

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

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COA CONSULT TRACKING NUMBER	C2017092
BLA NUMBER	125646
REFERENCED IND FOR NDA/BLA	16130
ESTABLISHED NAME/TRADE NAME	Tisagenlecleucel (KYMRIA TM)
APPLICANT	Novartis
INDICATION	Treatment of relapsed/refractory B-cell acute lymphoblastic leukemia
MEETING TYPE (A/B/C/WRO)	Not applicable
LETTER DATE	February 2, 2017
PDUFA GOAL DATE	October 3, 2017
DATE OF CONSULT REQUEST	March 22, 2017
REVIEW COMPLETION DATE	May 23, 2017
REVIEW DIVISION	Center for Biologics Evaluation and Research
TEAM LEADER (TL)	Maura Oleary, MD
REVIEW DIVISION PM	Erica Giordano
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COA TL	Selena Daniels, PharmD, MS
ASSOCIATE DIRECTOR, COA STAFF	Elektra Papadopoulos, MD, MPH
COA TYPE	Patient-Reported Outcome
INSTRUMENT(S)	PedsQL; EQ-5D-3L
ENDPOINT(S) CONCEPT(S)	Health-related quality of life; health status
INTENDED POPULATION(S)	Pediatric and young adult patients (3-25 years) with relapsed/refractory B-cell acute lymphoblastic leukemia
<i>Please check all that apply:</i>	<input checked="" type="checkbox"/> Rare Disease/Orphan Designation <input checked="" type="checkbox"/> Pediatric

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Tisagenlecleucel (KYMRIATM)

PedsQL (health related quality of life); EQ-5D-3L (health status)

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Center for Biologics Evaluation and Research (CBER) regarding BLA 125646. The Applicant (Novartis) completed an interim analysis of the phase 2, pivotal, single arm, open-label clinical trial intended to determine efficacy and safety of CTL019 (Tisagenlecleucel) in pediatric and young adult patients (3-23 years of age) with relapse and refractory B-cell acute lymphoblastic leukemia (ALL). The proposed indication is treatment of pediatric and young adult patients with relapsed/refractory B-cell ALL. The Applicant implemented the following patient-reported outcome (PRO) instruments in the phase 2 pivotal clinical trial to assess health related quality of life (HRQoL).

PRO Instrument	Concept(s)	Endpoint ¹	Copy of Instrument
PedsQL (children; 8-12 years)	Physical, emotional, social, and school functioning	Exploratory	Appendix A
PedsQL (teens; 13-17 years)			Appendix B
PedsQL (adult; 18-25 years)			Appendix C
EQ-5D-Y (children: 8-12 years)	Mobility; self-care; usual activity; pain/discomfort; anxiety/depression		Appendix D
EQ-5D-3L (13 years and above)			Appendix E

CBER consulted the COA Staff to assess the validity and reliability of the PedsQL, EQ-5D-Y, and EQ-5D-3L instruments to support medical product labeling claims. The proposed PRO labeling claims in the United States Package Insert (USPI) Section 14 are as follows:

“Health-related quality of life (HRQoL) was evaluated by PedsQLTM and EQ-5D questionnaires completed by patients aged 8 and above. The mean change from baseline in the PedsQL total score was 13.5 at Month 3 and 15.3 at Month 6, and the mean change from baseline in the EQ VAS score was 14.1 at Month 3 and 15.5 at Month 6, indicating an overall improvement in HRQoL following TRADENAME infusion.”

The COA review concludes that the evidence submitted by the Applicant is insufficient to demonstrate that the PedsQL, EQ-5D-Y, and EQ-5D-3L instruments are adequate to measure health-related quality of life (HRQoL) in the context of this drug development program. Additionally the PRO data may be challenging to interpret or describe clinical benefits without labeling implications because of many concerns related to clinical trial design and implementation and data quality. However, ultimately, we defer to the CBER whether the PRO data can be supportive of medical product labeling claims.

Specific Concerns Related To PRO Data Interpretation:

The concerns surrounding the PRO data interpretation include the following:

- The open-label, single-arm clinical trial design is a major limitation for PRO data interpretation because patient’s knowledge of treatment assignment may lead to systematic overestimation of the treatment effect.

¹ Please see Section D 1.3 for an expanded endpoint hierarchy.

