TRANSLATIONAL STATISTICAL ANALYSIS PLAN KTE-C19-108
TRANSLATIONAL ANALYSIS

Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Product Name:	KTE-X19
Protocol Title:	A Phase 1 Multicenter Study Evaluating the Safety and Tolerability of KTE-X19 in Adult Subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
Protocol Number	KTE-C19-108 (ZUMA-8)
Version Number:	Version 1.05
Release Date:	24 September 2021
Replaces Previous Version(s):	

CONFIDENTIALITY NOTICE

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LIST OF ABBREVIATIONS

AUC	Area under the curve
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CRP	C-reactive protein
CRS	Cytokine release syndrome
CXCL	C-X-C motif chemokine ligand
ddPCR	Droplet digital polymerase chain reaction
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ICAM	Intercellular adhesion molecule
IFN	Interferon
IL	Interleukin
LOQ	Limit of quantification
LYMLE	Lymphocyte (%)
MONOLE	Monocyte (%)
MRD	Minimal residual disease
MTD	Maximum toxicity dose
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamics
PK	Pharmacokinetic
SAP	Statistical analysis plan
TNF	Tumor necrosis factor
TSAP	Translational statistical analysis plan
VCAM	Vascular cell adhesion molecule
WBC	White blood cell count

1. INTRODUCTION

This translational statistical analysis plan (TSAP) outlines the analyses to be conducted for pharmacokinetics (PK) (levels of anti-CD19 CAR T cells), pharmacodynamics (levels of cytokines and other key analytes) and product characteristics data for Study KTE-C19-108 (ZUMA-8) titled "A Phase 1 Multicenter Study Evaluating the Safety and Tolerability of KTE-X19 in Adult Subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma", as described in protocol amendment 3 dated 01 September 2021.

2. OBJECTIVES

2.1. Objectives

- Characterize the anti-CD19 CAR T cell expansion (PK)
- Characterize profile for selected serum cytokines (PD)
- Characterize the product characteristics
- Characterize Minimal Residual Disease (MRD) data for bone marrow and peripheral blood samples

2.2. Hypothesis

The analyses outlined in this TSAP are CCI and no formal pre-specified hypothesis will be tested.

3. ENDPOINTS, SUBGROUPS AND COVARIATES

3.1. Datasets to be Included

Table 3-1. Data Overview on Assay Methods and Biomarker Lists

Data type	Assay Method/ Sample type	Biomarker Set	Assessment Time Points
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	CCI [redacted]
Product characteristics		Total T Cells (10^6), CD3 Cells (total number and %), CD4 Cells (total number and % of viable CD3+ cells), CD8 Cells (total number and % of viable CD3+ cells), CD4/CD8 Ratio, Central Memory Cells (total number and % of viable CD3+ cells), Effector Cells (total number and % of viable CD3+ cells), Effector Memory Cells (total number and % of viable CD3+ cells), Interferon Gamma level (pg/mL), Naïve Cells (total number and % of viable CD3+ cells), Total CAR+ T cells (10^6), Transduction Rate (%), Viability (%), Vector Copy Number, CCR7+ (Tnaive + Tcm) % and number, CCR7- (Tem + Teff) % and number.	
CCI [redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAR, chimeric antigen receptor; CD, cluster of differentiation; CRP, C-reactive protein; CXCL, C-X-C motif chemokine; ICAM, intercellular adhesion molecule; CCI [redacted]; CCI [redacted]; CCI [redacted]; CCI [redacted].

3.2. Endpoints

- Levels of anti-CD19 CAR T cells in blood samples measured as anti-CD19 CAR+ cells/µL by visit, peak, area under the curve (AUC) (from infusion to Day 28), and time-to-peak (details for the derivations are included in the definition Section 4.2)

- Levels of cytokines in serum by visit, change from baseline at Day 0, Day 1, Day 4 and Day 7, fold change from baseline at Day 0, Day 1, Day 4 and Day 7, peak, Day 0 – Day 28 AUC, and time to peak (details for the derivations are included in the definition Section 4.3)

- Product attributes measurements after product manufacturing and prior to dosing

- Levels of CLL of nucleated cells and of CD45+Lymphocytes by visit, Screening, Bridging Chemotherapy, Day 28, Month 3

3.3. Outcomes, Subgroups, and Covariates

No outcomes, subgroups and covariates will be used for analyses in this TSAP.

