of participation includes a 14 day screening period, up to a 14 week treatment period (6 weeks for cycle 1 in Period 1 and Period 2 and 6 weeks for the optional Cycle 2, separated by a 14 day treatment free interval), and a safety follow-up visit (30 days [+ 7 days] after the last dose of study treatment).

For subjects who complete the protocol from the date of first dose through optional Cycle 2, the entire duration of the study will take approximately 20 weeks to complete. However, individual study duration will vary depending on administration of a second cycle and tolerability of blinatumomab by an individual subject.

Treatment emergent adverse events (TEAEs)

A treatment emergent adverse event refers to the adverse event that starts on or after first dose of blinatumomab through 30 days after the last dose of blinatumomab. It is indicated by the flag whether an event start before first dose of blinatumomab on the Event CRF page. This reporting window also applies to treatment-emergent serious adverse events (SAEs).

7. Analysis Subsets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Full Analysis Set defined in Section 7.1.

7.1 Full Analysis Set

All subjects who receive blinatumomab are included in the full analysis set (FAS). This definition is in line with the intent-to-treat (ITT) principle in single-arm open-label studies. For the dose escalation part of the study subjects will be analyzed according to the initial blinatumomab dose received. For the dose expansion, subjects will be analyzed according to the dose selected for this part of the study.

7.2 Safety Analysis Set

For each part of the study, the safety analysis set will be the same as the FAS. All other analysis sets will be a subset of FAS.

7.3 DLT Analysis Set

All subjects who are DLT-evaluable are included in this analysis set as defined in section 8.1.1.2

7.4 Pharmacokinetic Analysis Set

All subjects who received any blinatumomab and had at least one PK sample collected will be included in the PK analysis set. These subjects will be evaluated for PK unless significant protocol deviations affect the data analysis or if key dosing, dosing interruption, or sampling information is missing.

7.5 Pharmacodynamic Analysis Set

All subjects who had cytokine and/or lymphocyte subset samples collected at baseline or any time during the study will be included in the PD analysis set.

8. Interim Analysis and Early Stopping Guidelines

8.1 Interim Analysis

Safety data will be reviewed on an ongoing basis using an as-is database snapshot. Amgen, in consultation with the site investigator, will review in DLRT meetings all available accumulating data by multiple subject cohort before making dosing decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and will be fully integrated into all DLRT meetings and considered in all enrollment and dosing decisions.

DLRT meetings will be held to review data, monitor safety, and make dosing decisions.

8.1.1 Dose-cohort Study Escalation and Stopping Rules

8.1.1.1 Dose Level Review Team

The DLRT meeting will be held to review data, monitor safety, and make decisions on dose escalation/change, or changes in pre-medication. The DLRT will be composed of the investigators or designees, and the following Amgen representatives: medical monitor, global safety officer or designee, clinical study manager, biostatistician, PK scientist (optional), and other functional area representatives as appropriate. A quorum as defined below must be in attendance for the DLRT. The quorum is defined as $>$ 50% of the participating investigators (defined as the number of investigators that had subjects enrolled on the cohort for that DLRT meeting) or their qualified designee (ie, sub-investigator or research nurse or study coordinator possessing written documentation [eg, e-mail] of the investigator`s vote), as well as $>$ 50% of Amgen representatives listed above. The medical monitor or designee must attend for the quorum to be reached. The DLRT will be rescheduled if a quorum is not reached.

The following members are responsible for DLRT decisions: investigators, Amgen medical monitor, and global safety officer or designee.

The following decisions may be made by the DLRT:

- dose escalation/de-escalation decisions
- changes in dosing frequency
- expansion of a cohort
- continuation, delay or termination of dosing

All available study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events, vital signs, laboratory data, and PK/PD information will be reviewed. In addition to DLTs, all $\geq$ grade 3 toxicities not

meeting DLT criteria will be reviewed and may be considered in DLRT decisions. Source data and queries do not need to be resolved before the DLRT. Continuous toxicity monitoring for early termination of the trial in Cycle 1/Period 2 will be performed. All adverse events that occur the DLT window will be reviewed and may be considered in DLRT decisions.

