CLINICAL PHARMACOLOGY BLA REVIEW

Division of Clinical Evaluation and Pharmacology/Toxicology Branch
Office of Tissues & Advance Therapies (OTAT)

STN 125646
Sponsor: NOVARTIS PHARMACEUTICALS CORPORATION
Product: TISAGENLECLEUCEL-T
Indication: For the treatment of pediatric and young adult patients with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL)
Submission Date: February 2, 2017
Reviewer: Iftekhar Mahmood, Ph.D.
RPM: Erica Giordano
Through: Lei Xu, M.D.

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INTRODUCTION

CTL019 consists of autologous T cells which are genetically modified ex vivo using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR). The CAR is comprised of a murine single chain antibody fragment (scFV) specific for recognizing CD19, followed by a CD8 hinge and transmembrane region which is fused to the intracellular signaling domains for 4-1BB (CD137) and CD3 zeta. CTL019 is supplied as a sterile frozen suspension and a single dose of CTL019 contains up to 2.5×10^8 transduced viable T cells.

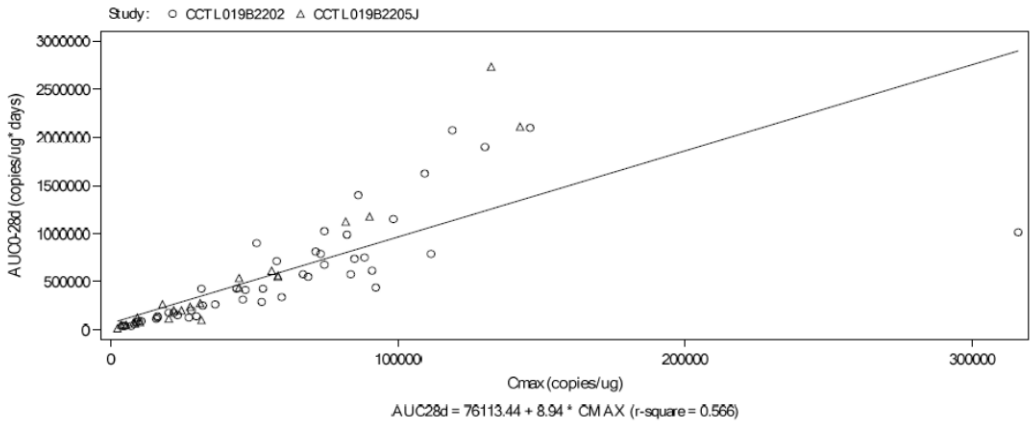
Comments

1. The population PK (POPPK) study described in this submission is non-traditional and unique. This is mainly due to the nature of drug which is based on cells described as 'cellular therapy'. The traditional POPPK models are based on clearance (CL) and volume of distribution (V) of a compound. However, such a model may not be applicable to cell based products because immediately after the administration of these products there is a rapid expansion (proliferation or multiplication) of the cells. Therefore, exact dose (or the number of cells) is not known hence, CL and V cannot be estimated accurately. Therefore, the reviewer agrees with the Applicant for using a non-traditional POPPK model.

2. The elimination half-life of 220 days of CTL019 should be interpreted with caution (most likely incorrect) as the half-life was estimated based on only 90 days of blood sampling. Although, blood samples of CTL019 were collected beyond 90 days, the fluctuation of data at the terminal phase will lead to the inaccurate estimation of half-life.

3. The Applicant stated that the PK analysis mainly focused on the C_{max} of CTL019 because it was noted that covariates impacting C_{max} would also impact the AUC. This statement may be true for some drugs but for CTL019 this is not the case. The relationship between C_{max} and AUC_{0-28d} was described by a linear regression with r^2 value of 0.566. The r^2 value does not suggest a strong correlation between C_{max} and AUC_{0-28d} of CTL019 (approximately 43% of variability remains unexplained).

Relationships between AUC0-28d and Cmax by qPCR SCP Pool



4. Data indicated that children <10 years of age have higher C_{max} and AUC (1.5 to 2-fold) than adults. Due to small sample size and high variability, it was difficult to assess the

impact of age on the PK of CTL019. However, higher AUC in younger children than adults is a common characteristic of medical products. The impact of age on the PK of a drug is an important issue and should also be thoroughly investigated for cell-based products.

5. In order to manage toxicity associated with cytokine release syndrome (CR), patients were given tocilizumab. Patients (n=18) treated with tocilizumab had 265% and 183% higher CTL019 AUC $_{0\text{-}28d}$ and C_{max}, respectively, as compared to patients (n=44) who did not receive tocilizumab. Similarly, patients who received corticosteroids had 89% higher $AUC_{0\text{-}28d}$ compared with patients who did not receive corticosteroids. The results of the POPPK study indicated that the increase in C_{max} and AUC of tocilizumab or corticosteroids following CTL019 administration may be the result of drug-drug interaction. Drug-drug interaction may result in reduced efficacy and/or increased toxicity therefore drug-drug interaction should be thoroughly investigated for cell-based products.

6. For CTL019, a dose finding study was not conducted. It is possible that a systematic study to find the optimum or near optimum dose may not only be therapeutically beneficial but may help to reduce CSR.

CLINICAL PHARMACOLOGY LABELING COMMENTS

7. DRUG INTERACTIONS

No pharmacokinetic drug interaction studies with TRADENAME have been performed. ~~as they are not applicable to a cell based therapeutic.~~ ~~[Clinical Overview – Section 3.1.5.2]~~

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TRADENAME is an autologous, immunocellular cancer therapy which involves reprogramming a patient's own T cells with a transgene encoding a CAR to identify and eliminate CD19 expressing malignant and normal cells. The CAR is comprised of a murine single chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains from 4-1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T-cell activation and antitumor activity while 4-1BB enhances the expansion and persistence of TRADENAME. Upon binding to CD19 expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination and persistence of the TRADENAME cells. ~~[Clinical Overview – Section 1.4] [Nonclinical Overview – Section 1].~~ Due to limited short spans of identical genetic material (RNA) between the lentivirus used to create TRADENAME and HIV, some commercial HIV nucleic acid test (NAT) tests may be falsely positive. ELISA or Western Blot tests for the presence of HIV antibodies should be used to provide specificity for HIV infection after administration of TRADENAME.

12.3 Pharmacokinetics

Following infusion (please insert the duration of infusion) of TRADENAME in pediatrics (3-<18 years of age) and young adults (18-25 years of age) r/r B-cell acute lymphoblastic leukemia (ALL) patients, TRADENAME ~~typically~~ exhibited an initial rapid expansion followed by a bi-exponential decline. Applicant: Please insert AUC (0-28d) and Cmax values for (CR/CRi) patients (n = ?). The Tmax in CR/CRi patients (n=62) occurred on day 10. The mean half-life of TRADENAME was approximately 17 days in the CR/CRi patients (n=54). The C_{max} and AUC(0-28d) were approximately 2-fold higher (please provide the values) in CR/CRi patients (n=61) compared with non-responding (NR) patients (n=7). The Tmax in NR patients (n=62) occurred on day 20.