4. DEFINITIONS

4.1. General

Study Day 0: defined as the day the subject received the first KTE-X19 infusion.

Baseline: the baseline value is defined as the last value taken prior to first dose of conditioning chemotherapy. If the enrolled subjects do not receive conditioning chemotherapy, the baseline value is defined as the last value taken prior to enrollment/leukapheresis.

4.2. Key Measurements of Anti-CD19 CAR+ T Cell

The presence, expansion, and persistence of anti-CD19 CAR T cells in peripheral blood will be measured by ddPCR analysis.

Scheduled blood draw for anti-CD19 CAR T cell: This TSAP will focus on the anti-CD19 CAR T cell data collected as per planned assessment, based on the analysis visits defined in Appendix Section 7.1.

Baseline number of anti-CD19 CAR T cells (cells/ µL) is defined as 0 before the KTE-X19 infusion on Day 0, and number of CAR T (cell/µL) will not be derived.

Number of anti-CD19 CAR T (cells/ µL) derivation:

Derivation 1

- Alpha = (CAR /µg DNA at timepoint) / 162,000
- Beta = (CAR /µg DNA of product / 162,000) / % Transduction (by flow of product)
- Optimized % CAR+ PBMC = (Alpha/Beta)
- Number of anti-CD19 CAR T (cells/µL blood) is defined as:

1000(WBC [10^9/L])*(MONOLE [%] + LYMLE [%])/100*Optimized %CAR+PBMC*

Peak of anti-CD19 CAR T cell (cells/ µL blood) is defined as the maximum absolute number of anti-CD19 CAR T (cells/ µL) in serum attained after Day 0.

Time to Peak of anti-CD19 CAR T cell is defined as the number of days from Day 0 to the day when the peak of anti-CD 19 CAR T cell was attained as "Peak date – KTE-X19 Dosing date + 1."

Area-Under-Curve (AUC) of level of anti-CD19 CAR T cell (cells/µL ▪ days) from Day 0 to Day 28 is defined as the AUC in a plot of levels of anti-CD19 CAR T cells against scheduled visits from Day 0 to Day 28. This AUC measures the total levels of anti-CD19 CAR T cells over time. Given the anti-CD19 CAR T cells are measured at certain discrete time points, the trapezoidal rule will be used to estimate the AUCs.

CCI [redacted]

4.4. Key Measurements of Product Characteristics

All product characteristics as defined in Table 3-1will be summarized individually.

In addition to all the measured product characteristics, the following additional analytes will be derived:

- 2 additional analytes will be derived for exploration:

CD4/CD8 Ratio is defined as: $\frac{\text{CD4 Cells (\%)}}{\text{CD8 Cells (\%)}}$

IFN-gamma/Transduction rate is defined as: Interferon-gamma normalized by transduction rate

$$\frac{\text{Interferon gamma level in product}}{\text{Transduction rate}}$$

5. ANALYSIS SETS

Translational analysis will use the analysis sets defined in clinical SAP unless otherwise specified. The following subjects will be involved in analysis:

- Safety Analysis Set

  The safety analysis set is defined as all subjects treated with any dose of KTE-X19. The safety analysis set will be the primary analysis set used to summarize the translational data in this TSAP.

6. STATISTICAL ANALYSIS

6.1. General Methods

The following methods will be applied to the data analysis when applicable.

- **Summary statistics**

  Summary statistics refers to the number of subjects, median, 1st quartile (Q1), 3rd quartile (Q3), minimum, and maximum for continuous measurements in overall and by cohorts.

6.2. Analysis

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2.2. Characterize Product Attributes

- The safety analysis set will be used to summarize the product characteristics data.
- Summary statistics will be generated in overall data and by cohorts.