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- Addition of PRO instruments after initiation of the phase 2 trial resulted in an opportunity missed for a significant number of patients to participate in PRO data collection, which might have resulted in a biased sample.
- Observed high attrition rate at months 3 and 6 could have potentially introduced bias in the reported PRO data. Study attrition creates bias in the direction of those who complete participation in longitudinal studies.
- While improvement was observed in each domain of the PedsQL and EQ-5D-Y/3L instruments², it is unclear whether these were clinically meaningful improvements. It is unknown what constitutes a meaningful change in these instruments.

COA Staff did not request additional PRO analyses (e.g., item-level analyses) after discussion with the review team (Clinical and Statistics) as the review team deemed the limitations of the PRO instruments (see below) and corresponding data interpretation inadequate for inclusion in medical product labeling.

Specific Comments Related to the PRO Instruments:

This submission did not include an evidence dossier describing the development of the PedsQL and EQ-5D-Y/3L instruments (i.e. qualitative patient interviews), hence the review was primarily based on information provided in the clinical study report and existing literature. There was limited information provided regarding the instrument's development (validity, reliability, ability to detect change), particularly related to the patient perspective regarding these instruments. The general recommendation is patient input in the form of qualitative research in the target patient population, which was not provided as part of this application.

We have the following comments and observations on the PedsQL that may be helpful to consider for this as well future drug development programs:

PedsQL

- While the PedsQL includes the domains that are relevant to the overall concept of HRQL (e.g., physical, social, and emotional health), there is limited information to support that the PedsQL is fit-for-purpose for the context of use of this drug development program given that evidence of patient input from the target patient population was not provided.
- Some of the PedsQL domains do not appear to be clearly defined (e.g., About my health and activities domain combines physical function concepts and symptoms), which may make it difficult to describe clinical benefit for labeling.
- While there is evidence in the literature that pediatric patients as young as 8 years may be able to self-report, there can be considerable variability in reliability of their self-reporting. As such, it is unknown whether younger patients completely understood the content in the PedsQL (e.g., how far a block is?). However, while this may increase error, it alone might not be a critical flaw of the instrument that would preclude labeling

²See Appendices F and G

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in the setting of an appropriately designed study (i.e., it would not likely result in false or potentially misleading claims).

- There is potential for recall error due to the long recall period for the PedsQL (i.e., ONE month). PRO instruments that call for patients to rely on memory, especially if they must recall over a long period of time are likely to increase measurement error. However, the lengthy recall period alone may not be a critical flaw of the instrument that would preclude labeling in the setting of an appropriately designed study (i.e., it would not likely result in false or potentially misleading claims).

EQ-5D-Y/3L

- For the EQ-5D-Y/3L, there is no evidence to support content relevancy and its ability to estimate clinical benefit in this target population, as the EQ-5D-Y/3L is a generic preference-based measure designed to provide a single health utility index value for use in economic analyses.

Best Practices When Developing COA Endpoint Measurement Strategy:

For future medical product development, if a claim of superiority in a particular PRO concept is sought, we recommend that the PRO hypothesis is pre-specified and tested within the statistical hierarchy of hypothesis testing in the clinical trial and controlled for type 1 error. Further, statistical analysis methods, including a threshold for meaningful change, should be prospectively defined, especially procedures for handling missing values. We recommend sponsors to engage FDA early (e.g., Pre-IND) and throughout drug development to discuss COA endpoint strategy to ensure the selected instruments are fit-for-purpose and are well-defined and reliable for the contexts of use prior to initiation of pivotal studies.

B. BACKGROUND

Tisagenlecleucel-T (KYMRIATM) is a novel autologous, immunocellular cancer therapy, which involves re-programming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal cells.

Materials reviewed:

- BLA 125646 CTL019B2202 Interim Clinical Study Report
- Daniels, AT 2016-007, IND 104628 (DARRTS Reference ID 3904340)
- Stansbury, AT 2013-153, IND (b) (4) (DARRTS Reference ID 3420651)

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C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