Applicant: Please provide the aforementioned information in a Tabulated form and then delete the description in the text.

TRADENAME was found to be present in the blood as well as bone marrow and was measurable beyond 2 years. Blood to bone marrow partitioning suggested that TRADENAME distribution in bone marrow was 44% of that present in blood at day 28 while at months 3 and 6 it distributed at 67% and 69%, respectively, indicating high distribution to bone marrow.

Children <10 years of age had higher C_{max} and AUC (1.5 to 2-fold) than adults. Due to small sample size and high variability, it is difficult to assess the impact of age on the PK of TRADENAME.

Patients (n=18) treated with tocilizumab had 265% and 183% higher TRADENAME AUC_{0-28d} and C_{max}, respectively, as compared to patients (N=44) that did not receive tocilizumab. Similarly, patients that received corticosteroids had 89% higher AUC_{0-28d} compared with patients that did not receive corticosteroids.

Hepatic and renal impairment studies of TRADENAME were not conducted.

~~The median time of maximal expansion, T_{max}, occurred at day 10 with a delayed T_{max} of 20 days in NR (n=7) patients as determined from quantitative polymerase chain reaction (qPCR).~~

~~The geometric mean half-life determined using at least the last three measurable time points was approximately 16.8 days in the CR/CRi patients (n=54) measured by qPCR.~~
~~There was insufficient data in the terminal phase of elimination to determine a half-life for NR patients.~~
~~The mean overall exposure at day 28 (AUC0-28d) was approximately 2-fold higher in CR/CRi patients (n=61) compared to NR patients (n=6) for the transgene encoding the chimeric antigen receptor signifying the potential roles of both expansion and persistence for eliciting a clinical response.~~ ~~[Summary of Clinical Pharmacology Section 1.2.1]~~

~~A marker for duration of transgene persistence (Tlast), demonstrated that transgene persisted in peripheral blood for a prolonged period of time in all three studies, and up to 780 days. in Study 3. In data pooled from~~
~~377 Study 1 and Study 2, the transgene was measureable up to 380 days in CR/CRi patients with a median of 102 days.~~
~~Thelast measurable time point was 84 days in NR patients.~~ ~~with a median of 27.8 days. The last measurable time point is~~
~~379 influenced by the time of data cut, as this parameter represents the last measurable or available sample collected from~~

380 each patient. [Clinical Overview – Section 3.1] [Summary of Clinical Pharmacology – Section 2.2]

381 *Distribution*

in Study TRADENAME was found to be present in the blood as well as bone marrow and was measurable beyond 2 years. Blood to bone marrow partitioning suggested that TRADENAME distribution in bone marrow was 44% of that present in blood at day 28 while at months 3 and 6 it distributed at 67% and 69%, respectively, demonstrating high trafficking to bone marrow.

(Study 3). In Study 1 and Study 2, the median time of maximal expansion, Tmax, occurred at 10 days in CR/CRi (n=61), and a delayed Tmax of 20 days occurred in NR (n=7) patients as determined from quantitative polymerase chain reaction (qPCR). [Summary of Clinical Pharmacology – Section 1.2.1] The Tmax for CD3+/tisagenlecleucel T+ by flow cytometry was approximately 9 days in CR/CRi patients. [Summary of Clinical Pharmacology – Section 2.2.1] The geometric mean Cmax was 21.4 % CD3+/tisagenlecleucel T+ cells. In Study 1 and Study 2, the blood to bone marrow partitioning suggested that TRADENAME distribution in bone marrow was 44% of that present in blood at Day 28 while at months 3 and 6 it distributed at 67% and 69%, respectively, demonstrating high trafficking to bone marrow. [Clinical Overview

390 3.1.3][Summary of Clinical Pharmacology – Section 3.2.1.2]

391 *Metabolism*

392 It is unknown if TRADENAME retains the properties of natural T cells; however, they are not expected to be metabolized

393 by or affect those enzymes or transporters involved in small molecule clearance. [Clinical Overview – Section 3.1.4]

394 *Elimination*

395 The elimination profile of TRADENAME includes a multi-exponential decline in peripheral blood. However, not all

396 patients have sufficient follow-up or sufficient time above the limit of quantification for the elimination phase to be

397 estimable. [Clinical Overview – Section 3.1.4]

398 *Linearity/non-linearity*

399 There is a flat relationship between dose and the cellular kinetic parameters, thus there is no apparent relationship with

400 AUC0-28d and Cmax with total transduced dose and total weight adjusted dose. [Summary of Clinical Pharmacology –

401 Section 1.2.2.1]

402 *Renal impairment*

403 TRADENAME is a cell based product, and based on the mechanism of action, renal impairment is not expected to impact

~~404 TRADENAME expansion and cellular kinetics; hence, no formal renal impairment studies were performed. [Clinical~~
~~405 Overview – Section 3.1.6] [Summary of Clinical Pharmacology – Section 3.3.3]~~
~~406 *Hepatic impairment*~~
~~407 TRADENAME is a cell based product, and based on the mechanism of action, hepatic impairment is not expected to~~
~~408 impact TRADENAME expansion and cellular kinetics; hence, no formal hepatic impairment studies were performed.~~
~~409 [Clinical Overview – Section 3.1.6] [Summary of Clinical Pharmacology – Section 3.3.4]~~

RECOMMENDATION

The study design and the results of the clinical pharmacology are acceptable. The Applicant should modify the clinical pharmacology labeling as suggested by the FDA.

Study title: Population cellular kinetics of tisagenlecleucel-T (CTL019) in pediatric and young adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL).

The objectives of the study were as follows:

- To develop a population pharmacokinetic (POPPK) model for CTL019
- To evaluate if there were differences in CTL019 peak levels between patients with and without tocilizumab and/or corticosteroids.
- To evaluate if there were changes in the rate of CTL019 expansion (cell multiplication) after tocilizumab and/or corticosteroids are given.
- To evaluate the impact of age, gender, and race on the pharmacokinetics (PK) of CTL019.

The data for POPPK analysis were obtained from two studies CCTL019B2205J and CCTL019B2202. The summary of the studies is provided in Table 1.

