Summary Basis for Regulatory Action Template

Date: February 5, 2021

From: Kimberly LW Schultz, PhD, Chair of the Review Committee

BLA STN#: 125714/0

Applicant Name: Juno Therapeutics, Inc.

Date of Submission: December 18, 2019

Goal Date: November 16, 2020

Proprietary Name/ Established Name: BREYANZI/lisocabtagene maraleucel

Indication: Treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least two or more lines of systemic therapy, 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.

Limitations of Use: BREYANZI is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma.

Recommended Action:
The Review Committee recommends approval of this product.

Office of Tissues and Advanced Therapies Signatory Authority:
Wilson W. Bryan, MD, Director

- ☑ **I concur with the summary review.**
- ☐ **I concur with the summary review and include a separate review to add further analysis.**
- ☐ **I do not concur with the summary review and include a separate review.**

Office of Compliance and Biologics Quality Signatory Authority:
Mary A. Malarkey, Director

- ☑ **I concur with the summary review.**
- ☐ **I concur with the summary review and include a separate review to add further analysis.**
- ☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

Document title	Reviewer name
CMC Review(s) • *CMC (OTAT/DCGT, OCBQ/DBSQC, and OCBQ/DMPQ)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report and pre-inspection document review (ORA/OMPTO/OBPO, OCBQ/DMPQ, and OTAT/DCGT)*	Kimberly LW Schultz, PhD (OTAT/DCGT/GTB) Nirjal Bhattarai, PhD (OTAT/DCGT/GTIB) Tiffany Lucas, PhD (OTAT/DCGT/GTB) Hyesuk Kong, PhD (OCBQ/DBSQC) Marie Anderson, PhD (OCBQ/DBSQC) Rabia Ballica, PhD, (OCBQ/DMPQ/MRB1) David Bailey (OCBQ/DMPQ/MRB1) Prabhu P. Raju (ORA/OMPTO/OBPO/TBIOL1) Eileen Liu (ORA/OMPTO/OBPO/ TBIOL1) Steven Bowen, PhD (ORA/OMPTO/OBPO/ TBIOL2) Scott Ballard (ORA/OMPTO/OBPO/BPOS) Lauren Lilly, PhD (ORA/OMPTO/OBPO/DBPOII)
Clinical Review(s) • *Clinical (OTAT/DCEPT)* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	Kavita Natrajan, MD (OTAT/DCEPT) Megha Kaushal, MD (OTAT/DCEPT) Deborah Thompson, MD (OBE) Christine Drabick, MS, (OCBQ/DIS/BMB)
Statistical Review(s) • *Clinical data*	Cong Wang, PhD (OBE/DB/TEB)
Pharmacology/Toxicology Review(s) • *Toxicology* • *Developmental toxicology* • *Animal pharmacology*	Christopher Saeui, PhD (OTAT/DCEPT)
Clinical Pharmacology Review	Xiaofei Wang, PhD (OTAT/DCEPT)
Labeling Review(s) • *APLB (OCBQ/APLB)*	Dana Jones (OCBQ/APLB)
Advisory Committee summary	No advisory committee meeting was held

1. Introduction

Juno Therapeutics, Inc. submitted a Biologics License Application (BLA), STN 125714, for licensure of lisocabtagene maraleucel, with the proprietary name of BREYANZI. 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 two or more lines of systemic therapy, including 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.

BREYANZI is comprised of genetically modified, antigen-specific autologous T cells administered as a defined composition of CAR-positive viable T cells (consisting of separate CD8 and CD4 drug products). The CAR is comprised of the FMC63 monoclonal antibody-derived single-chain variable fragment (scFv), IgG4 hinge region,

CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain. In addition, BREYANZI includes a nonfunctional truncated epidermal growth factor receptor (EGFRt) that is co-expressed on the cell surface with the CD19-specific CAR.

This document summarizes the basis for regular approval of BREYANZI. A single clinical trial, Study 017001, provides the primary evidence of safety and efficacy for the BLA submission. Our recommendation for approval is based on the complete response rate and duration of response demonstrated in the study. The major risks of BREYANZI include cytokine release syndrome (CRS) and neurologic toxicity, either of which can be life-threatening, as well as infections and prolonged cytopenias.

The review team recommends regular approval of this BLA with the Chemistry, Manufacturing, and Control (CMC) Postmarketing Commitment (PMC) and Postmarketing Requirements (PMRs) for:

- PMC: Juno Therapeutics, Inc., commits to prospectively validate the [redacted] per protocol [redacted] and will provide the validation report.