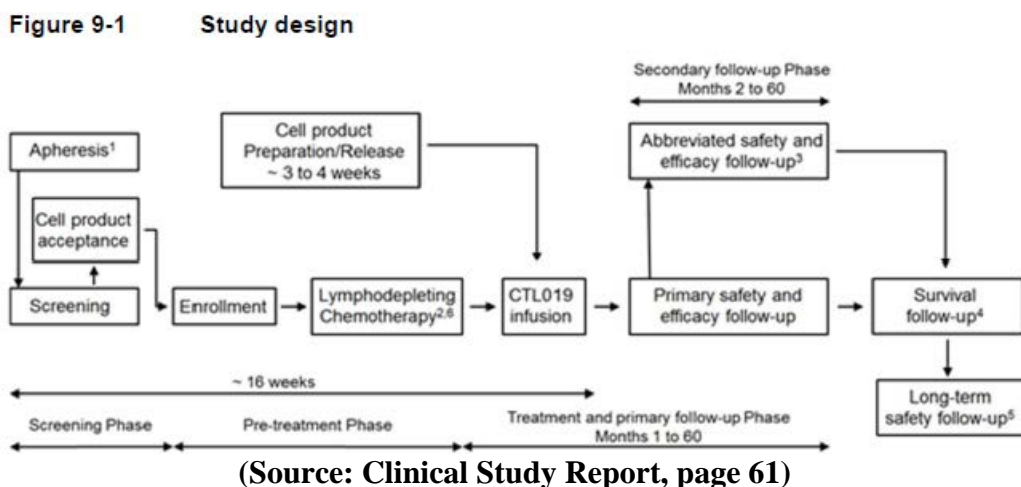
1.1 Clinical Trial Population

The pivotal clinical trial population included pediatric and young adult patients with relapsed and refractory B-cell acute lymphoblastic leukemia (ALL). The study included patients 3-23 years of age with B-cell ALL who were chemo-refractory, relapsed after allogeneic stem cell transplantation (SCT), or was otherwise ineligible for allogeneic SCT.

Refer to the Clinical review for additional background information.

1.2 Clinical Trial Design

The pivotal clinical trial was a phase 2, single-arm, multicenter to determine the efficacy and safety of tisagenlecleucel-T in pediatric and young adult patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Eighty-one (n=81) patients were enrolled in the trial. The study enrolled patients in 25 centers across US, EU, Canada, Australia, and Japan. Refer to the Clinical and Statistical reviews for additional background information.



Reviewer Comments: The open label, single-arm clinical trial design is a major limitation to the interpretability of PRO data. Patient's knowledge of treatment assignment may lead to systematic overestimation of the treatment effect.

1.3 Endpoint Hierarchy and Definition

The table below (created by this reviewer) shows select efficacy endpoints in the Study CTL019B2202 (Source: Clinical Study Report for Study CTL019B2202).

Concept	Endpoint	Assessment
Primary Endpoint		

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Overall Remission Rate (ORR)	ORR as assessed by independent review committee	--
Other Secondary Endpoint		
Health related quality of life	Describe the effect of CTL019 therapy on patient reported outcomes	PedsQL; EQ-5D -Y; EQ-5D-3L

Refer to the Clinical and Statistical reviews for additional background information.

Reviewer Comments: The PRO endpoints were not controlled for type 1 error. The pre-specified PRO endpoints analyses for PedsQL and EQ-5D for patients aged 8 and above included descriptive statistics (e.g., mean, median, and frequency) and change from baseline of the summary scores for each post-baseline time-point.

1.4 Labeling or promotional claim(s) based on the COA

The proposed PRO-related labeling claims in the Tisagenlecleucel-T United States Package Insert (USPI) Section 14 are as follows:

“Health-related quality of life (HRQoL) was evaluated by PedsQLTM and EQ-5D questionnaires completed by patients aged 8 and above. The mean change from baseline in the PedsQL total score was 13.5 at Month 3 and 15.3 at Month 6, and the mean change from baseline in the EQ VAS score was 14.1 at Month 3 and 15.5 at Month 6, indicating an overall improvement in HRQoL following TRADENAME infusion.”

2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The Applicant did not provide corresponding conceptual framework. This reviewer created the table below outlining the conceptual framework based on the copies of the instruments.

