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

CBER SENTINEL PROGRAM SUFFICIENCY MEMORANDUM

From:	Joyce Obidi Health Scientist, CBER Sentinel Program Office of Biostatistics and Epidemiology (OBE)
Through:	Azadeh Shoiabi Associate Director, Post-market Surveillance, CBER Sentinel Program, OBE
To:	Narayan Nair Director, Division of Epidemiology (DE), OBE
Subject:	CBER Sentinel Program Sufficiency Assessment
Product:	Breyanzi (JCAR017)
Sponsor:	Juno Therapeutics, Inc., a Celgene Company
STN:	125714/0
Proposed Indication:	Breyanzi is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies.
Approval Type:	☒ Priority ☐ Standard review
Submission Date:	December 18, 2019
Action Due Date:	August 17, 2020, extended to November 16, 2020, due to Major Amendment

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 Breyanzi, a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies, in lieu of a safety post-market requirement (PMR) study under FDAAA[1]. 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 125714/0 OBE/Division of Epidemiology (DE) review of the Pharmacovigilance Plan (PVP) for background on the serious risk for secondary malignancies. Breyanzi contains human blood cells that are genetically modified with lentiviral 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 lentiviral vectors for the potential risk of secondary malignancies due to insertional mutagenesis. For evaluation of secondary malignancies in patients treated with Breyanzi, tumor tissue will need to be obtained and sent to the sponsor to analyze for persistence of the vector used in Breyanzi.

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 Breyanzi was based on the following factors:

   2.1 Identification of exposure to Breyanzi

   2.2 Identification of the appropriate study population: relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies

   2.3 Characterization of occurrence of secondary malignancies in Breyanzi recipients

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

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[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 Breyanzi

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?	☐	☒
ii.	Can the exposure be identified using a billing or reimbursement coding system? *If yes, check all that apply:* ☒ CPT ☒ HCPCS ☒ NDC ☒ ICD ☐ *Other: [Coding system]*	☒	☐
iii.	Is the ISBT 128 coding system[2] needed for the product identification?	☐	☒
iv.	Can the reimbursement code of the product identify the brand name?	☐	☒
v.	Is a history of uptake for previously approved products for the same indication needed? *If yes*, list all products:	☐	☒
vi.	Is medical chart review needed to identify or validate the identification of this product?	☒	☐
vii.	Are claims data sources needed for exposure identification?	☒	☐
viii.	Are electronic health record (EHR) data sources needed for exposure identification?	☒	☐
ix.	Are any other health record type data sources needed for exposure identification? *If yes, all health record types needed: [e.g., Registries, any other health records]*	☐	☒
x.	Is product lot number needed for identification of this product?	☐	☒
xi.	Is there a care setting of interest required for identification of this product? *If yes, check all that apply:* ☒ *Inpatient* ☒ *Outpatient* ☐ *Emergency Room* ☐ *Other: Hospitalization*	☒	☐

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 Breyanzi* 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:** Adults patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies

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? *If yes, list the inclusion and exclusion criteria.. Check all that apply for the level of granularity in* ☒ *Days* ☒ *Months* ☒ *Years*	☒	☐
ii.	Does sex need to be identified? *If yes, list the inclusion [Male, Female, and Other] and exclusion criteria [List the sex to be excluded].*	☒	☐
iii.	Does race need to be identified? *If yes, list the inclusion [List race to be included] and exclusion criteria [List race to be excluded]*	☐	☒
iv.	Can the study population be identified in the data sources required for the exposure and outcome identification?	☐	☒
v.	Was this population previously identified within the CBER Sentinel Program activities?	☐	☒
vi.	Is there a requirement for linking mothers to their newborns in the data sources?	☐	☒

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 (R/R) large B-cell lymphoma after at least 2 prior therapies; a validated algorithm is not available.

2.3 **Assessment for characterization of occurrence of** secondary malignancies in Breyanzi 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? If _yes, check all that apply:_ ☒ _ICD_ ☐ _CPT_ ☐ _Other: Medical Record Review_	☒	☐
ii.	Are there surrogate data elements or biomarkers that can assist to identify the outcome of interest? If _yes, check all that apply:_ ☒ _Laboratory Test Results_ ☒ _Prescription drug_ ☒ _Order of lab test_ ☒ _Order of other diagnostic modalities_ ☐ _Other: [Data element/Biomarker]_	☒	☐
iii.	Are there specific care settings in which this outcome is identified? If _yes, check all that apply:_ ☒ _Inpatient_ ☒ _Outpatient_ ☒ _Emergency Room_ ☒ _Other: Hospitalization_	☒	☐
iv.	Was this outcome previously identified within the CBER Sentinel Program activities? If _yes, in what population was it used?_	☐	☒
v.	Is there a validated and acceptable algorithm available in the literature to identify the outcome of interest? If _yes, list the PPV [PPV] and describe the population in which it was validated:_	☐	☒
vi.	Is a minimum follow-up time needed to identify the outcome of interest? If _yes, what is the required follow-up period? At least 15 years of follow up_	☒	☐
vii.	Is medical chart review required to identify or validate the identification of the outcome?	☒	☐
viii.	Is the prevalence of the outcome known? If _yes, list background rates._ Second cancer incidence reached 12.3% within 25 years (95% CI=11.9%-12.7%)[2].	☒	☐
ix.	Are claims data sources needed for outcome characterization?	☒	☐
x.	Are electronic health record (EHR) data sources needed for outcome characterization?	☒	☐
xi.	Are any other health record type data sources needed for outcome characterization? If _yes, all health record types needed: [e.g., Registries, any other health records]_	☐	☒

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].

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

☒ Available data sources in the CBER Sentinel Program are *NOT sufficient to identify the outcome of* secondary malignancies in Breyanzi recipients due to reasons 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 Breyanzi. 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? *If **no**, skip to section III for Recommendation. If yes, list all products:*	☐	☐
ii.	Can the comparator product be identified using a billing reimbursement code? *If yes, check all that apply:* ☐ *CPT* ☐ *HCPCS* ☐ *NDC* ☐ *ICD* ☐ *Other:[Billing reimbursement code]*	☐	☐
iii.	Can the comparator product be exclusively identified using the billing reimbursement codes?	☐	☐
iv.	Is the ISBT 128 coding system[2] needed for the comparator product identification?	☐	☐
v.	Can the reimbursement code of the comparator product identify the brand name?	☐	☐
vi.	Is medical chart review needed to identify or validate the identification of this comparator product?	☐	☐
vii.	Are claims data sources needed for exposure identification of the comparator product?	☐	☐
viii.	Are electronic health record (EHR) data sources needed for exposure identification of the comparator product?	☐	☐

Please provide an answer for each question i – xi, including sub-questions		Yes	No
ix.	Are any other health record type data sources needed for exposure identification of the comparator product? *If yes, list all health record types needed: [e.g., Registries, any other health records]*	☐	☐
x.	Is product lot number needed for identification of this comparator product?	☐	☐
xi.	Is there a care setting of interest for identification of this comparator product? *If yes, check all that apply:* ☐ *Inpatient* ☐ *Outpatient* ☐ *Emergency Room* ☐ *Other: Hospitalization*	☐	☐

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 Breyanzi in lieu of a PMR study under FDAAA. The data sources available are unable to identify the specific brand Breyanzi 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 Breyanzi. CBER Sentinel data sources are unable to identify outcomes with such a long follow up period and collect tumor tissue needed for testing.