Table 1: Summary of the Studies

Study	Study	Allowable dose range	(Sample Size, n) Cellular Kinetic sample times, D1 = infusion
B2202	Phase II, single arm, multicenter trial to determine the efficacy and safety of tisagenlecleucel-T in pediatric and young adult patients with relapsed and refractory B-cell acute lymphoblastic leukemia	For patients ≤ 50 kg: 0.2 to 5.0 x 10^6 transduced viable T cells per kg body weight For patients >50 kg: 0.1 to 2.5 x 10^8 transduced viable T cells	n=61 D1-10min post dose, D4, D7, D11, D14, D21, D28, M3, M6, M9, M12, M18, M24, M30, M36, M42, M48, M54, M60
B2205J	Phase II, single arm, multicenter trial to determine the efficacy and safety of tisagenlecleucel-T in pediatric and young adult patients with relapsed and refractory B-cell acute lymphoblastic leukemia	For patients ≤ 50 kg: 0.2 to 5.0 x 10^6 transduced viable T cells per kg body weight For patients >50 kg: 0.1 to 2.5 x 10^8 transduced viable T cells	n=29 D1-10min post dose, D4, D7, D11, D14, D21, D28, M3, M6, M9, M12, M18, M24, M30, M36, M42, M48, M54, M60

CTL019 concentrations in blood were measured by two different assays:
Quantitative Polymerase Chain Reaction (q-PCR) and flow cytometry. q-PCR assay measures the number of copies of chimeric antigen receptor(CAR) per μg of DNA whereas the flow cytometry assay measures the percentage of CD3+ cells expressing the CAR receptor. Flow cytometry provides a more functional measure of CTL019 because only cells expressing the CAR receptor are active, but q-PCR is a more sensitive assay. Due to the modifications made to the method, q-PCR was the only assay for which data were available for all patients. Therefore, only the q-PCR data was used in the POPPK analysis.

There were 91 subjects in both studies. The demographics of the subjects are shown in Table 2. The POPPK analysis was based from the data obtained from studies B2202 and B2205J, and their pool (SCP Pool). The patient populations were similar across the studies B2202 and B2205J with a similar study design and evaluated the same target dose. Additionally, the CTL019 blood samples collected from studies B2202 and B2205J were analyzed using the same bioanalytical methods at the same laboratory (b) (4)

Table 2: Demographics in Study B2202 and Study B2205J

Demographic variable Statistics	Study B2202 N=62	Study B2205J N=29	All patients N=91
Age (years)			
N	62	29	91
Mean (SD)	12.2 (5.44)	12.6 (5.97)	12.3 (5.58)
Median	12.0	12.0	12.0
Min-Max	3-23	3-25	3-25
Age category (years) - n (%)			
<10	25 (40.3)	9 (31.0)	34 (37.4)
≥ 10 to <18	25 (40.3)	13 (44.8)	38 (41.8)
≥ 18	12 (19.4)	7 (24.1)	19 (20.9)
Sex - n (%)			
Female	28 (45.2)	18 (62.1)	46 (50.5)
Male	34 (54.8)	11 (37.9)	45 (49.5)
Race - n (%)			
White	45 (72.6)	25 (86.2)	70 (76.9)
Asian	6 (9.7)	2 (6.9)	8 (8.8)
Other	11 (17.7)	2 (6.9)	13 (14.3)
Ethnicity - n (%)			
Hispanic or Latino	14 (22.6)	7 (24.1)	21 (23.1)
Other	48 (77.4)	22 (75.9)	70 (76.9)
Weight for CTL019 manufacturing (kg)			
N	62	29	91
Mean (SD)	43.6 (25.05)	42.3 (19.59)	43.2 (23.35)
Median	37.8	42.6	40.5
Min-Max	14.4-137.0	16.2-84.0	14.4-137.0
Karnofsky/Lansky performance status - n (%)			
100	20 (32.3)	9 (31.0)	29 (31.9)
90	21 (33.9)	12 (41.4)	33 (36.3)
80	11 (17.7)	6 (20.7)	17 (18.7)
70	5 (8.1)	0	5 (5.5)
60	2 (3.2)	1 (3.4)	3 (3.3)
50	3 (4.8)	1 (3.4)	4 (4.4)

Blood samples for PK study were collected at days 1, 4, 7, 11, 14, 21, 28 and then at months 3, 6, 9, 12, and then every 6 months until month 60, where day 1 corresponds to the day of the first dose.

POPPK analysis was performed using a nonlinear mixed effects modeling (NONMEM) approach, where the model had two components: a structural model which accounts for the

systematic trends in the data and the random effects model, which accounts for both inter-subject variability and residual variability. The analysis was performed using the Monolix software system, version 4.3.2 utilizing the MODESIM high performance computing environment accessed from GPSII. The technical computing package R and Matlab were used for exploratory analysis, model building, and in reporting the final results.

It was noted that CTL019 cells undergo an exponential expansion at rate ρ until t_{max}, followed by a bi-exponential decline at rates α (initial slope) and β (terminal slope). The structural model that described this profile was based on a published model that was used to describe the murine immune response to an infection by listeria monocynogenes or lymphocytic choriomeningitis virus.

The structural model f(t) in the absence of co-medications was given by the equation below and the parameters are described in Table 3. This model also applies if all co-medications are given after t_{max}.

$$f(t) = \begin{cases} [C_{\max}/\text{foldx}]\, e^{(\log(\text{foldx})/t_{\max})t} & t \le t_{\max} \\ [C_{\max}\,(1-\text{FB})]\, e^{-\alpha(t-t_{\max})} + [C_{\max}\cdot\text{FB}]\, e^{-\beta(t-t_{\max})} & t > t_{\max} \end{cases}$$

Table 3: Structural Model Parameters

	Description	Units	Random Eff. Distribution
Cmax	Maximum q-PCR value in the absence of comedication	transgene copies/µg DNA	Lognormal
tmax	Time of maximum q-PCR value	day	Lognormal
foldx	Fold expansion from baseline	-	Lognormal
FB	Fraction of tisagenlecleucel-T that decline slowly	-	Logit
α	Rapid decline rate	1/day	Lognormal
β	Gradual decline rate	1/day	Lognormal
Ftoci	Tocilizumab effect on expansion rate	-	Fixed Effect
Fster	Corticosteroids effect on expansion rate	-	Fixed Effect

The structural model exhibits exponential expansion at rate $\rho = \log(\text{foldx})/t_{max}$ until t_{max}, when the peak transgene level is C_{max}. After t_{max}, there is a transition from expansion to a bi-exponential decline at rates α (initial slope) and β (terminal slope). The parameter FB denotes the fraction of cells contributing to C_{max} that exhibit a gradual decline at rate β. At t_{max}, both the top and bottom equation of f(t) are equal to C_{max}. The model was found to be more stable when parameterizing by the fold-expansion (foldx) instead of ρ, such that: $\text{foldx} = \exp(\rho \cdot \text{tmax})$ and $\rho = \log(\text{foldx})/\text{tmax}$.

The impact of tocilizumab and corticosteroids on CTL019 expansion was also explored based on two assumptions. One assumption was that tocilizumab might slow the rate of expansion. This relationship was explored by expanding the structural model to include a tocilizumab and corticosteroid impact on ρ. A second assumption was that patients with greater peak transgene

levels were more likely to have Grade 3 and 4 cytokine release syndrome and therefore were more likely to receive tocilizumab. This assumption was explored by treating tocilizumab (and corticosteroid) therapy as binary covariates that can impact C_{max}. Additional relationships are possible as tocilizumab could potentially impact any of the model parameters, but for simplicity, only these two co-medication effects were explored.

