Statistical Analysis Plan

NCT Number: NCT05442554

Title: A Phase 4, Single Arm, Open Label, Multicenter Study of Brentuximab Vedotin Treatment of Chinese Patients With CD30-Positive Cutaneous T-Cell Lymphoma

Study Number: C25029

Document Version and Date: Version 1.0, 13 Jul 2022

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STATISTICAL ANALYSIS PLAN

Study Number: C25029

Study Title: A Phase 4, Single Arm, Open Label, Multicenter Study of Brentuximab Vedotin Treatment of Chinese Patients With CD30-Positive Cutaneous T-Cell Lymphoma

Phase: Phase 4

Version: Final 1.0

Date: 13-Jul-2022

Prepared by: [redacted]

Based on: A Phase 4, Single Arm, Open Label, Multicenter Study of Brentuximab Vedotin Treatment of Chinese Patients With CD30-Positive Cutaneous T-Cell Lymphoma

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Date

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Date

Approved by: [redacted]
[redacted], Clinical Biostatistics

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Final 1.0		[Not Applicable]

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BSA	Body Surface Area
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DOR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
GRS	Global Response Score
HLT	High Level Term
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
IRC	Internal Review Committee
KM	Kaplan-Meier
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis Fungoides
mSWAT	Modified Severity Weighted Assessment Tool
NCI	National Cancer Institute
OC	Observed Cases
ORR	Objective Response Rate
OS	Overall Survival
pcALCL	Primary Cutaneous Anaplastic Large Cell Lymphoma
PD	Progressive Disease/Disease Progression
PET	Positron Emission Tomography
PK	Pharmacokinetic
PML	Progressive Multifocal Leukoencephalopathy
PR	Partial Response
PRO	Patient-Reported Outcomes
PT	Preferred Term
Q1	25th Percentile
Q3	75th Percentile

QOL	Quality of Life
SAE	Serious Adverse Event
sALCL	Systematic Anaplastic Large Cell Lymphoma
SAP	Statistical Analysis Plan
SD	Stable Disease
SMQ	Standardised Meddra Queries
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

The primary objective is to determine the objective response rate (ORR) lasting at least 4 months with brentuximab vedotin in patients with CD30+ MF or pcALCL.

1.1.2 Secondary Objective(s)

- To determine the complete response (CR) rate with brentuximab vedotin.
- To determine the ORR with brentuximab vedotin.
- To assess the Duration of response (DOR) with brentuximab vedotin.

1.1.3 Safety Objective(s)

- To assess the safety of brentuximab vedotin.

1.1.4 Additional Objective(s)

Not applicable.

1.2 Endpoints

1.2.1 Primary Endpoint(s)

The primary efficacy endpoint for this study is the ORR lasting at least 4 months (ORR4) with brentuximab vedotin in Chinese patients with CD30+ MF or pcALCL.

1.2.2 Secondary Endpoint(s)

1.2.2.1 Secondary Endpoints(s)

The secondary efficacy endpoints are:

- CR rate with brentuximab vedotin.
- ORR with brentuximab vedotin.
- Duration of response with brentuximab vedotin.

1.2.2.2 Other Secondary Endpoint(s)

Not applicable.

1.2.3 Exploratory Endpoint(s)

Not applicable.

1.2.4 Safety Endpoints

The secondary safety endpoints are:

- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs).
- Changes from baseline in the patient's vital signs.
- Eastern Cooperative Oncology Group (ECOG) performance status.
- Clinical laboratory results.

1.2.5 Other Endpoints

Not applicable.

1.3 Estimand(s)

Not applicable.

2.0 STUDY DESIGN

This is a phase 4, open-label, single-arm, multicenter, postapproval commitment study to be conducted in China. All patients must have histologically-confirmed CD30+ MF or pcALCL by local pathology assessment. CD30+ is defined as ≥ 10% target lymphoid cells demonstrating membrane, cytoplasmic, and/or Golgi staining pattern for CD30 at any intensity above background staining as noted on the corresponding negative control. Patients will receive treatment with brentuximab vedotin monotherapy on Day 1 of each 21-day cycle for up to 16 cycles total.