8.1.1.2 Dose Limiting Toxicity Rules

Cycle 1/Period 1

The DLT evaluation period includes the entire week 4 (7 days) which is the week that blinatumomab is administered SC during Cycle 1/Period 1 of the study. To be evaluable subjects need to fulfill the criteria described in section 6.

If ≤ 1 of the 6 evaluable subjects in a dose SC cohort experience a DLT during the SC administration, then the dose will be determined to be tolerable and the next dose-cohort level will be initiated in a new dose-cohort of subjects after review by the DLRT.

If ≥ 2 subjects of the 6 evaluable subjects in a SC dose cohort experience a DLT during SC administration then dosing will stop for individual subjects who experience a DLT, a DLRT meeting will be conducted, and further steps will be determined.

Additionally, the DLRT will meet:

- once dose-cohort 1 has completed subcutaneous dosing
- once dose-cohorts 2 and 3 have completed subcutaneous dosing
- once any additional cohorts complete dosing if additional dose-cohorts are tested to determine the MTD in Cycle 1/Period 1

Cycle 1/Period 2

For subjects who receive optional Cycle 2 (cIV dosing period) after Cycle 1/Period 2 (SC dosing period), the DLT evaluation period includes the entire duration of SC administration in Cycle 1 and 16 days following the last SC dose (56 days in total) or until the start of optional Cycle 2, whichever is longer, up to 30 days after the last SC dose of Cycle 1. For subjects who do not receive optional Cycle 2, the DLT evaluation period includes the entire duration of SC administration and 30 days following the last SC dose (70 days in total).Continuous monitoring for early termination of the trial will be performed by DLRT(refer to Section 3.1.3 and Section 8.1.1.).

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 (CDM) department will provide all data to be used in the planned analyses. The database will be subject to edit checks outlined in the Clinical Data Management Plan (DMP). See details of this section in the DMP.

9.3 Handling of Missing and Incomplete Data

The following imputation of missing values will be done:

- Incomplete adverse event and concomitant medication dates will be imputed as per Appendix A
- No data imputation for PK and biomarker data.

9.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations. The clinical study team will identify and document the criteria for important protocol deviations following Amgen SOP.

9.5 Outliers

Details of detecting outliers can be found in the DMP or other data management document. In addition, outliers may be identified via the use of descriptive statistics. All confirmed outlier data will be included in the analyses presented in this statistical analysis plan unless there is sufficient scientific justification to exclude them.

9.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. Data distribution will be explored, if required, data transformations or alternative non-parametric methods of analyses will be utilized.

9.7 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 version 9.4.

10. Statistical Methods of Analysis

10.1 General Principles

Descriptive statistics will be provided for selected demographics, safety, immunogenicity, PK, PD, and biomarker data. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Data will be summarized by dose cohort and by time as appropriate. Graphical summaries of the data may also be presented. When data are summarized by time, the scheduled time points listed in the protocol will be used). For statistical analyses comparing change from baseline, only subjects with both baseline and at least one post-baseline assessment will be included. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used.

The final analysis will be triggered when target enrolment is complete, and all subjects complete the study or withdraw from the study. The data will be analyzed once they have been entered, cleaned, and locked.

10.2 Subject Accountability

The number and percent of subjects who were screened, enrolled, received at least one dose of blinatumomab, completed investigational product, discontinued from investigational product (including reasons for discontinuing),completed study, discontinued the study (including reasons for discontinuing) will be summarized overall and by dose cohort.

Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented.

A subject listing and summary noting inclusion in each analysis subset will be provided for all subjects enrolled. A subject listing noting, reason for discontinuation of treatment, and reason for discontinuing the study will be provided. A list of subjects screened but not enrolled (screen failures) will be provided.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. If a snapshot is being taken during the study rather than a database lock at the end of the study, categories should be 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. Eligibility deviations are defined in the protocol. The final IPD list is used to produce the list of subjects with IPDs. In addition, a separate listing of all inclusion and exclusion deviations will be provided.

10.4 Demographic and Baseline Characteristics

Demographic (ie, age, age groups [18-64, 65-74, 75-84 and >= 85], sex, race, ethnicity) and baseline characteristics will be summarized by dose cohort and overall using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple race as well as by the combination of race.