<i>Domains</i>	<i>General Concept</i>
<ul style="list-style-type: none">• Emotional functioning• Social functioning• School functioning• Physical functioning	<i>Health related quality of life as assessed by PedsQL</i>
<ul style="list-style-type: none">• Mobility• Self-care• Usual activities• Pain/discomfort• Anxiety/depression• Global health	<i>Health status as assessed by EQ-5D</i>

3 CLINICAL OUTCOME ASSESSMENT(S)

Instruments:

- **Pediatric Quality of Life Inventory (PedsQL Version 4.0):** The PedsQL is a 23-item generic PRO instrument designed to measure health related quality of life (HRQoL) in children and youth aged 0-25 years. This instrument covers four dimensions of HRQoL: physical functioning, emotional functioning, social functioning, and school functioning. Patients rate each item on a 5-point Likert type frequency scale ranging from “Never”

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(equals 0) to “Almost always” (equals 4). The Applicant utilized three different age-appropriate versions of the PedsQL in the Study CTL019B2202 (PedsQL Children for 8-12 years old, PedsQL Teen for 13-17 years old, and PedsQL Adult for 18 years and older). While the overall dimensions of HRQoL remained same for various versions of the instrument, some item content differed for each age group. The PedsQL recall period is one-month.

- **EuroQoL (EQ-5D-3L):** The EQ-5D is a 5-item generic patient-reported preference-based instrument designed to assess health status in adults and in adolescents aged 12 to 18 years across five dimensions of HRQoL: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Patients rate each of the items as “no problem,” “some problem,” or “extreme problem.” The second section of the instrument measures self-rated (global) health status utilizing a vertically oriented visual analog scale where 100 represents the “best possible health state” and 0 represents the “worst possible health state.” Patients are asked to rate their current health by placing a mark along this continuum. The recall period is “today” for the entire instrument.
 - **Child-friendly version of EuroQoL (EQ-5D-Y Version 1.0):** The EQ-5D-Y is a pediatric version of the EQ-5D-3L designed to assess health status in pediatric patients between the ages of 8 and 12 years across five dimension of HRQoL and a global assessment similar to EQ-5D-3L above. The recall period is “today” for the entire instrument.

Prior versions: The corresponding documents were not provided.

User manuals: The corresponding documents were not provided.

Timing, data collection method, and mode of administration: The Applicant administered PedsQL (Children) and EQ-5D-Y to pediatric patients 8-12 years, PedsQL (Teen) and EQ-5D-Y to adolescents 13-17 years, and PedsQL (Adult) and EQ-5D-3L to adults 18 years and older (See table below). These instruments were self-administered using paper-pen method prior to treatment administration at baseline, Day 28, Month 3, and Month 6.

Age at study entry	PedsQL TM V4 Version	EQ-5D Version
2-4	Not Done	Not Done
5-7	Not Done	Not Done
8-12	PedsQL (Children)	EQ-5D-Y
13-17	PedsQL (Teen)	EQ-5D
18+	PedsQL (Adult)	EQ-5D

(Source: Clinical Study Report for Study CTL019B2202, Page 3576)

Training method/materials: The corresponding documents were not provided.

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4 CONTENT VALIDITY

The Applicant provided relevant literature references to help support the content validity of the PedsQL and EQ-5D instruments.

To date, the following information has been submitted (check all that apply):

- ☒ Literature review and/or publications
- ☐ Documentation of expert input
- ☐ Qualitative study protocols and interview guides for focus group or patient interviews
- ☐ Chronology of events for item generation, modification, and finalization (item tracking matrix)
- ☐ Qualitative study summary with evidence to support item relevance, item stems and response options, and recall period
- ☐ Qualitative support for meaningful change
- ☐ Quantitative study summary with evidence to support item retention and scoring
- ☐ Transcripts (if available)

Reviewer Comments:

PedsQL:

The PedsQL instruments may be widely used in clinical trials to assess health-related quality of life (HRQoL). Although health-related quality of life (HRQoL) may be important to patients, it is a complex, multi-domain concept that can be challenging to measure in clinical trials. Because HRQoL measures concepts that might be influenced by factors beyond the treatment and consequently not sensitive to treatment effect, this reviewer generally recommends sponsors to select and separately analyze the most important patient-reported symptoms and functional impacts (i.e., physical function) that are responsive to treatment.

While there is evidence in the literature that pediatric patients as young as 8 years may be able to self-report, there can be considerable variability in reliability of their self-reporting. For example, it is unknown whether young patients understood the content (e.g., how far a block is?). Furthermore, inclusion of certain content may be problematic. For example, are children with a serious illness such as relapsed/refractory B cell ALL cleared to play sports given their treatment protocol?