A covariate analysis was performed for exploratory purposes, to evaluate the effects of intrinsic and extrinsic factors (Table 4) on the pharmacokinetics of CTL019. The analysis mainly focused on the C_{max} of CTL019 because it was noted that covariates impacting C_{max} would also impact the AUC (questionable claim by the Applicant. Please see comment #3). For terminal half-life, some patients exhibited a rapid decline and other patients had a terminal half-life over 1 year, which was difficult to estimate without follow up over many years. The covariates used in the POPPK analysis are shown in Table 4.

Table 4: Covariates used in the POPPK analysis

Type	Covariate	Parameter	Reason/Comment
Study	Study, B2202 or B2205J	Cmax	
Demographics	Age, years. Three categories: <10, 10-17, ≥18	Cmax	
Demographics	Gender, male/female	Cmax	
Demographics	Race (Caucasian, Asian, or other)	Cmax	
Intrinsic factor	Down Syndrome	Cmax	
Extrinsic factors	Prior lymphodepleting chemotherapy with fludarabine	Cmax	May affect space for tisagenlecleucel-T expansion
Extrinsic factors	Prior stem cell transplant, yes/no	Cmax	May affect space for tisagenlecleucel-T expansion
Extrinsic factors	Tocilizumab, yes/no	Cmax	To evaluate correlation with expansion
Extrinsic factors	Corticosteroids, yes/no	Cmax	To evaluate correlation with expansion
Manufactured Product	Transduction efficiency, %	Cmax	May affect function of tisagenlecleucel-T cells
Dose	Weight adjusted dose, 10^6 transduced viable T cells/kg	Cmax	May affect maximum number of cells observed

The results of the POPPK analysis are shown in Table 5. Based on the analysis, distribution half-life ($t_{1/2}$-α) was 4.3 days. The elimination half-life was 220 days. The elimination half-life should be interpreted with caution as the half-life was estimated based on only 90 days of blood sampling. Although, blood samples of CTL019 were collected beyond 90 days, the fluctuation of data at the terminal phase restricted the accurate estimation of half-life.

Concentration-time profile of CTL019 is shown in Figure 1. The PK parameters of all three studies are summarized in Table 6.

Table 5: Full Model Parameter

Type	Parameter	Estimate	RSE %	Eta Shrinkage	Units
Fixed Effect	foldx	3900	30	-	-
Fixed Effect	tmax	9.3	4.2	-	days
Fixed Effect	Cmax	24000	20	-	DNA cop./ug
Fixed Effect	Ftoci	1.2	7.5	-	-
Fixed Effect	Fster	1	9	-	-
Fixed Effect	alpha	0.16	11	-	1/day
Fixed Effect	FB	0.0079	15	-	-
Fixed Effect	beta	0.0032	23	-	1/day
Random Effect	foldx	2.4	9.5	0.39	-
Random Effect	tmax	0.38	7.9	0.14	-
Random Effect	Cmax	0.65	10	0.29	-
Random Effect	alpha	0.91	8.8	0.27	-
Random Effect	FB	0.8	15	0.53	-
Random Effect	beta	0.86	23	0.82	-
Residual Error	a	0.56	3.3	-	-
log Cmax Covariate Effect	Female (vs Male)	0.25	72	-	-
log Cmax Covariate Effect	Asian (vs Cauc.)	0.13	250	-	-
log Cmax Covariate Effect	Race Other/Unknown (vs Cauc.)	0.33	76	-	-
log Cmax Covariate Effect	Downs Syndrome	0.25	130	-	-
log Cmax Covariate Effect	Received HSCT	0.29	62	-	-
log Cmax Covariate Effect	No Fludarabine Received	-0.63	69	-	-
log Cmax Covariate Effect	Study B2205J vs B2202	-0.11	190	-	-
log Cmax Covariate Effect	Transduction Efficiency	0.22	72	-	-
log Cmax Covariate Effect	Dose normalized by body weight	0.093	140	-	-
log Cmax Covariate Effect	Received Tocilizumab	0.44	59	-	-
log Cmax Covariate Effect	Received Corticosteroids	-0.36	75	-	-

RSE denotes the relative standard error of the parameter. Eta shrinkage for each parameter is calculated by the formula: $(1-var(\eta))/\omega^2$.

Figure 1: Concentration-time data of CTL019

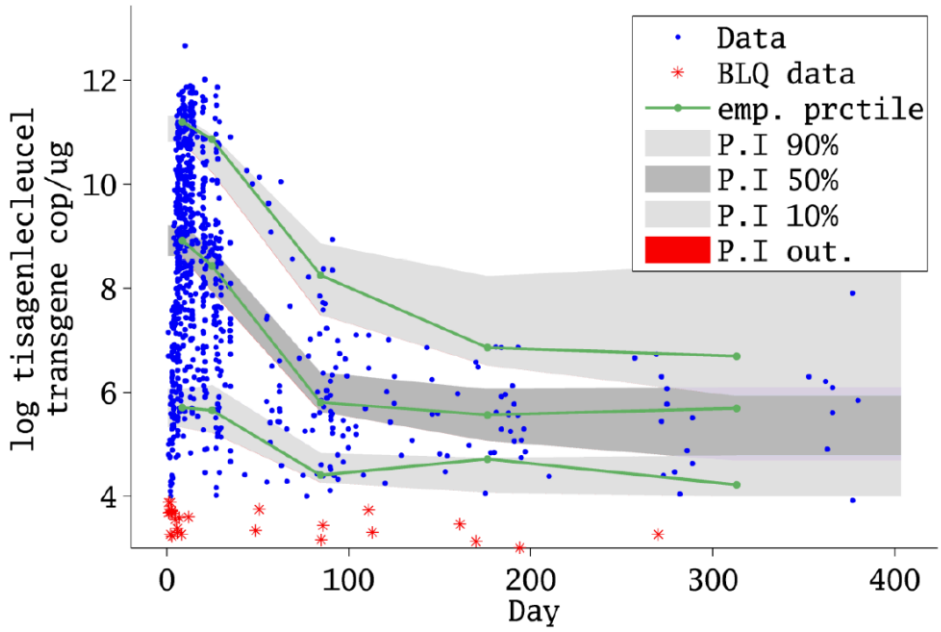


Table 6: Summary of peripheral blood cellular kinetic parameters of CTL019 by qPCR (Studies B2202, B2205J, B2101J and SCP pool)