- PMR: A postmarketing observational study to assess the long-term safety of BREYANZI, including the risk of secondary malignancies.

The approval of this BLA also requires a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) for the management of cytokine release syndrome (CRS) and neurologic toxicity.

2. Background

Disease Background

DLBCL, which comprises 30-40% of Non-Hodgkin's lymphoma (NHL), is fatal if not cured. Primary mediastinal B-cell lymphoma (PMBCL) and transformed or grade 3B follicular lymphoma (FL) are typically treated along a DLBCL paradigm. Approximately half of all patients with aggressive B-cell NHL have R/R disease, with an estimated 10-15% of patients with DLBCL having primary refractory disease and an additional 20-30% relapsing after an initial objective response. High-grade B-cell lymphomas with aberrations in MYC, BCL2, and/or BCL6 ("double hit" and "triple hit" lymphomas) are associated with an inferior prognosis, even in the newly diagnosed setting. Patients with untreated R/R aggressive B-cell lymphoma have a median survival of approximately 3-4 months.

Available Therapies

The following are the available therapies for the overlapping indication of R/R large B-cell lymphoma in addition to the multiple standard of care salvage regimens.

Axicabtagene ciloleucel (YESCARTA) and tisagenlecleucel (KYMRIAH) have regular approval for the treatment of adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified (NOS), high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma (FL), and (for axicabtagene ciloleucel) primary mediastinal large B-cell lymphoma.

Selinexor is a first-in-class, small molecule inhibitor of the nuclear export protein, exportin 1 which has accelerated approval for the treatment of adult patients with R/R DLBCL, NOS, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy.

Polatuzumab in combination with Bendamustine and Rituximab has accelerated approval for the treatment of adult patients with R/R DLBCL after at least two prior therapies.

Tafasitamab in combination with lenalidomide has accelerated approval for the treatment of adult patients with R/R DLBCL, NOS, including DLBCL arising from low grade lymphoma, who are not eligible for autologous stem cell transplant.

Regulatory History

Study 017001, which is the basis for submission of this BLA for BREYANZI, was allowed to proceed on 06/26/2015 under IND 16506. BREYANZI was granted orphan designation for the following: DLBCL on 04/27/2016, follicular lymphoma on 09/07/2017 and PMBCL on 07/12/2018. Breakthrough therapy designation was granted for treatment of subjects with R/R large B-cell lymphoma, including DLBCL not otherwise specified-de novo or transformed from indolent lymphoma, PMBCL and grade 3B FL, on 12/15/2016. RMAT designation was granted for the same indication (as Breakthrough Therapy designation) on 10/20/2017.

The pre-BLA meeting was held on 08/05/2019. The first component of the rolling BLA submission was submitted on 09/30/2019, and the last component was submitted on 12/18/2019. A major amendment was designated on 05/05/2020, for substantial new manufacturing and facility information needed for review. The PDUFA goal date is 11/16/2020.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

The CMC review team concludes that the BREYANZI manufacturing process and controls are capable of yielding a product with consistent quality attributes, and the CMC review team recommends approval.

Product Description
BREYANZI is composed of autologous CD4+ and CD8+ T cells that are genetically modified with a replication-incompetent lentivirus vector (b) (4) encoding a CD19-specfic chimeric antigen receptor (CAR) and a truncated epidermal growth factor receptor (EGFRt). The CD19-specific CAR consists of an extracellular FMC63 murine anti-human CD19-specific antibody single-chain variable fragment (scFv) binding domain, fused in sequence to the IgG4 hinge, the CD28 transmembrane domain, and the 4-1BB and CD3ζ (zeta) chain signaling domains. BREYANZI consists of the CD8 and CD4 drug products that are supplied together.

Manufacturing Summary
Patient leukapheresis material is collected at qualified apheresis centers and is shipped to the Juno manufacturing facility (JuMP) to initiate BREYANZI manufacturing. CD8+ and CD4+ T cells are sequentially selected from the patient-specific material and the remainder of the manufacturing process is conducted separately for the CD8 and CD4 drug products (DP) but follows a similar manufacturing configuration. The T cells are activated with CD3/(b) (4) and transduced with the lentivirus vector. The T cells are expanded in culture (b) (4) harvested, and washed. The T cells are immediately formulated into an infusible cryopreservation solution containing (b) (4) human serum albumin (HSA), and CryoStor® CS10. The CD4 drug product and CD8 drug product are separately filled into 5 mL vials and cryopreserved at ≤ -130°C in vapor-phase liquid nitrogen until lot release testing is complete. The volume of each drug product required to meet the intended dose is determined after formulation and reported on the Release for Infusion certificate. BREYANZI is shipped in a vapor-phase liquid nitrogen dry shipper (dewar) to the clinical infusion center for administration back to the same patient.