Additionally, the PedsQL recall period of one-month is a limitation. PRO instruments that call for patients to rely on memory, especially if they must recall over a long period of time, compare their current state with an earlier period, or average their response over a period of time, are likely to undermine content validity. Response is likely to be influenced by patient's state at the time of recall. The choice of recall period that is most suitable depends on the instrument's purpose and intended use; the variability, duration, frequency, and intensity of the concept measures; the disease or condition's characteristics; and the tested treatment.

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EQ-5D-Y/3L:

The EQ-5D-Y/3L instruments are generic preference-based measures commonly used to provide a single health utility index value for use in economic analyses and lack evidence of content validity for use in estimating clinical benefit for labeling claims. Additionally, although there is evidence in the literature that pediatric patients as young as 8 years may be able to self-report, there can be considerable variability in reliability of their self-reporting as described above. However, this reviewer acknowledges that the EQ-5D-Y/3L may be necessary for other regulatory authorities and/or payers.

We recommend sponsors to engage FDA early (e.g., Pre-IND) and throughout drug development to discuss COA/PRO endpoint strategy to ensure the selected instruments are fit-for-purpose and are well-defined and reliable for the contexts of use.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The Applicant submitted relevant literature references to help support other measurement properties. However, because there are some concerns regarding the content validity, it is not possible to interpret the quantitative findings.

Reviewer comments: The Applicant used the EQ-5D-Y/3L in the registrational trial. There are some known measurement challenges for this version that has been highlighted in the literature. The EQ-5D-5L shows better measurement properties than the EQ-5D-3L (more discriminative, lower ceiling effects)³.

6 INTERPRETATION OF SCORES

The Applicant did not provide corresponding information.

7 SCORING ALGORITHM

The PRO instruments were scored according to corresponding scoring algorithms where the raw scores were transformed to 0-100-point scale, generating individual domain and summary scores. Higher scores on both PRO instruments were indicative of better quality of life. The PedsQL, EQ-5D-3L, and EQ-5D-Y scoring algorithms are publically available:

- PedsQL: <http://www.pedsqol.org/PedsQL-Scoring.pdf>
- EQ-5D-3L: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/EQ-5D-3L_UserGuide_2015.pdf

³ Agborsangaya, C.B., Lahtinen, M., Cooke, T. & Johnson, J.A. (2014). Comparing the EQ-5D 3L and 5L: measurement properties and association with chronic conditions and multimorbidity in the general population. *Health and Quality of Life Outcomes*, 12: 74-80.

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- EQ-5D-Y:
http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/EQ-5D-Y_User_Guide_v1.0_2014.pdf

8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The Applicant required patients to use translated PRO instruments per patients' preferred language. The PedsQL, EQ-5DY, and EQ-5D-3L are available in multiple languages.

9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable

10 REVIEW USER MANUAL

The Applicant did not provide corresponding user manuals.

11 KEY REFERENCES FOR COA

Ewing JE, King MT, Smith NF (2009) Validation of modified forms of the PedsQL generic core scales and cancer module scales for adolescents and young adults (AYA) with cancer or a blood disorder. Qual Life Res; 18:231-44.

Pickard AS, Neary MP, Cella D (2007) Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes; 5:70.

Varni JW, Burwinkle TM, Katz ER, et al (2002) The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. Cancer. 94:2090-106.

Varni JW, Burwinkle TM, Seid M, et al (2003) The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr; 3:329-41.

Wille N, Badia X, Bonsel G, et al (2010) Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Qual Life Res; 19:875-86.

E. APPENDICES

Appendix A: PedsQL (Children 8-12 years)

Appendix B: PedsQL (Teens 13-17 years)

Appendix C: PedsQL (Ages 18-25 years)

Appendix D: EQ-5D-Y

Appendix E: EQ-5D-3L

Appendix F: PedsQL PRO Results

Appendix G: EQ-5D PRO Results

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Appendix A: PedsQL (Children 8-12 years)

PedsQL
Pediatric Quality of Life Inventory
CHILD REPORT (ages 8-12)

Date of assessment
DD-MON-YYYY

In the past ONE month, how much of a problem has this been for you?