		Study B2202		Study B2205J		Study B2101J		SCP Pool	
Parameter	Statistics	CR/CRi N=42	NR N=3	CR/CRi N=20	NR N=5	CR/CRi N=52	NR N=3	CR/CRi N=62	NR N=7
AUC0-28d (copies/µg DNA×days)	n	42	3	19	3	52	3	61	6
	Geo-mean	349000	210000	260000	116000	343000	105000	318000	156000
	Geo-CV%	159.3	151.5	226.4	54.5	158.5	1170.0	177.8	99.4
AUC0-84d (copies/µg DNA×days)	n	35	1	17	1	43		52	2
	Geo-mean	497000	1930000	384000	270000	437000		456000	721000
	Geo-CV%	193.3	N/A	273.5	N/A	145.9		214.5	243.5
Cmax (copies/µg)	n	42	3	19	4	50	3	61	7
	Geo-mean	41000	23500	24000	17700	48000	17200	34700	20000
	Geo-CV%	135.8	110.2	187.3	53.5	132.3	779.4	155.4	71.6
Tmax (days)	n	42	3	19	4	50	3	61	7
	Median	9.96	26.9	7.81	20.0	11.0	13.0	9.91	20.0
	[Min; Max]	[0.00764, 27.0]	[19.0, 62.7]	[0.0111; 15.0]	[0.0278; 22.8]	[2.00; 31.0]	[8.00; 16.0]	[0.00764; 27.0]	[0.0278; 62.7]
T1/2 (days)	n	36	2	18	1	37	3	54	3
	Geo-mean	16.0	3.28	18.6	1.48	19.6	1.84	16.8	2.52
	Geo-CV%	140.0	304.2	198.0		319.7	47.0	155.9	171.9
Clast (copies/µg)	n	42	3	20	5	33	1	62	8
	Geo-mean	274	1140	263	1750	292	26.4	270	1490
	Geo-CV%	294.1	75.4	156.6	264.3	360.5	N/A	239.9	170.8
Tlast (days)	n	42	3	20	5	33	1	62	8
	Median	92.5	67.7	190	26.9	196	23.0	102	27.8
	[Min; Max]	[26.5, 366]	[29.2, 83.9]	[17.8; 380]	[20.9; 28.8]	[18.0; 780]	[23.0; 23.0]	[17.8; 380]	[20.9; 83.9]

NR = non responders; CR = complete response; CRI = complete response with incomplete hematologic recovery; qPCR = quantitative polymerase chain reaction

Following infusion, CTL019 exhibited an initial rapid expansion (proliferation or multiplication) phase achieving maximal concentration (C_{max}) around day 10 followed by a slower bi-exponential decline in complete remission/complete remission with incomplete hematologic recovery (CR/CRi) patients on day 28. In all three studies, the C_{max} and $AUC_{0\text{-}28d}$ were higher in CR/Cri patients as compared with non-responder (NR) patients. T_{max} of CTL019 occurred much later in non-responders than responders. The half-life was much shorter in non-responders than responders. It should be however, noted that the sample size for non-responders was very small as compared with the responders. The percent coefficient of variation (%CV) was >100% in AUC and C_{max} for responders which makes it difficult (in association with small sample size) to make any direct comparison with the non-responders. Despite small sample size, it appears that the non-responders had at least 50% AUC and C_{max} values than responders.

Impact of Race on the PK of CTL019:

Race does not appear to impact CTL019 exposure. Analysis with Asians, Whites and other races (not described in the submission) with the SCP Pool indicated that $AUC_{0\text{-}28d}$ and C_{max} were 13% and 17% higher in the Asians than the Whites, respectively (Table 7). In the other race, $AUC_{0\text{-}28d}$ and C_{max} were 200% and 132% higher, respectively, as compared to Whites. Considering that the analysis is based on small sample size, it is difficult to draw any definite conclusion.

Table 7: Impact of race on the PK parameters of CTL019 (SCP Pool)

					Treatment comparison 90% CI		
Parameter (unit)	Treatment	n[1]	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	Lower	Upper
AUC0-28d	White	55	264000				
(copies/µg DNA×days)	Asian	5	299000	Asian/White	1.13	0.473	2.72
	Other	10	791000	Other/White	3.00	1.57	5.71
Cmax	White	59	29500				
(copies/µg genomic DNA)	Asian	5	34500	Asian/White	1.17	0.519	2.65
	Other	10	68200	Other/White	2.32	1.27	4.21

Model is a linear mixed effects model of the log-transformed cellular kinetic parameters. Included in the model was ethnicity as a fixed effect
The results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI.
n[1] = number of observations used for the analysis.

Impact of Gender on the PK of CTL019:

No difference in the $AUC_{0\text{-}28d}$ and C_{max} of CTL019 was found between male and female subjects.

Impact of Age on the PK of CTL019:

Three age categories (categories <10 years, ≥ 10 to<18 years, and ≥ 18 years were used to explore the impact of age on the PK of CTL019. The geometric mean $AUC_{0\text{-}28d}$ and C_{max} was highest in the patients <10 years of age. In the SCP Pool, patients <10 years had approximately 118% and 85% higher $AUC_{0\text{-}28d}$ and C_{max}, respectively as compared to patients ≥ 18 years (Table 8). Both $AUC_{0\text{-}28d}$ and C_{max} decreased with increasing age. However, due to high variability in $AUC_{0\text{-}28d}$ and C_{max} of CTL019 it is difficult to draw a definitive conclusion. Figures 2-3 show the relationship between age and the PK parameters of CTL019 and no relationship was found between age and PK parameters of CTL019.

Table 8: Impact of age on the PK parameters of CTL019

Parameter	Statistics	<10 years N=19	>=10 years to <18 years N=21	>=18 years N=10
AUC0-28d (copies/µg*days)	n	18	20	9
	Mean (SD)	701000 (613000)	572000 (530000)	343000 (332000)
	CV%	87.4	92.7	96.6
	Geo-mean	403000	378000	229000
	Geo-CV%	209.6	130.8	120.6
	Median	594000	422000	150000
	[Min; Max]	[35100; 2070000]	[41800; 2100000]	[73300; 1030000]
AUC0-84d (copies/µg*days)	n	14	16	8
	Mean (SD)	1230000 (1050000)	993000 (1210000)	642000 (749000)
	CV%	85.4	122.0	116.7
	Geo-mean	712000	551000	345000
	Geo-CV%	232.3	169.9	180.1
	Median	983000	514000	297000
	[Min; Max]	[41600; 3630000]	[45900; 4730000]	[82500; 1930000]
Cmax (copies/µg)	n	18	20	9
	Mean (SD)	73600 (72500)	57100 (36600)	39800 (31400)
	CV%	98.4	64.1	78.9
	Geo-mean	43100	44900	28600
	Geo-CV%	193.7	92.1	111.5
	Median	69200	51500	23200
	[Min; Max]	[4040; 316000]	[7150; 146000]	[8780; 92200]

n: number of patients with non-missing values.
CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Figure 2: $AUC_{0\text{-}28d}$ of CTL019 as a function of age (SCP Pool)

