DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

March 9, 2026

Juno Therapeutics Inc., a Bristol-Myers Squibb Company
Attention: Nicole Van De Vaarst/Amanda Pisciotta
3401 Princeton Pike
Lawrence Township, NJ 08648

RE: BREYANZI (lisocabtagene maraleucel)
BLA 125714/733, 735

Dear Ms. Van De Vaarst and Ms. Pisciotta:

The Advertising and Promotional Labeling Branch (APLB) of the U.S. Food and Drug Administration (FDA) has reviewed various promotional materials for BREYANZI® (lisocabtagene maraleucel) suspension, for intravenous infusion, from Juno Therapeutics Inc., a Bristol-Myers Squibb Company (BMS) that include exploratory analyses, such as Progression-Free Survival (PFS) data and Overall Survival (OS) data, in conjunction with representations or suggestions that BREYANZI is effective for these types of clinical benefits. See, for example:

- BREYANZI HCP Website Campaign Update[1] -CLL (2009-US-2500225)
- Promotional Labeling, Breyanzi HCP CTAM LBCL CVA - dPDF Q3 2025 Update (2009-US-2500682)

The promotional materials make false or misleading claims and representations about the benefits of BREYANZI. Thus, the promotional materials misbrand BREYANZI within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and make its distribution violative. 21 U.S.C. 321(n); 331(a); 352(a), (n). See 21 CFR 202.1(e)(5). These violations are particularly concerning from a public health perspective because the promotional materials make misleading representations about BREYANZI being more effective or having greater clinical benefit than has been demonstrated. This may cause doctors and patients to inaccurately weigh the risks versus benefits of treatment with BREYANZI, which can be fatal or life-threatening.

[1] The website is available at: https://www.BREYANZIhcp.com/ (last accessed March 2026).

Background

According to the FDA-approved prescribing information (PI) for BREYANZI:

BREYANZI is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

- adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:
  - refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
  - refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
  - relapsed or refractory disease after 2 or more lines of systemic therapy.
  - Limitations of Use: BREYANZI is not indicated for the treatment of patients with primary central nervous system lymphoma.
- adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
- adult patients with relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior lines of systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
- adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor.
- adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least 2 prior lines of systemic therapy.

The PI for BREYANZI also includes a BOXED WARNING and WARNINGS AND PRECAUTIONS including, but not limited to, fatal or life-threatening reactions of Cytokine Release Syndrome, fatal or life-threatening neurological toxicities, secondary malignancies, fatal or life-threatening severe infections, prolonged cytopenia, hypogammaglobulinemia, and fatal or life-threatening Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome.

BREYANZI's CLL, SLL, and FL indications were approved under the accelerated approval pathway. This pathway can allow for earlier approval of drugs intended to treat serious conditions and fill an unmet medical need. Accelerated approval is based on an effect on a surrogate or intermediate clinical endpoint that is thought to be reasonably

likely to predict clinical benefit, rather than on a direct measurement of clinical benefit. FDA has required sponsors of drugs approved under the accelerated approval pathway, including BREYANZI, to conduct a confirmatory trial to verify and describe the clinical benefit of the drug.[2]

False or Misleading Benefit Presentation

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading with respect to efficacy. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication. See section 201(n) of the FD&C Act, 21 U.S.C. 321(n).

You include representations in BREYANZI's promotional materials suggesting that it is effective in providing PFS and OS benefits for CLL, SLL, and FL indications. For example, BREYANZI's healthcare professional website includes headlines such as, "**74% of patients survived with no signs of disease progression at 18 months** [PFS in the TRANSCEND FL trial]," "**Median PFS of 12 months was observed in TRANSCEND CLL 004,"** and "**Median OS of 33.6 months was observed in TRANSCEND CLL 004**." Your presentations include data for time-to-event endpoints from this single-arm trial, such as PFS and OS, that have statistical limitations rendering such endpoints uninterpretable. Specifically, TRANSCEND was designed as a single-arm trial (i.e., with no comparator arm), and the CLL, SLL, and FL indications were approved based on response rate (overall response (OR), complete response (CR), and partial response (PR)) and the duration of response (DOR). In the absence of an appropriate comparator for BREYANZI, it is not possible to determine if the observed effect you represented is attributable to BREYANZI or to other factor(s), such as the natural history of the disease. Consequently, your promotional advertising and labeling that represents or suggests BREYANZI is effective in providing PFS or OS is misleading.

We acknowledge that your presentations include, but are not limited to, the following statements (in smaller less prominent font) next to the PFS and OS presentations (in pertinent part; footnotes omitted):

- *PFS data are not in the Prescribing Information and should be interpreted with caution*
- *PFS was a secondary endpoint in TRANSCEND CLL 004 and was not statistically tested in the setting of a single-arm trial. It is not possible to determine if the observed effect is attributable to BREYANZI or to the natural history of the disease*
- *The statistical significance of PFS is not known*

[2] We note that a post-marketing, multicenter, prospective, observational study to assess the long-term safety and the risk of secondary malignancies occurring after treatment with lisocabtagene maraleucel is currently ongoing; however, this study has not been completed (See: https://www.clinicaltrials.gov/study/NCT06794268?term=AREA%5BBasicSearch%5D(Lisocabtagene%20maraleucel)&rank=4)

- *PFS was a secondary endpoint in TRANSCEND FL and was not statistically tested in the setting of a single-arm trial. It is not possible to determine if the observed effect is attributable to Breyanzi or to the natural history of the disease*
- *OS data are not in the Prescribing Information and should be interpreted with caution*
- *OS was a secondary endpoint in TRANSCEND CLL 004 and was not statistically tested in the setting of a single-arm trial. It is not possible to determine if the observed effect is attributable to Breyanzi or to the natural history of the disease*
- *The statistical significance of OS is not known*

In further support of these representations, you cite a few references, including the BREYANZI PI, *Data on File* with BMS, and abstracts presented at the American Society of Hematology 2024 Annual Meeting.

However, these statements and references do not sufficiently mitigate the overall misleading message conveyed by these materials.

Conclusion and Requested Action

For the reasons discussed above, your promotional materials misbrand BREYANZI within the meaning of the FD&C Act and make its distribution violative. See 21 U.S.C. 321(n), 331(a), and 352(a), (n); 21 CFR 202.1(e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. APLB requests that you cease any violations of the FD&C Act. Within 15 working days of receipt, please submit a written response to this letter addressing the concerns described, listing all advertising and promotional labeling materials (including the dissemination/publication date and Material ID Code) for BREYANZI that contain the same or similar representations or suggestions, and explaining your plans for discontinuation of such.

If you believe that your product is not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with all applicable requirements of the FD&C Act and its implementing regulations.

Please submit your response to your eCTD under the heading 1.15.1.6 and email a copy of your response to CBERAPLB@fda.hhs.gov. We remind you that only written communications are considered official responses. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter and refer to the BLA/STN numbers.

Questions related to the submission of your response letter should be emailed to CBERAPLB@fda.hhs.gov.

Sincerely,

Melissa Mendoza, J.D.
Office Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research