ABOUT MY HEALTH AND ACTIVITIES
(problems with)

1. It is hard for me to walk more than one block
2. It is hard for me to run
3. It is hard for me to do sports activity or exercise
4. It is hard for me to lift something heavy
5. It is hard for me to take a bath or shower by myself
6. It is hard for me to do chores around the house
7. I hurt or ache
8. I have low energy

Never	Almost Never	Some- times	Often	Almost Always
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

ABOUT MY FEELINGS (problems with)

1. I feel afraid or scared
2. I feel sad or blue
3. I feel angry
4. I have trouble sleeping
5. I worry about what will happen to me

Never	Almost Never	Some- times	Often	Almost Always
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

HOW I GET ALONG WITH OTHERS (problems with)

1. I have trouble getting along with other kids
2. Other kids do not want to be my friend
3. Other kids tease me
4. I cannot do things that other kids my age can do
5. It is hard to keep up when I play with other kids

Never	Almost Never	Some- times	Often	Almost Always
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

ABOUT SCHOOL (problems with)

1. It is hard to pay attention in class
2. I forget things
3. I have trouble keeping up with my schoolwork
4. I miss school because of not feeling well
5. I miss school to go to the doctor or hospital

Never	Almost Never	Some- times	Often	Almost Always
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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Appendix B: PedsQL (Teens 13-17)

PedsQLTM
Pediatric Quality of Life Inventory
TEEN REPORT (ages 13-18)

Date of assessment
DD-MON-YYYY

In the past ONE month, how much of a problem has this been for you

ABOUT MY HEALTH AND ACTIVITIES (problems with;)

- | | Never | Almost
Never | Some-
times | Often | Almost
Always |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. It is hard for me to walk more than one block | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. It is hard for me to run | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. It is hard for me to do sports activity or exercise | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. It is hard for me to lift something heavy | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. It is hard for me to take a bath or shower by myself | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. It is hard for me to do chores around the house | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. I hurt or ache | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. I have low energy | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

ABOUT MY FEELINGS (problems with;)

- | | Never | Almost
Never | Some-
times | Often | Almost
Always |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. I feel afraid or scared | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. I feel sad or blue | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. I feel angry | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. I have trouble sleeping | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. I worry about what will happen to me | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

HOW I GET ALONG WITH OTHERS (problems with;)

- | | Never | Almost
Never | Some-
times | Often | Almost
Always |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. I have trouble getting along with other teens | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Other teens do not want to be my friend | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Other teens tease me | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. I cannot do things that other teens my age can do | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. It is hard to keep up when I play with other teens | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

ABOUT SCHOOL (problems with;)

- | | Never | Almost
Never | Some-
times | Often | Almost
Always |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. It is hard to pay attention in class | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. I forget things | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. I have trouble keeping up with my schoolwork | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. I miss school because of not feeling well | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. I miss school to go to the doctor or hospital | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Clinical Outcome Assessment Review

Nikunj Patel, PharmD

BLA 125646

Tisagenlecleucel (KYMRIATM)

PedsQL (health related quality of life); EQ-5D-3L (health status)

Appendix C: PedsQL (Ages 18-25)

PedsQL

Young Adult Quality of Life Inventory
YOUNG ADULT REPORT (ages 18-25)

Date of assessment
DD-MON-YYYY

In the past ONE month, how much of a problem has this been for you?

ABOUT MY HEALTH AND ACTIVITIES (problems with)

1. It is hard for me to walk more than one block
2. It is hard for me to run
3. It is hard for me to do sports activity or exercise
4. It is hard for me to lift something heavy
5. It is hard for me to take a bath or shower by myself
6. It is hard for me to do chores around the house
7. I hurt or ache
8. I have low energy

Never	Almost Never	Some- times	Often	Almost Always
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

ABOUT MY FEELINGS (problems with)

1. I feel afraid or scared
2. I feel sad or blue
3. I feel angry
4. I have trouble sleeping
5. I worry about what will happen to me

Never	Almost Never	Some- times	Often	Almost Always
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

YOUNG ADULT REPORT (ages 18-25)

HOW I GET ALONG WITH OTHERS (problems with)

1. I have trouble getting along with other adults
2. Other adults do not want to be my friend
3. Other adults tease me
4. I cannot do things that other my age can do
5. It is hard to keep up with my peers

Never	Almost Never	Some- times	Often	Almost Always
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

ABOUT MY WORK/STUDIES (problems with)

1. It is hard to pay attention at work or school
2. I forget things
3. I have trouble keeping up with my work or studies
4. I miss work or school because of not feeling well
5. I miss work or school to go to the doctor or hospital

Never	Almost Never	Some- times	Often	Almost Always
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Clinical Outcome Assessment Review

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Tisagenlecleucel (KYMRIATM)

PedsQL (health related quality of life); EQ-5D-3L (health status)

Appendix D: EQ-5D-Y

EQ-5D-Y

Describing your health TODAY

Under each heading, please tick the ONE box that best describes your health TODAY.