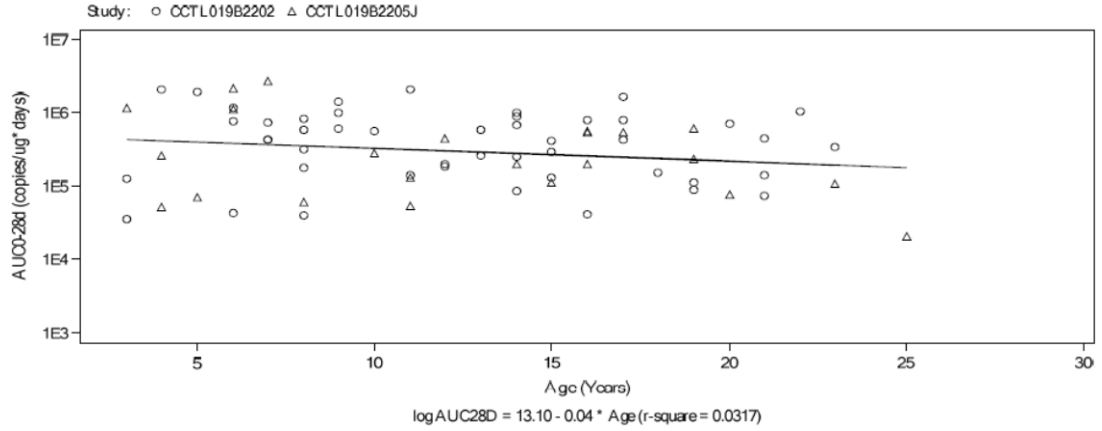
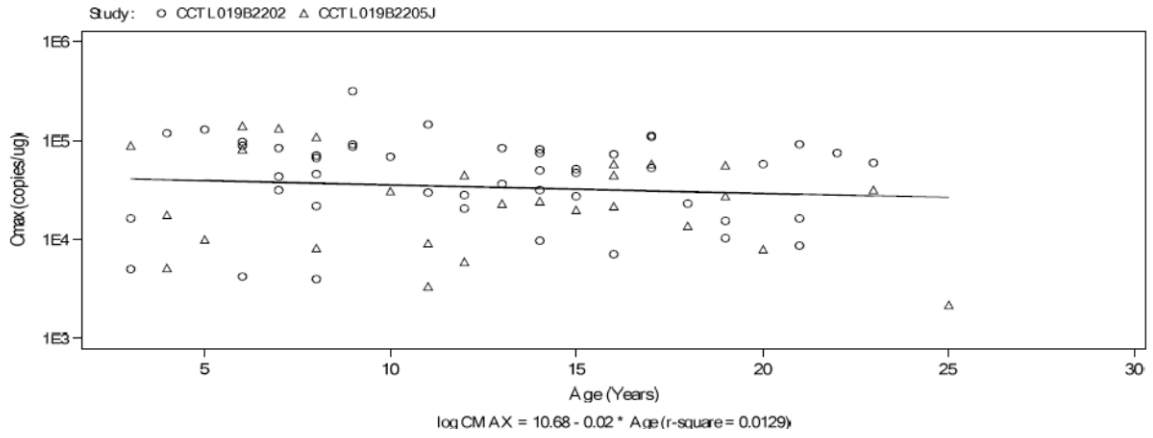


Figure 3: C_{max} of CTL019 as a function of age (SCP Pool)



Dose-response:

CTL019 dosing was administered on a weight adjusted basis for patients ≤ 50 kg and as a non-weight adjusted dose for patients >50 kg. Therefore, two logistic models were used to evaluate the dose-response (same as exposure-response relationship; Table 9) relationship. One model was based on total dose and another was based on weight adjusted dose. Both models used all patients from Studies B2202 and B2205J. In both models, a factor was used to estimate the effect of weight group (≤ 50 kg or > 50 Kg) on response and an additional interaction between weight group and dose was included to investigate the impact of weight group on the dose-response relationship.

The logistic regression for dose-response curve for patients ≤50 kg showed an increasing probability of response for dose $<2.0\times10^6$ CTL019 per kg and the probability of response plateaued for higher doses (Figure 4). Similarly, the logistic regression for dose response curve for patients >50 kg showed an increasing probability of response for dose $<1.0\times10^8$ CTL019 while the probability of response plateaued for doses higher than 1.0×10^8 (Figure 5). The probability of response derived from the model estimates were 43% for doses of 0.2×10^8 per kg for patients ≤ 50 kg and 30.9% for doses of 0.1×10^8 CTL019 for patients >50 kg.

Figure 4: Logistic regression of day 28 response vs body weight (≤ 50 kg)

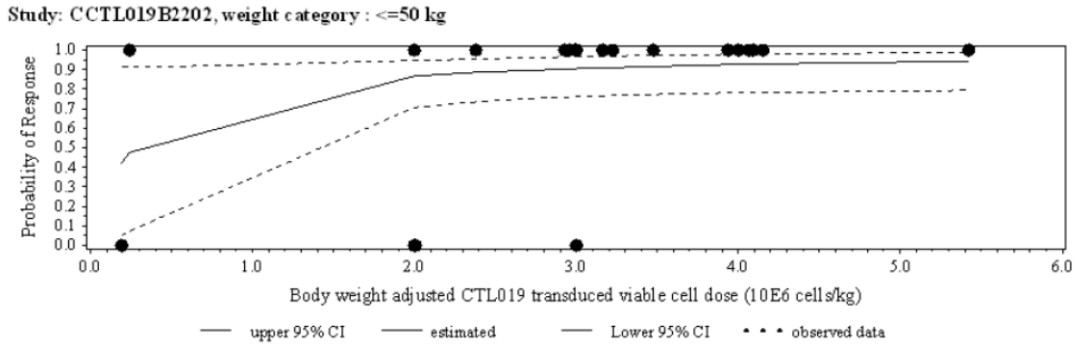
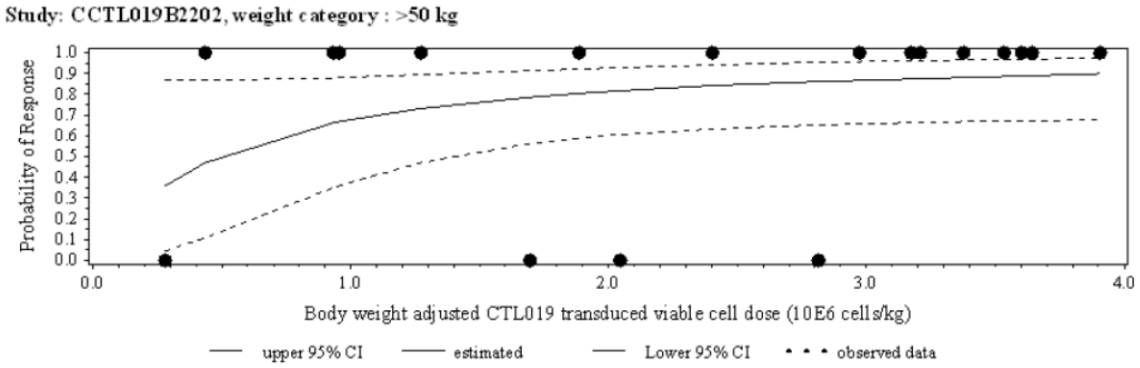


Figure 5: Logistic regression of day 28 response vs body weight (>50 kg)



Exposure-response analysis:

Exposure-response analyses were conducted to explore the relationship between CTL019 exposure metrics (C_{max} and AUC) and efficacy endpoints including day 28 response, duration of remission (DOR), and event free survival (EFS) (Table 9). In addition, the relationship of CTL019 exposures on time to B-cell recovery was also evaluated.