Objective response over the course of the study, per investigator assessment, will be assessed by global response score, which consists of skin evaluation (a modified severity weighted assessment tool [mSWAT]), nodal and visceral radiographic assessment, and detection of circulating Sezary cells (MF only). Objective response will be evaluated at the end of Cycles 3, 6, 9, 12, and 15, and at the end of treatment (EOT) visit.

Approximately 10 evaluable patients will be enrolled and dosed in this study from approximately 3 to 5 study centers in China.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

Not Applicable.

4.0 SAMPLE-SIZE DETERMINATION

Per China Health Authority requirement, approximately 10 evaluable patients with CD30+ MF or pcALCL are needed for this post approval commitment study.

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The safety analysis set will consist of all enrolled patients who receive at least 1 dose of study

drug.

5.2 Full Analysis Set

Full analysis set (FAS) is defined as all enrolled patients identified as CD30 positive and received at least 1 dose of the study drug. FAS will be used for the primary and secondary efficacy analyses unless specified otherwise.

5.3 Response-evaluable set

The response-evaluable population will include a subset of the FAS patients with measurable disease at baseline and with at least 1 post-baseline response assessment. Patients who were discontinued due to death before a post-baseline evaluation happens, will be used for analyses of response.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

There is no pre-planned hypothesis testing for this study. Analysis for this study will mostly be descriptive. 2-sided 95% confidence intervals will be presented, where applicable.

Where applicable, variables will be summarized descriptively by study visit. For the categorical variables, the counts and proportions of each possible value will be presented. The denominator for the proportion will be based on the number of subjects who provided non missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated. For time-to-event variables, the summary statistics will include median time to event-free survival, 25th and 75th percentiles and number of patients at risk at specified time points.

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified.

6.2 Disposition of Subjects

The disposition of patients includes the number and percentage of patients for the following categories: patients treated (safety population), patients in the FAS population, patients in the Response-Evaluable population, patients discontinued from study treatment, and patients discontinued from the study. All percentages will be based on the number of patients treated.

The primary reason for study and treatment discontinuation will also be summarized in this table.

A listing will present data concerning patient disposition.

A by-subject listing of protocol deviations will be provided.

Patient eligibility including inclusion criteria that are not met and exclusion criteria that are met at enrollment will be summarized for all enrolled patients.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all patients treated. Baseline demographics and baseline characteristics to be evaluated will include age, gender, race, height, weight, body surface area (BSA), primary diagnosis (MF or pcALCL), Eastern Cooperative Oncology Group (ECOG) performance status (0, 1, 2), Ann Arbor staging and other parameters as appropriate.

The formulation for BSA is:

BSA = sqrt(height(cm) x weight (kg) / 3600).

No inferential statistics will be generated.

6.3.2 Medical History

Medical history will be listed for all patients.

6.4 Prior Medications and Concomitant Medications

6.4.1 Prior Medications

Prior medications are defined as the medication(s) used during screening phase but discontinued prior to the first dose of study drug.

Prior medications will be coded by generic term using World Health Organization (WHO) Drug Dictionary. The number and percentage of normal subjects taking concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug generic term. Prior medications will also be listed for all patients.

6.4.2 Concomitant Medications

Concomitant medication is defined as a medication where any amount of drug was taken between the first day of study drug and 30 days after the last dose of study drug.

Concomitant medications will be coded by generic term using World Health Organization (WHO) Drug Dictionary. The number and percentage of normal subjects taking concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug generic term. Concomitant medications will also be listed for all patients.

Concomitant procedures will not be coded but will be presented in a data listing.

6.5 Efficacy Analysis

All efficacy evaluations will be conducted using the FAS population unless specified otherwise.

The response-evaluable population will be used for the sensitivity analyses of ORR4, CR rate, ORR and duration of response, as needed.

6.5.1 Primary Endpoint(s) Analysis

6.5.1.1 Derivation of Endpoint(s)

The primary endpoint of this study is ORR4. ORR4 is defined as the proportion of patients achieving an objective response that lasts at least 4 months (i.e., duration from first response to last response is ≥ 4 months) on study.

Patients whose first response occurs after the start of subsequent anti-cancer therapy but otherwise meet the primary endpoint criteria will be excluded from numerator.