Mobility (*walking about*)

I have no problems walking about ☐

I have some problems walking about ☐

I have a lot of problems walking about ☐

Looking after myself

I have no problems washing or dressing myself ☐

I have some problems washing or dressing myself ☐

I have a lot of problems washing or dressing myself ☐

Doing usual activities (*for example, going to school, hobbies, sports, playing, doing things with family or friends*)

I have no problems doing my usual activities ☐

I have some problems doing my usual activities ☐

I have a lot of problems doing my usual activities ☐

Having pain or discomfort

I have no pain or discomfort ☐

I have some pain or discomfort ☐

I have a lot of pain or discomfort ☐

Feeling worried, sad or unhappy

I am not worried, sad or unhappy ☐

I am a bit worried, sad or unhappy ☐

I am very worried, sad or unhappy ☐

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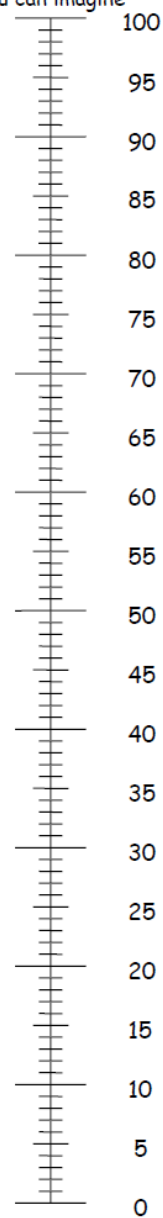
Tisagenlecleucel (KYMRIATM)

PedsQL (health related quality of life); EQ-5D-3L (health status)

How good is your health TODAY

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Please mark an X on the line that shows how good or bad your health is TODAY.

The best health
you can imagine



The worst health
you can imagine

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Appendix E: EQ-5D-3L

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

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Tisagenlecleucel (KYMRIATM)

PedsQL (health related quality of life); EQ-5D-3L (health status)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**

Best
imaginable
health state

100

90

80

70

60

50

40

30

20

10

0

Worst
imaginable
health state

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Tisagenlecleucel (KYMRIATM)

PedsQL (health related quality of life); EQ-5D-3L (health status)

Appendix F: PedsQL PRO Results

(Source: Clinical Study Report for Study No. CTL019B2202, page 123)

Table 11-12 PedsQL scores and change from Baseline at Month 3 and Month 6 (Interim efficacy analysis set - Patients 8-year-old and older)

	Statistics	Subscale					Total score N=39
		Emotional	Social	School	Physical	Psychosocial Health	
BL	n	34	34	31	34	34	34
	Mean (SD)	62.8 (19.82)	74.1 (19.48)	56.6 (24.61)	47.4 (28.05)	64.5 (18.60)	58.4 (20.53)
	Median	60.0	75.0	60.0	48.5	68.3	59.3
	Min-Max	20.0-100.0	30.0-100.0	5.0-95.0	0-96.9	18.3-98.3	19.6-97.8
Month 3	n	26	26	25	26	26	26
	Mean (SD)	79.0 (18.97)	80.2 (16.88)	66.8 (24.49)	66.9 (22.46)	75.7 (17.81)	72.7 (17.52)
	Median	85.0	80.0	70.0	68.8	76.7	70.7
	Min-Max	35.0-100.0	30.0-100.0	10.0-100.0	14.3-100.0	25.0-100.0	33.7-100.0
Month 3 change from BL	n	26	26	23	26	26	26
	Mean (SD)	15.4 (18.27)	7.5 (15.38)	9.1 (13.11)	19.2 (20.71)	10.8 (14.02)	13.9 (15.25)
	Median	17.5	7.5	10.0	23.5	11.7	12.0
	Min-Max	-20.0-40.0	-30.0-40.0	-15.0-35.0	-31.3-52.3	-21.7-37.5	-25.0-43.9
Month 6	n	15	15	15	15	15	15
	Mean (SD)	76.0 (26.40)	78.0 (16.45)	68.7 (17.06)	66.1 (17.99)	74.3 (16.96)	71.4 (15.35)
	Median	85.0	80.0	70.0	65.6	71.7	69.6
	Min-Max	15.0-100.0	50.0-100.0	40.0-95.0	37.5-96.9	38.3-98.3	51.1-95.7
Month 6 change from BL	n	15	15	13	15	15	15
	Mean (SD)	13.3 (22.73)	6.7 (19.88)	13.5 (13.29)	16.3 (31.23)	10.7 (16.00)	12.8 (20.41)
	Median	5.0	5.0	15.0	18.8	6.7	9.8
	Min-Max	-35.0-45.0	-35.0-30.0	-5.0-35.0	-31.3-64.8	-16.7-32.7	-21.8-46.2