The (b) (4) lentivirus vector is manufactured by (b) (4) The lentivirus vector (b) (4) lentivirus. The (b) (4) lentivirus is then (b) (4) as the lentivirus (b) (4) . Testing is conducted on the vector (b) (4) lentivirus, as appropriate.

Manufacturing Controls
The chain of identity and chain of custody (COI/COC) are established at the time of leukapheresis collection and maintained throughout the manufacturing process to administration, by a validated computer-based system, to ensure that the patient received the correct autologous lot.

The manufacturing control strategy begins with raw material and reagent qualification program consisting of source material risk assessment, vendor qualification, confirmation of the certificate of analysis and material testing. Raw materials derived from animals and humans are controlled to ensure the absence of microbial contaminants. Critical process parameters are established for unit operations based on

process characterization and risk assessment studies. In-process monitoring and controls are implemented throughout the process to support process consistency.

Lot release testing is performed on material collected at appropriate stages of the manufacturing process to evaluate product safety and function. Specifically, mycoplasma testing is performed on material at the time of (b) (4) . The drug product is formulated based on total cell counts necessary to achieve dose with final dose determination assays, including (b) (4) . Safety testing, potency, and general testing on the formulated drug product include sterility, endotoxin, (b) (4) , purity, (b) (4) , and appearance testing. Because the CD4 and CD8 drug products are manufactured separately, the lot release testing is performed separately, and the acceptance criteria are based on the experience for each.

Process Validation

The commercial BREYANZI manufacturing process was assessed at the Juno Manufacturing Plant (JuMP) using healthy donor leukapheresis material. The process validation was assessed against established process parameters and predefined release criteria. The manufacturing process validation demonstrated removal of process-related impurities, including residuals associated with vector manufacturing. Shipping was validated for all shipping steps, including the vector, leukapheresis material to the manufacturing site, and drug product from the manufacturing site. Additional validation studies included aseptic process simulations, COI/COC, and (b) (4) vector manufacturing.

Manufacturing Risks, Potential Safety Concerns, and Management

Product mix-up

BREYANZI is an autologous product; as such, product mix-ups, either of autologous lots or with other CAR T cells manufactured at the same facility, would result in potential risks, including infection, graft versus host disease, and lack of anti-tumor effect. The COI/COC ensures that the patient receives their autologous lot. COI/COC is established at the point of leukapheresis collection; checkpoints are indicated throughout the manufacturing process; and patient identifiers are confirmed prior to administration with identifiers printed on the label. The COI/COC is maintained through integrated computer-based programs with human-readable identifiers present on all labels as well.

BREYANZI is manufactured in a multiproduct manufacturing facility. Products are spatially segregated in the facility with manufacturing occurring in rooms on a campaign basis. Prior to transduction, the vector label is confirmed to ensure the correct lentivirus vector is used. Additionally, lot release testing confirms CAR identity and CD19-specific activation.

Replication Competent Lentivirus

Replication-competent lentivirus (RCL) are a theoretical concern for the BREYANZI manufacturing process. The likelihood of RCL generation is reduced by the (b) (4)

design: (b) (4) are tested by (b) (4) in accordance with current FDA guidance (b) (4) CAR T cell manufacturing process. To date, no RCL has been detected in clinical trial lots of (b) (4) transduced cell product.

Insertional Mutagenesis
Vector integration poses a risk for insertional mutagenesis. Activation of proto-oncogenes or disruption of tumor suppressor genes has the potential to cause secondary malignancies. To mitigate the risk of insertional mutagenesis, the vector used for BREYANZI manufacturing was designed to remove any known viral enhancer elements (self-inactivating design). Insertion-site analysis did not identify any areas of increased or preferred integration. CAR T cell (b) (4) clinical trial experience (b) (4) for the CD8 DP component and (b) (4) for the CD4 DP component).

Specifications
The final lot release specifications are shown in Table 1. The analytical methods and their validations and/or qualifications reviewed for BREYANZI drug product release were found to be adequate for their intended use.