Table 9: Exposure-response analyses

Efficacy endpoints	Analysis by exposure endpoints	Methods
Study B2202 and B2205J (individual and pooled)		
Day 28 Response	AUC0-28d and Cmax by Day 28 response	Logistic Regression and estimates
DOR	DOR and AUC0-28d and AUC0-84d based on qPCR	Kaplan-Meier plot and estimates
		Cox regression
EFS	AUC0-28d and Cmax	Summary statistics
B cell recovery	B cell recovery and AUC0-28dand AUC0-28d and AUC0-84d based on qPCR	Kaplan-Meier plot and estimates
		Cox regression
		Summary Statistics

DOR: Duration of remission (time from achievement of CR or CRi to relapse or death)
EFS: Event free survival
CR: complete response; CRi: complete response with incomplete bone marrow recovery

Based on EFS category in the SCP Pool (EFS event ≥ 3 months, EFS event <3 months, EFS censor <3 months, treatment failure, and other), it was observed that treatment failure patients tend to have lower $AUC_{0\text{-}28d}$ and C_{max} as compared with other EFS categories (Table 10). EFS event categories <3 months and treatment failures tend to have prolonged T_{max} (median of 19.6 and 19.9 days respectively) compared with EFS event ≥ 3 months (median 9.8 days).

Table 10: Summary of peripheral blood cellular kinetic parameters for CTL019 by qPCR by EFS category

Parameter	Statistics	EFS event >=3 months N=41	EFS event <3 months N=2	EFS censor <3 months N=2	Treatment failure N=5	Other N=0
AUC0-28d (copies/µg* days)	n	41	2	2	2	0
	Mean (SD)	571000 (515000)	1250000 (1160000)	494000 (252000)	118000 (45100)	
	CV%	90.1	93.0	51.0	38.1	
	Geo-mean	350000	943000	460000	114000	
	Geo-CV%	159.3	157.2	57.4	40.6	
	Median	427000	1250000	494000	118000	
	[Min; Max]	[35100; 2100000]	[428000; 2070000]	[316000; 672000]	[86500; 150000]	
AUC0-84d (copies/µg* days)	n	37	1	0	0	0
	Mean (SD)	987000 (1070000)	1730000			
	CV%	108.8				
	Geo-mean	532000	1730000			
	Geo-CV%	193.1				
	Median	632000	1730000			
	[Min; Max]	[41600; 4730000]	[1730000; 1730000]			
Cmax (copies/µg)	n	41	2	2	2	0
	Mean (SD)	61200 (55200)	81300 (53000)	60200 (20200)	16500 (9560)	
	CV%	90.1	65.2	33.6	58.1	

- n: number of patients with non-missing values.
- CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

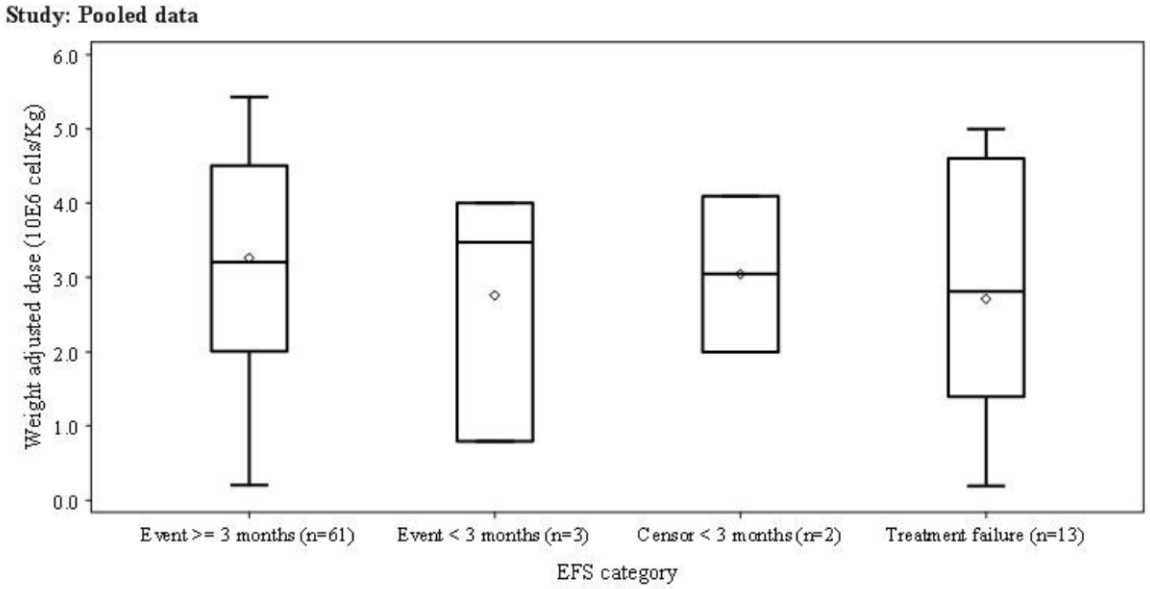
Table 10 continued:

Parameter	Statistics	EFS event >=3 months N=41	EFS event <3 months N=2	EFS censor <3 months N=2	Treatment failure N=5	Other N=0
Tmax (days)	n	41	2	2	2	0
	Median	9.95	23.3	11.9	40.9	
	[Min; Max]	[0.00764; 26.9]	[19.6; 27.0]	[10.9; 13.0]	[19.0; 62.7]	
Clast (copies/µg)	n	41	2	2	2	0
	Mean (SD)	534 (1060)	40200 (54000)	1100 (1140)	1340 (1110)	
	CV%	197.7	134.5	103.5	82.5	
	Geo-mean	230	12400	749	1090	
	Geo-CV%	175.9	2951.7	216.6	119.8	
	Median	203	40200	1100	1340	
	[Min; Max]	[28.2; 5540]	[1980; 78400]	[295; 1900]	[559; 2120]	
Tlast (days)	n	41	2	2	2	0
	Median	93.9	56.2	44.5	48.5	
	[Min; Max]	[27.0; 366]	[26.5; 85.9]	[27.1; 61.8]	[29.2; 67.7]	

Dose-event free survival:

The impact of dose on EFS was evaluated by analyzing the weight-adjusted dose by EFS category (EFS event ≥ 3 months, EFS event <3 months, EFS censor <3 months, treatment failure, and other) boxplot. The results of dose and EFS category analysis indicated that there was no effect of dose on EFS categories analyzed (Figure 6).

