



**U.S. FOOD & DRUG
ADMINISTRATION**

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research**

CBER SENTINEL PROGRAM SUFFICIENCY MEMORANDUM

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Subject: CBER Sentinel Program Sufficiency Assessment

Product: Brexucabtagene Autoleucel (KTE-X19)

Sponsor: Kite Pharma Inc.

STN: 125703/0

Proposed Indication: Brexucabtagene Autoleucel is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

Approval Type: ☒ Priority ☐ Standard review

Submission Date: December 11, 2019

Action Due Date: August 10, 2020

1. Objectives/Scope:

This memo reviews the capability and sufficiency of the CBER active post-market risk identification and analysis system referred to as the CBER Sentinel Program to evaluate the serious risk for secondary malignancies associated with brexucabtagene autoleucel (referred to as KTE-X19 in this memo), a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL), in lieu of a safety post-market requirement (PMR) study under FDAAA¹. The CBER Sentinel Program covers activities conducted through the contract with the Harvard Pilgrim Health Care Institute, the current and future contracts through the Biologics Effectiveness and Safety (BEST) Initiative, and the interagency agreement with the Centers for Medicare and Medicaid (CMS). Please see the STN 125703/0 OBE/Division of Epidemiology (DE) review of the Pharmacovigilance Plan (PVP) for background on the serious risk for secondary malignancies. KTE-X19 contains human blood cells that are genetically modified with retroviral vector. FDA Guidance document on *Long Term Follow-up After Administration of Human Gene Therapy Products (2020)* recommends 15-year long-term follow-up for integrating vectors such as retroviral vectors for the potential risk of secondary malignancies due to insertional mutagenesis. For evaluation of secondary malignancies in patients treated with KTE-X19, tumor tissue will need to be obtained and sent to the sponsor to analyze for persistence of the vector used in KTE-X19.

2. CBER Sentinel Program Sufficiency Assessment:

Determination of the sufficiency of the CBER Sentinel Program to further characterize the serious risk of secondary malignancies associated with KTE-X19 was based on the following factors:

2.1 Identification of exposure to KTE-X19

2.2 Identification of the appropriate study population: Adult patients with relapsed or refractory mantle cell lymphoma (MCL)

2.3 Characterization of occurrence of secondary malignancies in KTE-X19 recipients

2.4 Identification of exposure to comparator product: not applicable for this memo

¹ Under section 901 of the Food and Drug Administration Amendments Act (FDAAA), “The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient to meet the purposes set forth in subparagraph (B).” NOTE: The active post-market risk identification and analysis system under subsection (k)(3) refers to the Sentinel program.

² ISBT 128 is a global standard for the safe identification, accurate labeling, and efficient information transfer of medical products of human origin (including blood, cells, tissues, milk, and organ products) across disparate national and international health care systems. <https://www.iccbba.org/isbt-128-basics>

2.1 Assessment for identification of exposure to KTE-X19

2.1.1. Is the CBER Sentinel Program able to identify the product (exposure) of interest?

Please answer each question i – xi, including sub-questions.		Yes	No
i.	Is this the first or the only FDA-approved product for the indication?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
ii.	Can the exposure be identified using a billing or reimbursement coding system? <i>If yes, check all that apply:</i> <input checked="" type="checkbox"/> CPT <input checked="" type="checkbox"/> HCPCS <input checked="" type="checkbox"/> NDC <input checked="" type="checkbox"/> ICD <input type="checkbox"/> Other: [Coding system]	<input checked="" type="checkbox"/>	<input type="checkbox"/>
iii.	Is the ISBT 128 coding system ² needed for the product identification?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
iv.	Can the reimbursement code of the product identify the brand name?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
v.	Is a history of uptake for previously approved products for the same indication needed? <i>If yes, list all products:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
vi.	Is medical chart review needed to identify or validate the identification of this product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
vii.	Are claims data sources needed for exposure identification?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
viii.	Are electronic health record (EHR) data sources needed for exposure identification?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
ix.	Are any other health record type data sources needed for exposure identification? <i>If yes, all health record types needed: [e.g., Registries, any other health records]</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
x.	Is product lot number needed for identification of this product?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
xi.	Is there a care setting of interest required for identification of this product? <i>If yes, check all that apply:</i> <input checked="" type="checkbox"/> Inpatient <input checked="" type="checkbox"/> Outpatient <input type="checkbox"/> Emergency Room <input type="checkbox"/> Other: Hospitalization	<input checked="" type="checkbox"/>	<input type="checkbox"/>