Table 1. BREYANZI lot release specifications

Quality Parameter	**Attribute**	**Sampling Point**	**Analytical Procedure**	**Acceptance Criteria CD8 DP**	**Acceptance Criteria CD4 DP**
Appearance	Color	Cryopreserved DP (≤ -130°C), Post Thaw	Visual inspection (b) (4)	Colorless to Yellow or Brownish-Yellow, (b) (4)	Colorless to Yellow or Brownish-Yellow, (b) (4)
	Clarity			Slightly-Opaque (b) (4)	Slightly-Opaque (b) (4)
Identity	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Quality Parameter	Attribute	Sampling Point	Analytical Procedure	Acceptance Criteria CD8 DP	Acceptance Criteria CD4 DP
Purity	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)			(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Strength[1]	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Safety	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Sterility	(b) (4)	(b) (4)	No Growth	No Growth
	Mycoplasma	(b) (4)	(b) (4)	Not Detected	Not Detected
	Endotoxin	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Abbreviations: DP = drug product; CAR = chimeric antigen receptor; (b) (4)

[1]Strength is determined by (b) (4)

Impurity Profile

Product-related impurities, including cellular impurities derived from the leukapheresis material and non-viable cells, are evaluated during (b) (4) . The active ingredient in BREYANZI is transduced viable T cells. Overall T cell purity was (b) (4) throughout the clinical study; consequently, T cell purity is (b) (4) , allowing no more than (b) (4) non-T cells in the final product. Contaminating (b) (4) were not detected in any lots produced for the clinical study. The major (b) (4) in the CD8 drug product and

(b) (4) in the CD4 drug product. There is a minor population of (b) (4) detected in the CD8 drug product as well. The level of (b) (4) is monitored (b) (4) .

Manufacturing process improvements during development improved the product viability levels and were used to set the commercial lot release criterion. The BREYANZI manufacturing process is designed (b) (4) during the clinical study. Developmental studies indicate that (b) (4) in the patient-derived leukapheresis material influence (b) (4) . The minimum allowable (b) (4) for the CD4 and CD8 drug products was determined independently based on the clinical study experience. The (b) (4) of each drug product required to meet the intended dose.

Process-related impurities include ancillary materials and reagents that are not intended to be present in the final product. Process performance runs demonstrated that the process consistently removes impurities to safe levels and below the assay detection limits. Of note, (b) (4) are evaluated for lot release and are regularly below the level of quantitation. The lentivirus vector is (b) (4) residual lentivirus vector has not been detected in the drug product.

Container Closure

BREYANZI consists of CD8+ and CD4+ T cell components, and each component is independently filled and cryopreserved in a 5 mL, sterile, single-use (b) (4) vial at ≤ -130°C in vapor phase liquid nitrogen. The vials are supplied by (b) (4) . The vials containing cryopreserved cells are thawed and visually inspected for leaks and damages prior to infusion.

(b) (4) test methods were validated for the integrity evaluation of the (b) (4) . The results were acceptable.

Stability

Long-term stability studies support 13 months of storage for BREYANZI when stored at ≤ -130°C in vapor phase of liquid nitrogen. The stability studies utilized a combination of lots produced from healthy donor and patient material and across a range of viable cell concentrations to determine product shelf-life. Results from stress studies demonstrate that both viability and potency are stability-indicating attributes and are significantly changed at stressed conditions. In-use stability testing supports a post-thaw expiry of 2 hours, with cell recovery decreasing through the time course, indicating that the product is not stable at room temperature after thaw and that the time to administration should be minimized as possible during dose preparation. An acceptable post-approval long-term stability protocol, which includes maintenance of sterility testing at the end of the expiry period, is provided.

b) CBER Lot Release

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. The basis for this decision is that BREYANZI is an autologous product; as such, each lot will treat a single patient. Failure of a single lot will have minimal potential impact on public health.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be acceptable. The facilities involved and the activities performed in the manufacture of lisocabtagene maraleucel are listed in the Table 2 and are further described in the paragraphs that follow.

Table 2. Manufacturing Facilities Table for BREYANZI

Name/Address/Activity	**FEI number**	**DUNS number**	**Inspection/ waiver**	**Justification /Results**
Juno Therapeutics, Inc. 1522 217th Pl. SE Bothell, WA 98021, US -Drug Substance (DS) and Drug Product (DP) Manufacturing -Primary and Secondary Packaging -DP Release Testing	3011834594	079941307	Pre-License Inspection	ORA 10/07-09/2020, 10/13- 16/2020 VAI
(b) (4)	(b) (4)	(b) (4)	Pre-License Inspection	ORA (b) (4) VAI
(b) (4)	(b) (4)	(b) (4)	Waived	CBER Pre-Approval Inspection (b) (4) VAI

ORA conducted a pre-license inspection (PLI) of Juno Therapeutics, Inc., Bothell, WA, from October 7-9 and 13-16, 2020 for lisocabtagene maraleucel drug substance and drug product manufacturing. At the conclusion of the inspection, a Form FDA 483 was issued. The firm responded to the observations and the corrective actions were found to be adequate. The inspection was classified as voluntary action indicated (VAI).