Figure 6: Boxplot of weight adjusted CTL019 dose by event free survival category- SCP Pool



Analyses of duration of remission (DOR):

Based on the Kaplan-Meier analysis of DOR, limited conclusions could be derived due to the small number of events/patients. Initial separation between Kaplan-Meier curves observed at around 2 months was maintained until about 6 months suggested that patients with higher exposure ($AUC_{0\text{-}28d}$ greater than the median) tend to have more durable remission; but overall the difference was small.

Analyses of exposure and B-cell recovery:

The patients with $AUC_{0\text{-}28d}$ greater than the median have slower B cell recovery than in patients with higher $AUC_{0\text{-}28d}$.

Relationship between CTL019 dose and C_{max} orAUC:

Based on linear regression, there was no relationship between CTL019 dose and C_{max} or AUC of CTL019.

Impact of Tumor Burden on the PK of CTL019:

Tumor burden had substantial impact on the C_{max} and $AUC_{0\text{-}28d}$ of CTL019. In studies B2202 and B2205J, tumor burden was assessed at screening whereas in study B2101J, tumor burden was assessed immediately prior to CTL019 infusion. Based on the analyses of treatment tumor burden data for study B2101J, the $AUC_{0\text{-}28d}$, $AUC_{0\text{-}84d}$, and C_{max} were approximately 243%, 273%, and 144% higher in high tumor burden (maximum morphologic blast count and MRD in

bone marrow was ≥ 50%) patients compared with low tumor burden patients. Down syndrome patients (n=6) had similar exposure ($AUC_{0\text{-}28d}$) and CRS grades compared to patients without Down Syndrome.

Impact of Stem Cell Transplantation (SCT):

The number of lines of prior therapy or prior stem-cell transplant (SCT) did not impact the PK of CTL019. $AUC_{0\text{-}28d}$ and C_{max} of CTL019 were comparable in patients who had prior SCT and in patients who did not have SCT.

Impact of lymphodepleting regimens: The majority of patients were treated with lymphodepleting regimens. However due to small sample size of non-lymphodepleting treated patients (n = 4), it was difficult to assess the impact of lymphodepleting regimens on the kinetics of CTL019.

Impact of Disease status:

Similar exposures were observed in patients with chemo-refractory and primary refractory disease compared with relapse disease, indicating disease status did not impact the exposure of CTL019. Based on the SCP pool analysis, the $AUC_{0\text{-}28d}$ and C_{max} were similar for chemo-refractory (n =15) and primary refractory (n = 64) (pooled data; n = 79) with relapsed disease. The mean $AUC_{0\text{-}28d}$ was 330000 (%CV = 170%) and 308000 (%CV = 174%) copies/µg in patients with refractory and relapsed disease, respectively. The mean C_{max} was 33000 (%CV = 129%) and 33400 (%CV = 153%) copies/µg genomic in patients with refractory and relapsed disease, respectively.

CRS management with tocilizumab:

The administration of CTL019 led to cytokine release syndrome (CRS). In order to manage CRS toxicity, patients received tocilizumab, a humanized anti-IL6 receptor monoclonal antibody. Seventy five (82.4%) patients who were infused with CTL019 experienced CRS and 32 (42.7%) patients were treated with tocilizumab. Patients with severe CRS (grade 3-4) received tocilizumab around the time of maximal expansion.

Based on the SCP Pool, CR/CRi patients (n=18) treated with tocilizumab had 265% and 183% higher CTL019 $AUC_{0\text{-}28d}$ and C_{max}, respectively as compared to patients (n=44) that did not receive tocilizumab as measured by qPCR. Patients with grade 3-4 CRS who received tocilizumab had higher C_{max} and $AUC_{0\text{-}28d}$. T_{max} of CTL019 was comparable between patients that received tocilizumab and patients who did not received tocilizumab. The relationship between CRS grade and exposure metrics ($AUC_{0\text{-}28d}$ and C_{max}) suggested a trend for higher exposure associated with higher CRS grade.

CRS management with corticosteroids:

Patients with CRS that did not respond to tocilizumab received corticosteroids. CR/CRi patients that received corticosteroids had 89% higher $AUC_{0\text{-}28d}$ compared with CR/CRi patients that did not receive corticosteroids.

CTL019 in bone marrow by day 28:

On day 28, in CR/CRi patients (n = 17), the mean concentration of CTL019 in bone marrow was 1140 (CV = 1022%) copies/µg. There was high variability in CTL019 concentrations ranging from 72 to 77200 copies/µg. CTL019 concentrations declined over time and were measurable at month 3 and 6 at levels of 336 copies/µg (CV%: 103%) and 142 copies/µg (CV%: 145%), respectively.

Conclusions

- Following infusion, CTL019 exhibited an initial rapid expansion phase achieving maximal concentration (C_{max}) around day 10 followed by a slower bi-exponential decline in complete remission/complete remission with incomplete hematologic recovery (CR/CRi) patients on day 28.

- In all three studies, the C_{max} and $AUC_{0\text{-}28d}$ were higher in CR/Cri patients as compared with non-responder (NR) patients.

- Race and gender had no impact on the $AUC_{0\text{-}28d}$ and C_{max} of CTL019.

- Data indicated that children <10 years of age have higher C_{max} and AUC (1.5 to 2-fold) than adults. Both $AUC_{0\text{-}28d}$ and C_{max} decreased with increasing age. However, due to small sample size and high variability, it was difficult to assess a definitive impact of age on the PK of CTL019.

- The logistic regression for dose response curve for patients >50 kg showed an increasing probability of response for dose $<1.0\times10^8$ CTL019 while the probability of response plateaued for doses higher than 1.0×10^8. Similarly, for patients ≤ 50 kg, the dose-response curve showed an increasing probability of response for dose $<2.0\times10^6$ CTL019 per kg and the probability of response plateaued for higher doses.

- The probability of response derived from the model estimates were 43% for doses of 0.2×10^8 per kg for patients ≤ 50 kg and 30.9% for doses of 0.1×10^8 CTL019 for patients >50 kg.

- The $AUC_{0\text{-}28d}$, $AUC_{0\text{-}84d}$, and C_{max} were approximately 243%, 273%, and 144% higher in high tumor burden (maximum morphologic blast count and MRD in bone marrow was ≥ 50%) patients compared with low tumor burden patients.

- CR/CRi patients (n=18) treated with tocilizumab had 265% and 183% higher CTL019 $AUC_{0\text{-}28d}$ and C_{max}, respectively as compared to patients (n=44) that did not receive tocilizumab.

- CR/CRi patients that received corticosteroids had 89% higher $AUC_{0\text{-}28d}$ compared with CR/CRi patients that did not receive corticosteroids.

- The relationship between CRS grade and exposure metrics ($AUC_{0\text{-}28d}$ and C_{max}) suggested a trend for higher exposure associated with higher CRS grade.

- On day 28, in CR/CRi patients (n = 17), the mean concentration of CTL019 in bone marrow was 1140 (CV = 1022%) copies/µg. CTL019 concentrations declined over time and were measurable at month 3 and 6 at levels of 336 copies/µg (CV%: 103%) and 142 copies/µg (CV%: 145%), respectively.