2.1.2. Summary for product exposure identification

- ☐ Available data sources in the CBER Sentinel Program are *sufficient to identify the exposure of the product [name] due to reasons identified in [list all bullets from 2.1.1.i.—2.1.1.xi. that support sufficiency]*.
- ☒ Available data sources in the CBER Sentinel Program are *NOT sufficient to identify the exposure of the product KTE-X19 due to reasons identified in 2.1.1.iv. The CPT and ICD procedure codes used for billing do not specifically indicate brand name. This will lead to incomplete ascertainment of exposure to the product.*

2.2. Assessment for identification of the appropriate study population: Adult patients with relapsed or refractory mantle cell lymphoma (MCL)

2.2.1. Is the CBER Sentinel Program able to identify the study population of interest?

Please provide an answer for each question i – vi, including sub-questions.		Yes	No
i.	Does age need to be identified? <i>If <u>yes</u>, list the inclusion and exclusion criteria.. Check all that apply for the level of granularity in</i> <input checked="" type="checkbox"/> Days <input checked="" type="checkbox"/> Months <input checked="" type="checkbox"/> Years	<input checked="" type="checkbox"/>	<input type="checkbox"/>
ii.	Does sex need to be identified? <i>If <u>yes</u>, list the inclusion Female, Male and Other. There are no exclusion criteria</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
iii.	Does race need to be identified? <i>If <u>yes</u>, list the inclusion [List race to be included] and exclusion criteria [List race to be excluded]</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
iv.	Can the study population be identified in the data sources required for the exposure and outcome identification?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
v.	Was this population previously identified within the CBER Sentinel Program activities?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
vi.	Is there a requirement for linking mothers to their newborns in the data sources?	<input type="checkbox"/>	<input checked="" type="checkbox"/>

2.2.2. Summary for identification of study population

- ☐ Available data sources in the CBER Sentinel Program are *sufficient to identify the study population of interest* due to reasons identified in [list all bullets from 2.2.1.i.—2.2.1.vi. that support sufficiency].
- ☒ Available data sources in the CBER Sentinel Program are *NOT sufficient to identify the study population of interest* due to reasons identified in 2.2.1.iv. This study population cannot be identified within the CBER Sentinel data sources due to the complexity of the diagnosis of relapsed or refractory mantle cell lymphoma (MCL); a validated algorithm is not available.

2.3 Assessment for characterization of occurrence of secondary malignancies in KTE-X19 recipients

2.3.1 Is the CBER Sentinel Program able to identify the outcome(s) of interest?

Please provide an answer for each question i – xi, including sub-questions.		Yes	No
i.	Can the outcome of interest be identified using a billing or reimbursement coding system? <i>If yes, check all that apply:</i> <input checked="" type="checkbox"/> ICD <input type="checkbox"/> CPT <input type="checkbox"/> Other: <i>Medical Record Review</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
ii.	Are there surrogate data elements or biomarkers that can assist to identify the outcome of interest? <i>If yes, check all that apply:</i> <input checked="" type="checkbox"/> Laboratory Test Results <input checked="" type="checkbox"/> Prescription drug <input checked="" type="checkbox"/> Order of lab test <input checked="" type="checkbox"/> Order of other diagnostic modalities <input type="checkbox"/> Other: <i>[Data element/Biomarker]</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
iii.	Are there specific care settings in which this outcome is identified? <i>If yes, check all that apply:</i> <input checked="" type="checkbox"/> Inpatient <input checked="" type="checkbox"/> Outpatient <input checked="" type="checkbox"/> Emergency Room <input checked="" type="checkbox"/> Other: <i>Hospitalization</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
iv.	Was this outcome previously identified within the CBER Sentinel Program activities? <i>If yes, in what population was it used?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
v.	Is there a validated and acceptable algorithm available in the literature to identify the outcome of interest? <i>If yes, list the PPV [PPV] and describe the population in which it was validated:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
vi.	Is a minimum follow-up time needed to identify the outcome of interest? <i>If yes, what is the required follow-up period?</i> <i>15 years</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
vii.	Is medical chart review required to identify or validate the identification of the outcome?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
viii.	Is the prevalence of the outcome known? <i>If yes, list background rates.</i> Second cancer incidence reached 12.3% within 25 years (95% CI=11.9%-12.7%) ² .	<input checked="" type="checkbox"/>	<input type="checkbox"/>
ix.	Are claims data sources needed for outcome characterization?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
x.	Are electronic health record (EHR) data sources needed for outcome characterization?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
xi.	Are any other health record type data sources needed for outcome characterization? <i>If yes, all health record types needed: [e.g., Registries, any other health records]</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

2.3.2 Summary of outcome characterization

☐ Available data sources in the CBER Sentinel Program are *sufficient to identify the outcome of [serious risk]* due to reasons identified in [list all bullets from 2.3.1.i.—2.3.1.xi. that support sufficiency].