ORA conducted a PLI of (b) (4) manufacturing. At the conclusion of the inspection, a Form FDA 483 was issued. The firm responded to the observations and the corrective actions were found to be adequate. The inspection was classified as VAI.

(b) (4) manufactures the (b) (4) CBER had previously inspected (b) (4) . All inspectional issues were resolved, and the inspection was classified as VAI.

d) Environmental Assessment

A request for categorical exclusion from an Environmental Assessment per 21 CFR 25.31(c) was provided in the BLA. This request and supporting information provided by Juno Therapeutics is acceptable to conclude that lisocabtagene maraleucel poses a negligible risk to the environment or to the general public. The risk of vector recombination into a replication competent form is assessed as extremely low to negligible. The potential for the lentivirus vector or lisocabtagene maraleucel to persist in the environment is negligible. There is a potential risk for exposure of healthcare staff during product administration, but this can be effectively mitigated by universal precautions that are already established at healthcare facilities and by additional training provided by Juno Therapeutics during treatment site qualification. Overall, there are no significant environmental or public health impacts posed by the lentiviral vector or by lisocabtagene maraleucel. Categorical exclusion under 21 CFR 25.31(c) is therefore acceptable.

e) Product Comparability

Studies to demonstrate comparability of products manufactured using processes version 2, 3, and 4 were performed under IND16506. These studies demonstrated that CD19 CAR-positive T cells manufactured with each process were comparable. Studies provided in the BLA indicated that BREYANZI manufactured with (b) (4) are comparable. No future manufacturing changes to be evaluated under a comparability protocol were proposed in the BLA.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

In vitro pharmacology studies support the purported mechanism of action of BREYANZI by showing cytokine release, CAR T cell expansion, and tumor cell cytotoxicity following exposure to CD19-expressing cancer cells. Additional *in vitro* studies showed that BREYANZI, in combination with various small molecule drugs, (b) (4)

anti-tumor activity. Dose-dependent anti-tumor activity and improved animal survival were demonstrated in immunocompromised rodent models engrafted with CD19-expressing tumor cells following administration of BREYANZI.

Animal studies to assess the long-term safety of BREYANZI were limited because BREYANZI does not survive in immunocompetent rodents and induces graft-versus-host disease in immunocompromised mice. (b) (4) studies and (b) (4) against a panel of normal human tissues showed that on-target/off-tumor and non-specific recognition against off-target tissues are not a major safety concern. *In vivo* studies in tumor-bearing murine models showed significant reduction of BREYANZI following administration of cetuximab; thus, administration of antibodies targeting the truncated EGFR domain on the surface of BREYANZI may reduce/eliminate the CAR T cells *in vivo*.

The risk of insertional mutagenesis with lentiviral transduction of the T cells, leading to malignant transformation, was studied using unbiased, genome-wide bioinformatics methods. The resulting data show that the lentivirus used to manufacture BREYANZI does not preferentially integrate at specific genomic sites of concern for oncogenic transformation. In addition, long-term cellular growth assays evaluating the purity and identity profile of BREYANZI suggest that no shift in cellular phenotype due to clonal expansion occurs over time. These data support the conclusion that any insertional events resulting from lentiviral transduction methods used to generate BREYANZI have minimal risk for oncogenic transformation.

No animal reproductive and developmental toxicity studies were conducted with BREYANZI, which is acceptable based on the product characteristics and safety profile.

5. CLINICAL PHARMACOLOGY

The clinical pharmacology section of this BLA is supported by one Phase 1 clinical study that evaluated the safety, antitumor activity, and pharmacokinetics (PK) of BREYANZI in subjects with R/R large B-cell lymphoma after at least 2 prior therapies. The proposed BREYANZI dosing regimen is a single dose of 50 to 110 x 10^6 CAR-positive viable T cells (consisting of a 1:1 ratio of the CD8 and CD4 DP components). BREYANZI is to be administered via intravenous (IV) infusion.