For objective response, a patient must achieve a CR or PR. The objective response will be considered maintained for patients with a previous CR who experience recurrent disease (i.e. Relapse) unless the criteria for progressive disease are met. Determination of objective response will be based on a global response score (GRS), which consists of skin evaluation (mSWAT assessment) by investigator, nodal and visceral radiographic assessment, and detection of circulating Sezary cells (MF only).

GRS will be assessed at the end of Cycles 3, 6, 9, 12, and 15 (Days 16-21 or before dosing on Day 1 of the subsequent cycle), at EOT. GRS will be determined based upon the most recent disease assessments for each component (mSWAT, CT scans, Sezary cell count for MF patients). For patients without baseline nodal/visceral involvement, the nodal/visceral response component should be based upon the most recent CT scan findings before the GRS assessment time point. Additional unscheduled GRS determinations may occur following a change in response in skin or at the time of a CT scan. Relapse will be categorized in the study endpoints definition as recurrent disease in patients with complete response.

6.5.1.2 Main Analytical Approach

The count, proportion as well as the 95% CI of the ORR4 will be presented. No imputation will be conducted for missing data. Patients who do not have any post baseline response assessment as specified in the protocol, or patients who have no response before dropout, will be counted as non-responders.

6.5.1.3 Sensitivity Analysis

Sensitivity analysis will be performed using Response-Evaluable population to assess the robustness of the primary analysis.

6.5.1.4 Supplementary Analyses

Not applicable.

6.5.2 Secondary Endpoint(s) Analysis

CR rate, ORR, and DOR are designated as secondary endpoints.

6.5.2.1 Derivation of Endpoint(s)

CR rate is defined as the proportion of patients who achieved a CR as their best response on study.

Overall response rate (ORR) is defined as the proportion of patients who achieve CR or PR on study.

Duration of response (DOR) is defined as the time between first documentation of response and PD (or death in the absence of disease progression).

6.5.2.2 Main Analytical Approach

CR and ORR will be analyzed in a similar fashion as the primary endpoint.

No imputation will be conducted for missing data. Patients who do not have any post baseline response assessment as specified in the protocol will be counted as non-responders. Patients whose first response occurs after the start of subsequent anti-cancer therapy but otherwise meet the primary endpoint criteria will be excluded from numerator.

DOR will be summarized using the Kaplan-Meier method with the associated 95% CIs when estimable. The analysis of DOR will only include responders. Patients who are lost to follow-up, withdraw consent, or discontinue treatment due to undocumented PD after the last adequate disease assessment will be censored at the last disease assessment.

If the patient starts new antineoplastic therapy before PD, the patient is treated as progressed at the date of assessment at which PD was documented.

If death or PD occurs after a missed visit, then the patient is treated as progressed at the date of death or PD. Patients without baseline and/or no sufficient post baseline data for disease assessment and with no death recorded will be censored at the date of the first dose. If PD is documented between scheduled visits, then the date of the documented PD is the date of progression.

6.5.2.3 Sensitivity Analysis

Sensitivity analyses will be performed for CR, ORR and DOR based on the Response-Evaluable population.

6.5.2.4 Supplementary Analyses

Not applicable.

6.5.3 Other Secondary Endpoints Analysis

Not applicable.

6.5.4 Subgroup Analyses

Not applicable.

6.6 Safety Analysis

Safety evaluations will be based on the incidence, severity, type of adverse events (AEs), clinically significant changes, or abnormalities in the subject's physical examination, vital signs, ECOG performance status, and clinical laboratory results.

These analyses will be performed using the safety population.

6.6.1 Adverse Events

6.6.1.1 Adverse Events

Treatment-emergent AEs (TEAEs) will be tabulated by primary System Organ Class (SOC), High Level Term (HLT), and Preferred Term (PT). A TEAE is defined as any AE that occurs after administration of the first dose of study drug and up through 30 days after the last dose of study drug. AEs will be tabulated according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) by SOC, HLT, and PT and will include the following categories:

- TEAEs
- Study drug-related TEAEs
- Grade 3 or higher TEAEs
- Grade 3 or higher drug-related TEAEs
- TEAEs leading to study drug modification and discontinuation.
- Serious AEs (SAEs), including study drug-related SAEs
- AEs of peripheral neuropathy identified by the broad search MedDRA SMQ "Peripheral neuropathy"

Additional analyses of peripheral neuropathy may also be presented.