The baseline characteristics to be summarized include:

- Height
- Weight
- NHL Subtype: FL, Marginal zone lymphoma, Lymphoplasmocytic lymphoma, MCL and Small lymphocytic lymphoma
- Line of Previous Therapies: 1st line, 2nd line, 3rd line, 4th line and Other

A listing of Non-Hodgkins Lymphoma Medical History will be provided.

10.5 Safety Analyses

Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the full analysis set, which includes subjects that are enrolled and received at least 1 dose of blinatumomab.

10.5.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or later will be used to code all adverse events to a system organ class and a preferred term.

The severity of each adverse event will be graded using CTCAE version 4.0 criteria. Subject incidence of treatment emergent events and treatment related treatment emergent events will further be summarized by worst severity grade.

Subject incidence of all treatment emergent, serious treatment emergent, treatment related, serious treatment related, those leading to withdrawal of investigational product or other protocol-required therapies, and fatal adverse events will further be tabulated by system organ class and preferred term for each dose cohort in descending order of frequency. The above adverse event tables will include disease related events and will not be created if two or fewer subjects in the study experience the adverse event. Similar summaries will be repeated for EOIs. Time to onset and duration of selected EOIs (infection and neurologic events) may also be summarized.

Subject incidence of disease related events and fatal disease related events will be tabulated by system organ class and preferred term for each dose cohort. All DREs and fatal DREs would be tabulated by system organ class and preferred term separately.

DREs should be included with AEs in any submission datasets, integrated summaries and in CTD reporting.

Tables with AEs as above will be produced for period 1 for SC and cIV dosing separately.Listings of any on-study deaths, including early withdrawals due to adverse events will be provided should they occur.

10.5.1.1 Dose Limiting Toxicities

The analysis of dose limiting toxicities (DLT) will be based on the DLT Analysis Set defined in Section 7.3. A listing and summary of the subject incidence of dose limiting toxicities (DLT) during period 1 will be provided should they occur.

10.5.2 Laboratory Test Results

10.5.2.1 Chemistry, Hematology and Coagulation

Individual chemistry, hematology and coagulation laboratory data will be listed and may also be plotted for selected parameters. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. CTCAE grades will also be highlighted where appropriate. Unscheduled assessments will be incorporated in the laboratory analyses where possible.

The number and percentage of subjects experiencing treatment emergent laboratory toxicities with worst post dose CTCAE grades of ≥ 1, ≥ 2, ≥ 3 and 4 will be presented. The direction of the laboratory worsening will be denoted. The summary will be presented for all laboratory parameters for which at least one subject experienced a treatment emergent toxicity with a worst grade ≥ 3.

Additionally, the number and percentage of subjects experiencing 1, 2, 3 and 4 worsening CTCAE grade shifts from baseline will be presented. The direction of the laboratory worsening will again be denoted.

Shifts tables indicating the change between the baseline and the maximum post dose CTCAE grades for an increased value, and the maximum post dose grade for a decreased value will be provided for selected laboratory parameters of interest.

A listing of CTCAE grade 3 or higher laboratory toxicities will be provided. This listing will include all laboratory data for the subject and laboratory parameter of interest in order to provide proper context. A flag will indicate the grade 3 or higher toxicity.

Summaries of the absolute value and/or changes from baseline at each scheduled assessment will be provided for selected laboratory parameters of interest.

A summary of the change from baseline to the post dose maximum, time to post-dose maximum, change from baseline to the post dose minimum, and the time to the post dose minimum may also be provided for selected parameters of interest.

10.5.2.2 Urinalysis

Individual urinalysis data will be listed.

Blood, protein and glucose will be graded in the following manner: 0=’0 or Trace’, 1=’1+’, 2=’2+’, 3=’3+’, 4=’4+’. The number and percent of subjects by worst post-dose levels will be presented for blood, protein and glucose in the urine).

10.5.3 Vital Signs

Vital signs data will be reviewed for each subject. Depending on the size and scope of the changes, the analyses of vital signs may include summary statistics over time and/or changes from baseline over time by dose cohort.

10.5.4 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG performance status scores will be summarized at each assessed time point. The change in scores from screening to safety follow-up (end of study) or last post-baseline value (if safety follow-up is not available) will also be summarized.