The clinical pharmacology assessments included cellular kinetic/pharmacokinetic (PK) assessment, pharmacodynamic (PD) assessment, immunogenicity assessment and replication-competent lentivirus (RCL) testing.

The pharmacokinetic profiles of BREYANZI were assessed using two validated methods:

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- (b) (4)

PK assessments of BREYANZI were primarily based on (b) (4) measurements. PK measurements by (b) (4) assay were assessed in an exploratory and supportive manner. The following summarize the important clinical pharmacology findings.

General Cellular Kinetics/Pharmacokinetics

- BREYANZI cellular kinetics comprise lag, expansion, contraction and persistence phases in treated subjects. Following infusion, BREYANZI exhibited an initial expansion followed by a bi-exponential decline. The median time to reach peak levels in peripheral blood was 12 days post-dose. Persistence of BREYANZI transgene was observed up to 2 years.
- Compared to CD4+ EGFRt+ subset T cells, CD8+ EGFRt+ subset of T cells had a higher expansion after infusion.
- Some subjects in Study 17001 received additional doses of BREYANZI in the following situations: two-dose schedule, retreatment cycles, and additional cycles.
  - In a two-dose schedule, the second dose infusion (14 days after first dose) did not increase JCR017 expansion. The cellular kinetics/pharmacokinetics for the two-dose schedule were similar to the single-dose schedule.
  - Retreatment cycles were defined as further cycles administered to subjects who had progressive disease (PD) following complete response (CR) to previous BREYANZI treatment. Additional cycles were defined as further BREYANZI treatment cycles for subjects who had stable disease (SD) or partial response (PR) as their best overall response (BOR) after the initial response assessment. In Study 17001, subjects who received retreatment cycles or additional cycles of BREYANZI treatment had substantially lower BREYANZI expansion, compared to subjects who received a single-dose of BREYANZI.

Critical Factors Impacting BREYANZI Cellular Kinetics/Pharmacokinetics

- BREYANZI expansion decreased with increased age. Subjects < 65 years old had a 3.06-fold and 2.30-fold higher median Cmax and $AUC_{0\text{-}28d}$, respectively, compared to subjects ≥ 65 years old.
- Subjects with a higher tumor burden had a 2.28-fold and 1.76-fold higher median Cmax and $AUC_{0\text{-}28d}$, respectively, compared to subjects with a lower tumor burden.
- The following product characteristics showed positive correlative relationships with BREYANZI (b) (4)

Drug-Drug Interactions

- Tocilizumab and corticosteroids were used in the management of CRS and neurologic adverse events after treatment with BREYANZI. Continued expansion of BREYANZI was observed in subjects who received tocilizumab and corticosteroids.

Exposure-Response Relationship

- In the DLBCL Cohort, no clear dose-response was observed for BREYANZI with respect to PK (b) (4) data), PD and immunogenicity.
- Responders (CR and PR) had a 2.48-fold, 1.91-fold and 2.13-fold higher median Cmax, $AUC_{0\text{-}28d}$, and expansion rate, respectively, compared to non-responders (SD and PD) (b) (4) data). (b) (4) data showed similar trend with CD3+EGFRt+, CD4+EGFRt+, and CD8+EGFRt+ T cells. Higher expansion of CD3+EGFRt+, CD4+EGFRt+ T cells were positively associated with best overall response (BOR).
- Higher BREYANZI exposure was associated with higher incidence of any grade cytokine release syndrome (CRS) and neurologic toxicities (NT).
- (b) (4) data showed similar exposure-response relationship results. (b) (4) analysis data indicated that subjects with Grade ≥ 3 neurologic toxicities (NT) had substantially higher (more than 10-fold higher) median Cmax and $AUC_{0\text{-}28d}$, and expansion rates for CD4+EGFRt+, respectively, compared with subjects with Grade 0-2 NT.