☒ Available data sources in the CBER Sentinel Program are *NOT sufficient to identify the outcome of secondary malignancies in KTE-X19 recipients* due to reasons

² https://seer.cancer.gov/archive/publications/mpmono/MPMonograph_complete.pdf

identified in bullet 2.3.1.vi. Since the outcome takes a long time to develop and to manifest any signs and symptoms, a minimum follow up time of 15 years is required to assess and diagnose the outcome of secondary malignancies. CBER Sentinel Program data sources do not have sufficient longitudinal data on patients to conduct this study. Also, tumor tissue will need to be obtained to analyze for persistence of the vector used in KTE-X19. CBER Sentinel Program does not collect biospecimens and does not have access to pathology results if such diagnostic examination is performed.

2.4. Assessment for identification of exposure to comparator product: There is no comparator product therefore this section is not applicable.

2.4.1. Is the CBER Sentinel Program able to identify the required comparator product?
Respond to the questions below, if applicable.

Please provide an answer for each question i – xi, including sub-questions		Yes	No
i.	Is a comparator product needed for the assessment? <i>If no, skip to section III for Recommendation. If yes, list all products:</i>	<input type="checkbox"/>	<input type="checkbox"/>
ii.	Can the comparator product be identified using a billing reimbursement code? <i>If yes, check all that apply: <input type="checkbox"/> CPT <input type="checkbox"/> HCPCS <input type="checkbox"/> NDC <input type="checkbox"/> ICD <input type="checkbox"/> Other: [Billing reimbursement code]</i>	<input type="checkbox"/>	<input type="checkbox"/>
iii.	Can the comparator product be exclusively identified using the billing reimbursement codes?	<input type="checkbox"/>	<input type="checkbox"/>
iv.	Is the ISBT 128 coding system ² needed for the comparator product identification?	<input type="checkbox"/>	<input type="checkbox"/>
v.	Can the reimbursement code of the comparator product identify the brand name?	<input type="checkbox"/>	<input type="checkbox"/>
vi.	Is medical chart review needed to identify or validate the identification of this comparator product?	<input type="checkbox"/>	<input type="checkbox"/>
vii.	Are claims data sources needed for exposure identification of the comparator product?	<input type="checkbox"/>	<input type="checkbox"/>
viii.	Are electronic health record (EHR) data sources needed for exposure identification of the comparator product?	<input type="checkbox"/>	<input type="checkbox"/>
ix.	Are any other health record type data sources needed for exposure identification of the comparator product? <i>If yes, list all health record types needed: [e.g., Registries, any other health records]</i>	<input type="checkbox"/>	<input type="checkbox"/>
x.	Is product lot number needed for identification of this comparator product?	<input type="checkbox"/>	<input type="checkbox"/>

Please provide an answer for each question i – xi, including sub-questions		Yes	No
xi.	Is there a care setting of interest for identification of this comparator product? <i>If yes, check all that apply:</i> <input type="checkbox"/> <i>Inpatient</i> <input type="checkbox"/> <i>Outpatient</i> <input type="checkbox"/> <i>Emergency Room</i> <input type="checkbox"/> <i>Other: Hospitalization</i>	<input type="checkbox"/>	<input type="checkbox"/>

2.4.2. Summary for comparator exposure identification

- ☐ Available data sources in the CBER Sentinel Program are *sufficient to identify the comparator product* due to reasons identified in [list all bullets from 2.4.1.i.—2.4.1.xi. that support sufficiency].
- ☐ Available data sources in the CBER Sentinel Program are *NOT sufficient to identify the comparator product* due to reasons identified in [list all bullets from 2.4.1.i.—2.4.1.xi. that support insufficiency].

3. Recommendation:

- ☐ The CBER Sentinel Program is *sufficient* to assess the serious risk of [describe] associated with [product] at this time. [Summarize all bullets 2.1.—2.4. that support sufficiency]
- ☒ The CBER Sentinel Program is *NOT* sufficient to assess the serious risk of secondary malignancies associated with KTE-X19 in lieu of a PMR study under FDAAA. The data sources available are unable to identify the specific brand KTE-X19 using CPT and ICD 10 billing codes. In addition, the identification of the serious risk of secondary malignancies requires a very long follow up period (15 years) and tumor tissue will need to be obtained and analyzed for persistence of the vector used in KTE-X19. CBER Sentinel data sources are unable to identify outcomes with such a long follow up period and collect tumor tissue needed for testing.