BL: Baseline (the most current assessment on or prior to the date of enrollment).

n for each time point is the number of patients with non-missing score at that time point.

n for change from Baseline is the number of patients with non-missing score both at Baseline and at that post-Baseline visit.

Source: [Table 14.2-12.1](#)

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Tisagenlecleucel (KYMRIATM)

PedsQL (health related quality of life); EQ-5D-3L (health status)

Appendix G: EQ-5D PRO Results

(Source: Clinical Study Report for Study No. CTL019B2202, pp125-126)

Table 11-13 EQ VAS values and change from Baseline by visit (Interim efficacy analysis set - Patients 8-year-old and older)

	Statistics	All Patients N=39
Baseline	n	33
	Mean (SD)	69.4 (19.60)
	Median	73.0
	Min-Max	25-100
Month 3	n	27
	Mean (SD)	84.3 (15.11)
	Median	88.0
	Min-Max	50-100
Month 3 change from BL	n	24
	Mean (SD)	13.7 (21.23)
	Median	11.5
	Min-Max	-40.0-51.0
Month 6	n	14
	Mean (SD)	86.0 (13.29)
	Median	85.5
	Min-Max	55-100
Month 6 change from BL	n	14
	Mean (SD)	10.9 (20.49)
	Median	14.5
	Min-Max	-40.0-40.0

Baseline = The most current assessment on or prior to the date of enrollment.

n for each visit is the number of patients with non-missing score at that visit.

n for change from Baseline is the number of patients with non-missing score both at Baseline and at that post-Baseline visit.

Source: [Table 14.2-11.2](#)

EQ-5D questionnaire

CTL019 infusion led to a decrease in the severity of problems related to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression at Month 3 and Month 6 compared to Baseline as assessed via the EQ-5D questionnaire ([Table 11-14](#)).

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PedsQL (health related quality of life); EQ-5D-3L (health status)

Table 11-14 EQ-5D at Baseline, Month 3 and Month 6 (Interim efficacy analysis set - Patients 8-year-old and older)

Timepoint EQ-5D Dimension	Total n	All Patients N=39		
		Level 1 n (%)	Level 2 n (%)	Level 3 n (%)
Baseline				
Mobility	34	11 (32.4)	19 (55.9)	4 (11.8)
Self-Care	34	21 (61.8)	11 (32.4)	2 (5.88)
Usual Activities	33	9 (27.3)	17 (51.5)	7 (21.2)
Pain/Discomfort	34	10 (29.4)	19 (55.9)	5 (14.7)
Anxiety/Depression	34	20 (58.8)	14 (41.2)	0
Month 3				
Mobility	27	16 (59.3)	11 (40.7)	0
Self-Care	27	22 (81.5)	5 (18.5)	0
Usual Activities	27	17 (63.0)	10 (37.0)	0
Pain/Discomfort	27	16 (59.3)	11 (40.7)	0
Anxiety/Depression	27	17 (63.0)	10 (37.0)	0
Month 6				
Mobility	15	7 (46.7)	8 (53.3)	0
Self-Care	15	13 (86.7)	2 (13.3)	0
Usual Activities	15	8 (53.3)	7 (46.7)	0
Pain/Discomfort	15	8 (53.3)	7 (46.7)	0
Anxiety/Depression	15	11 (73.3)	4 (26.7)	0

Level 1 = no problems; Level 2 = some problems, Level 3 = severe problems.

The total n is the total number of patients with non-missing value for that dimension at the corresponding time point.

The percentages are based on the respective total N in that row for each time point

Source: [Table 14.2-11.1](#)