Pharmacodynamics

- B-cell aplasia (defined as CD19+ B cells comprising less than 3% of peripheral blood lymphocytes) is observed in the majority of BREYANZI-treated subjects for up to 1 year.
- Transient elevations of soluble biomarkers, such as cytokines and chemokines, were observed after infusion of BREYANZI. Peak elevation of soluble biomarkers was observed within the first 14 days after BREYANZI infusion, which returned to baseline levels within 28 days.
- Higher baseline levels of the following biomarkers were observed in subjects with any grade of CRS compared to subjects with no CRS: c-reactive protein (CRP), ferritin, intercellular adhesion molecule 1 (ICAM1), IL-6, macrophage inflammatory protein 1α (MIP1α), serum amyloid A1 (SAA1), and TNFα.
- Higher baseline levels of the following biomarkers were observed in subjects with any grade of neurologic toxicity (NT) compared to subjects with no NT: c-reactive protein (CRP), ferritin, ICAM1, IL-6, IL-10, MIP1α, SAA1, TNFα, and vascular cell adhesion molecule 1 (VACM1).
- Peak levels of 25 soluble biomarkers, including ICAM1, IL-2, IL-6, IL-8, IFNγ-induced protein 10 (IP-10), MIP1α, transforming growth factor beta 3 (TGFβ3), and TNFα were associated with CRS.
- Peak levels of 22 soluble biomarkers, including ICAM1, IL-2, IL-6, IL-8, IL-10, IP-10, MIP1α, and TNFα were associated with NT.

Immunogenicity

- Prevalence and incidence of anti-therapeutic antibody (ATA) were approximately 10%. No specific conclusions can be drawn regarding immunogenicity as the relationship between the ATA status and BREYANZI PK was not conclusive due to small sample number of subjects who had pre-existing ATA, treatment-induced or treatment-boosted ATA.

Replication-competent Lentivirus (RCL) Testing

- No RCL has been detected in the blood in any treated subjects.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

The clinical review team's recommendation for regular approval of BREYANZI for the for the treatment of adult patients with R/R large B-cell lymphoma, after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) NOS (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B is based on the clinical study, Study 017001.

Limitations of Use: BREYANZI is not indicated for the treatment of patients with primary central nervous system lymphoma.

a) Clinical Program

Study 017001 was a single-arm, Phase 1, multicenter study of the efficacy and safety of BREYANZI in subjects in the Diffuse Large B-cell Lymphoma (DLBCL) cohort which included r/r DLBCL not otherwise specified (NOS), high-grade lymphoma (HGL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma (FL) grade 3B after at least two lines of systemic therapy. The primary endpoint was objective response rate (ORR), defined as rate of complete response (CR) plus rate of partial response (PR), as determined by an Independent Review Committee (IRC) applying the 2014 Lugano criteria. Secondary endpoints included duration of response (DOR) when a minimum required follow-up of 6 months after response was first documented and CR rate. The efficacy-evaluable population was drawn from a pool of 269 subjects with an updated data cutoff of August 12, 2019. Primary safety analyses were performed on 268 subjects who received conforming CAR T cell product at the primary data cutoff of April 12, 2019. Primary efficacy analyses were performed on the DLBCL efficacy-evaluable set, comprised of 256 subjects infused with a single dose of 40-150 x 10^6 CAR-positive viable T cells and followed for at least six months after their first objective disease response. Bridging therapy was allowed at the investigators' discretion during product manufacturing. The study permitted a second dose at the time of disease progression; however, the protocol-specified primary efficacy analysis was based on ORR and duration of response observed following the first dose.

Efficacy Results

The majority of subjects (192/256; 75%) received the study drug at the recommended dose schedule (50-110 x 10^6 CAR-positive viable T cells per kilogram body weight). Of these 192 evaluated for efficacy, ORR, by independent review committee (IRC) assessment, was 73.4% (95% Confidence Interval [CI] 66.6%, 79.5%) and complete response (CR) was 54.2% according to Lugano criteria, with a median DOR of 16.7 months. Of the 141 subjects who achieved

an objective response, 57.1% maintained response for at least 6 months and 52.8% maintained a response for at least 12 months. Efficacy results in Study 017001 DLBCL cohort met the study objective that ORR was statistically significantly greater than the pre-specified null hypothesis threshold rate of 40% at a single dose with a dose range of 50-110 x 10^6 CAR-positive viable T cells per kilogram body weight. An additional sensitivity analysis for efficacy that evaluated ORR in all subjects who were leukapheresed, a cohort representative of the intent-to-treat population, demonstrated that the lower bounds of the 95% CI was greater than the protocol-specified null hypothesis threshold (ORR 59%; CI 53%, 64%).

In summary, Study 017001 represents an adequate and well-controlled trial that demonstrated high response rates and durability of CR rate. The basis of FDA's conclusion of substantial evidence of effectiveness is the magnitude of benefit primarily driven by durable complete response rate. Therefore, the results support a traditional approval for BREYANZI.

Note that the indication statement in the label includes a broader population of R/R large B-cell lymphomas as it represents a similar prognostic group of tumors with CD19 expression as the tumor histologies evaluated in Study 017001. Therefore, we expect that the beneficial activity seen in the clinical trial can be reasonably extrapolated to similar beneficial activity in the broader population of R/R large B-cell lymphomas.