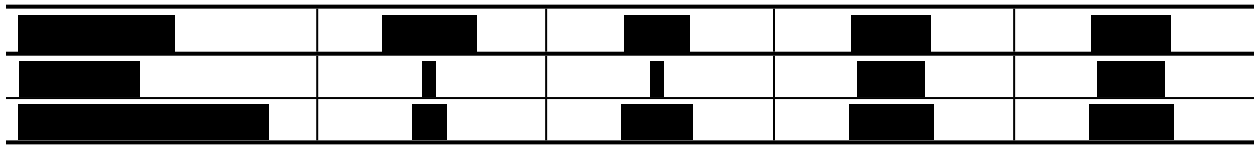
CCI [redacted]

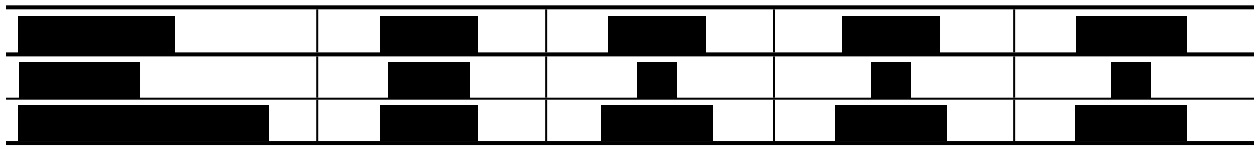
[redacted]

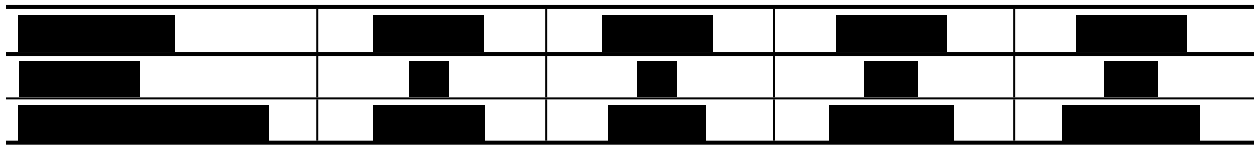
7. APPENDIX

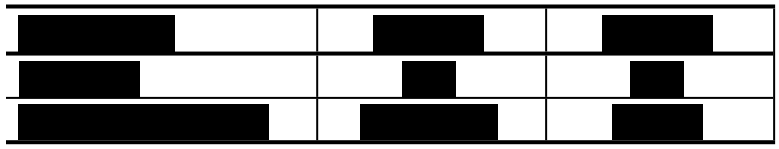
CCI [redacted]

[redacted]









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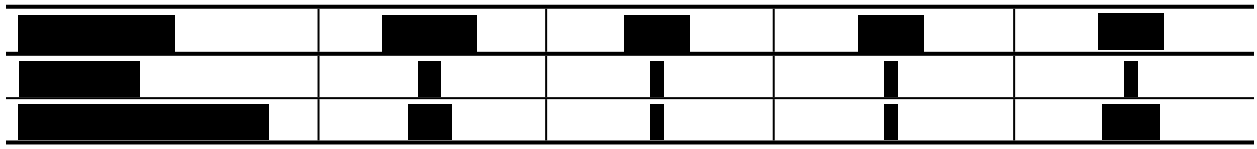
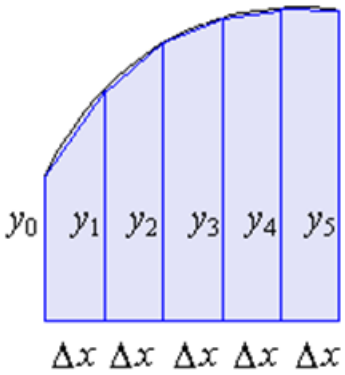


7.3. Using Trapezoidal Rule to Approximate the Area under the Curve (AUC)



$$\text{AUC} \approx \frac{1}{2}(y_0 + y_1) \cdot \Delta x + \frac{1}{2}(y_1 + y_2) \cdot \Delta x + \frac{1}{2}(y_2 + y_3) \cdot \Delta x + \ldots$$