6.6.1.2 Serious Adverse Events

The number and percentage of subjects experiencing at least 1 treatment-emergent SAE will be summarized by MedDRA primary SOC, HLT, and PT.

In addition, a by-subject listing of the SAEs will be presented.

6.6.1.3 Deaths

A by-subject listing of the deaths will be presented. A summary of deaths will be provided with number and percentage of patients.

6.6.1.4 Adverse Events Resulting in Discontinuation of Study Drug

A by-subject listing of AEs resulting in discontinuation of study drug will be presented.

6.6.1.5 Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a nonnumeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

If a subject has repeated laboratory values for a given time point, the value from the last evaluation will be used.

All laboratory data recorded in the eCRF will be listed.

The actual values in clinical laboratory parameters (hematology and serum chemistry) will be summarized at baseline and over time; summary statistics for change from baseline in laboratory parameters will also be presented.

In addition, hematology and serum chemistry parameters will be summarized in shift tables comparing the baseline visit to the worst post baseline value (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] grade, version 5.0 for the following parameters if applicable.

- Hematology: hemoglobin, platelet count, neutrophils (absolute neutrophil count [ANC]), lymphocyte counts, and leukocyte counts
- Chemistries: bilirubin (total), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), amylase, and lipase.

Urinalysis results will be presented in a listing.

6.6.1.6 Electrocardiograms

Electrocardiogram results will be presented in a listing.

6.6.1.7 Vital Signs

The actual values of vital sign parameters, including blood pressure, heart rate, temperature and weight when available, will be summarized over time.

6.6.1.8 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status and change from baseline will be summarized. Shifts from baseline to the worst postbaseline score will be tabulated. Patients who have ECOG performance scores that worsen postbaseline compared to baseline will be listed with other pertinent patient information.

6.6.2 Other Safety Analysis

Pregnancy testing results will be presented in a by-subject listing.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of study drugs.

6.6.3 Extent of Exposure and Compliance

The exposure to study drug will be characterized by total amount of dose taken in mg, total number of dose taken, number of treated cycles, duration of treatment, numbers and percentages of patients in treated cycle categories (1, 2⋯,16), and dose intensity (mg/week).

Dose intensity (mg/week) will be calculated as total dose administered (mg)/(3 * number of treated cycles) where a treated cycle is defined as a 21-day period during which the patient received any amount of brentuximab vedotin (scheduled for a single dose in a 21-day cycle). The duration of treatment is defined as time from the first study dose to 21 days after the last study dose ([last dose date + 21] – first dose date) of brentuximab vedotin.

Relative dose intensity (%) will be calculated as (Total Dose Administered/Total Dose Expected) * 100 and summarized.

All extent-of-exposure data will be summarized as continuous variables in the safety population. Study drug administration and exposure information will also be presented in a by-subject data listing.

6.6.4 Treatment Modifications

Action on study drug (including dose reduction) will be summarized by cycle, and overall.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

Not applicable.

6.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

Not applicable.

6.9 Other Analyses

Not applicable.

6.10 Interim Analyses

No interim analysis is planned.

6.11 Data Monitoring Committee/Internal Review Committee

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- Mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value, and minimum and maximum values will be presented to the same number of decimal places as the measured value. If the measured value is large (eg, > 100), fewer decimal places may be displayed.
- CIs intervals will be presented using the same number of decimal places as the parameter estimate.
- Percentages will be rounded to one decimal place;
- All p-values reported will be 2-tailed and rounded to 3 decimal places prior to assessment of statistical significance. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999."
- 1 month = 30.4375 days. Month is calculated as (days/30.4375) rounded to 1 decimal place;
- 1 year = 365.25 days. Year is calculated as (days/365.25) rounded to 1 decimal place.

9.2.2 Definition of Baseline

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but before, the start of study drug administration.

9.2.3 Definition of Visit Windows

All data will be categorized based on the scheduled visit at which they were collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

9.3 Analysis Software

SAS version 9.4 (or higher) will be used for all analyses.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	14-Jul-2022 15:06 UTC
[redacted]	Biostatistics Approval	15-Jul-2022 01:33 UTC