10.5.5 Antibody Formation

The presence of anti-blinatumomab binding antibodies will be assessed using a validated assay. The incidence of anti-blinatumomab antibodies will be listed for each subject. The number and percentage of subjects who have developed

anti-blinatumomab antibodies (binding and if positive, neutralizing) at any time, at baseline and during post-baseline visits will be summarized by dose cohort.

10.5.6 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by dosing schedule for cIV and SC separately. The number of cycles, number of doses of investigational product and the total dose in µg will be summarized.

Details for each blinatumomab administration will be listed for every subject. In addition, a listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

10.5.7 Exposure to Concomitant Medication

All medication will be coded using the WHO drug dictionary. A subject listing of all prior and concomitant medications will be presented.

10.6 Efficacy Analyses

Statistical analyses of efficacy endpoints will be considered secondary. Efficacy data will be conducted on the Full Analysis Set.

10.6.1 Analyses of Secondary Efficacy Endpoint(s)

The efficacy endpoint of the study is ORR (CR+PR) after blinatumomab treatment based on Chesons' 2007 criteria (Appendix B). The analysis is based on the response evaluation recorded in the CRF for subjects in the full analysis set. Subjects will be considered as non-responders if there is no response assessment available. The rate will be estimated along with its 95% Clopper-Pearson exact confidence interval by dose group and overall. Subject listings with related collected parameters will also be provided.

Summary of other best responses status by each response category will be also provided. The number and percentage of subjects with a disease response of complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) will be presented for the dose escalation and/or expansion parts of the study.

Subject listings with related collected parameters will also be provided.

10.6.2 Analyses of Exploratory Endpoints

Overall Response Rate (CR+PR) after blinatumomab treatment based on Lugano criteria (Appendix C) will be presented using the same methods as the secondary ORR endpoint.

Graphical summaries of changes from baseline over time in biomarker levels may be provided. Association between baseline levels or presence of tumor biomarkers will be explored graphically for ORR and PD effects.

10.7 Pharmacokinetic Analysis

The PK analysis will be based on the PK analysis set described in section 7.4. Blinatumomab serum concentration-time data will be used to determine the PK parameters under cIV and subcutaneous administration, respectively, using non-compartmental methods and will be listed for individual subjects. All concentration values below the quantifiable limits were set to zero before pharmacokinetic analysis. Actual dose and actual sampling time will be used for PK analysis. Summary statistics, including mean, standard deviation, median (range), geometric mean and CV% of geometric mean will be computed for each pharmacokinetic parameter and grouped by dose, period and route of administration. Individual concentration-time data will be tabulated and presented graphically. Mean concentration-time profiles for each dose will be provided.

The following PK parameters will be estimated:

- The steady state serum concentration (C_{ss}) under continuous IV infusion (cIV), summarized as the observed concentrations collected after 5 half-lives after the start of the IV infusion of each dose (ie, 9, 28 and 112 µg/day).
- Systemic clearance (CL) following cIV; calculated as $CL=R_0/C_{ss}$; where R_0 is the infusion rate (µg/hr) and C_{ss} is the average C_{ss}. Both R_0 and C_{ss} were dose-normalized to 112 µg/day for this calculation.
- The maximum observed blinatumomab concentration (C_{max}) after subcutaneous administration
- The time (t_{max}) at which C_{max} occurred after subcutaneous administration
- The area under the concentration-time curve (AUC) after the first and the last subcutaneous doses for a dosing interval τ ($AUC\tau$); estimated using the linear trapezoidal method; where τ is a dosing interval (eg, 12 hr or 24 hr)
- C_{min}, defined as trough concentration at 12 hrs for q12h regimen or at 24 hrs for q24h regimen after subcutaneous administration
- The apparent clearance (CL/F) after subcutaneous dosing; calculated as $CL/F = Dose_{sc} / AUC\tau_{-ss}$ (at steady state)
- The volume of distribution based on terminal phase (V_z/F) after subcutaneous administration; calculated as $V_z/F=CL/F / \lambda_z$, where λ_z was the first-order rate constant estimated via linear regression of the terminal log-linear decay phase as determined from the noncompartmental analysis

- Terminal half-life ($t_{1/2,z}$) after subcutaneous administration; calculated as $t_{1/2,z} = \ln(2) / \lambda_z$
- Accumulation ratio after subcutaneous administration, calculated as the ratio of AUCτ (last dose) / AUC (first dose)
- Bioavailability (F); calculated as F = (CL * $AUC_{\tau\text{-ss}}$) / $Dose_{sc}$

10.8 Pharmacodynamic Analysis

Time profiles of pharmacodynamic markers (eg, T-cell, B-cell, cytokines) may be provided if data are sufficient. Mean (SD) peak (eg, cytokine) or trough concentrations (eg, B-cells) of pharmacodynamic markers will be summarized with descriptive statistics by dose level, cohort and route of administration. Time to reach peak or trough concentrations of pharmacodynamic markers may be summarized by dose, cohort and route of administration.

11. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

12. Literature Citations / References

Cheson B, Pfistner B, Juweid M, et al. Revised response criteria for malignant lymphoma. Jour of Clin Oncol 2007;25(5):579-586.

Cheson B, Fisher R, Barrington, S, et al. Recommendations for initial evaluation,staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The LuganoClassification. Jour of Clin Oncol 2014;32(27):3059-3068.

Clopper CJ, Person ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika.* 1934;26:404-413.

Thall PF, Simon RM, and Estey EH. Bayesion sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat. Med. 1995 Feb 28; 14(4):357-79.

13. Prioritization of Analyses

There is no prioritization of analyses.

14. Data Not Covered by This Plan

Exploratory data not included in this plan may be analyzed at a later date or may be analyzed by a different Amgen Department.

15. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures

Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. 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 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial.

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. 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 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial.

		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		
Start Date		<1st Dose	≥1st Dose	<1st Dose yyyymm	≥1st Dose yyyymm	<1st Dose yyyy	≥1st Dose yyyy	Missing
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

Note:

- For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.
- If the start date imputation leads to a start date that is after the stop date, then do not impute the start date

Appendix B. Modified Cheson Criteria for Evaluation of Extramedullary Disease

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	• FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET • Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Appendix C. Response Assessment Per the Lugano Classification

5- point scale

1, no uptake above background;

2, uptake ≤ mediastinum;

3, uptake > mediastinum but ≤ liver;

4, uptake moderately > liver;

5, uptake markedly higher than liver and/or new lesions;

X, new areas of uptake unlikely to be related to lymphoma.

Response	**Complete Response**	**Partial Response**	**Stable Disease**	**Progressive Disease**
PET-CT Response	**Complete Metabolic Response**	**Partial Metabolic Response**	**No Metabolic Response**	**Progressive Metabolic Disease**
Target Masses	Score 1, 2, or 3 with or without a residual mass	Score 4 or 5 reduced uptake compared with baseline residual mass(es) of any size	Score 4 or 5 no significant change in FDG uptake from baseline	Score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma
New Lesions	None	None	None	New FDG-avid foci consistent with lymphoma rather than another etiology
Bone Marrow	No FDG avid focal lesions	Residual uptake higher than uptake in normal marrow but reduced compared with baseline	No change from baseline	New or recurrent FDG-avid foci

Appendix D. Code Fragments

Provisional Code Fragments for calculating a confidence interval using the Clopper Pearson Method. The following example SAS code will be utilized for the response rate analysis providing the proportion of subjects responding to treatment with corresponding 95% confidence intervals.

```
proc freq data=<dataset> ;
  tables <response variable> / binomial (exact) alpha=.05;
run;
```

Appendix E. Reference Values/Toxicity Grades

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used and is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix F. DLRT Output List

Following analyses will be done by Biostatistical Science group and the output will be sent to Clinical Study Manager by a pre-defined timeline. In addition to the following list PK data is essential for the DLRT decision making which will be provided from PK group. Also, if available Antibody, Cytokine and Lymphocyte subset data will also be presented in DLRT.

Listings:

For each cohort, following data listings will be provided in an Excel spreadsheet where each listing will be included in a separate worksheet.

1. Subject demographics
2. Date, time, dose of investigational product administration
3. Vital signs
4. Reported adverse events (AEs)
5. Safety laboratory data (Chemistry, Hematology, Urinalysis, Coagulation)
6. Medical history
7. Concomitant medications
8. Prior therapy data

Figures:

Following line plots will be presented for each individual subject:

1. Line plot of vital signs by time course
2. Line plot of all safety labs (Chemistry, Hematology, Urinalysis) by time course