Additionally, Section 14 of the label will include the following information:

a) ORR in all subjects who were leukapheresed in addition to the ORR in the DLBCL cohort (primary analysis set) and
b) information for subjects who had active central nervous system (CNS) disease and who received CNS-directed bridging therapy to inform prescribers of the feasibility of treating subjects with active CNS disease. Note that the efficacy responses at CNS sites were confounded by effects of bridging therapy.

Pharmacovigilance

Please refer to Section 11 c regarding Post-Marketing Requirements and Post-Marketing Commitments.

Bioresearch Monitoring

Bioresearch Monitoring (BIMO) inspections were performed at three clinical sites participating in the conduct of study protocol 017001. The inspections did not reveal substantive problems impacting the data submitted in the application.

b) Pediatrics

The application does not trigger PREA nor PMR requirements to demonstrate clinical benefit under 21CFR 601.41. BREYANZI received orphan drug designation (ODD)

prior to the submission of the BLA for the treatment of large B-cell lymphoma. Per the Pediatric Research Equity Act (PREA) and 21 Code of Federal Regulations (CFR) 314.55(d), ODD products are exempt from pediatric study requirements. As such, the Applicant did not include a pediatric assessment in this BLA.

c) Other Special Populations

BREYANZI has not been studied in any special populations.

7. SAFETY

The primary safety population for Study 017001 (TRANSCEND) included a total of 268 subjects at the original data cutoff of April 12, 2019 who were treated with BREYANZI. Treatment-emergent adverse events (TEAEs) were defined as all AEs occurring after initiation of BREYANZI administration through and including 90 days after the final cycle of BREYANZI. The majority of the 268 subjects received a single dose of BREYANZI. Subjects were assigned to one of the following dose levels: i) dose level 1 single (DL1S): 50 x 10^6 viable CAR T cells; ii) dose level 2 single (DL2S): 100 x 10^6 viable CAR T cells; or iii) dose level 3 single (DL3S): 150 x 10^6 viable CAR T cells. Dose level 1, 2-dose (indicated by DL1D) and dose level 2, 2-dose (indicated by DL2D) were used in a total of 6 subjects. Ninety-nine percent (266/268) of subjects experienced at least one adverse event following BREYANZI administration. Table 3 provides a summary of the incidence of adverse events (AEs) and serious adverse events (SAEs) in Study 017001.

Table 3. Summary of Adverse Events in Study 017001

AE/SAE	**DL1S N = 45 n (%)**	**DL2S N = 176 n (%)**	**DL3S N = 41 n (%)**	**DL1D N = 5 n (%)**	**DL2D N = 1 n (%)**	**Overall N = 268 n (%)**
All-Grade AEs	44 (98)	176 (100)	40 (98)	5 (100)	1 (100)	266 (99)
Grade 3-5 AEs	36 (80)	138 (78)	32 (78)	5 (100)	0	211 (79)
Grade 3	12 (27)	47 (27)	15 (37)	1 (20)	0	75 (28)
Grade 4	22 (49)	84 (48)	16 (39)	4 (80)	0	126 (47)
AEs leading to death*	2 (4.4)	9 (5)	1 (2.4)	0	0	12 (4.5)
SAEs	16 (36)	83 (47)	20 (49)	3 (60)	0	122 (46)

Source: FDA Analysis using adae.xpt, adsl.xpt study 017001
**Excludes death from progressive disease*
AE: Adverse event/s; SAE: serious adverse event/s
DL1S: dose level 1 single; DL2S- dose level 2 single; DL3S: dose level 3 single; DL1D: dose level 1, 2-dose; DL2D: dose level 2, 2-dose

Adverse events of special interest (AESI) include cytokine release syndrome (CRS), neurologic toxicity (NT), prolonged cytopenias not resolved by Day 29, infections, secondary malignancies, tumor lysis syndrome, hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS), autoimmune events, infusion reactions and hypogammaglobulinemia. Table 4 denotes AESIs of all grades and grade 3 and higher in Study 017001 during the treatment-emergent AE evaluation period (within and

including 90 days following BREYANZI infusion). There were no reports of autoimmune events or HLH/MAS in Study 017001.

Table 4. Adverse Events of Special Interest in Study 017001

Adverse Event of Special Interest	**All Grades N (%)**	**≥ Grade 3 N (%)**
Cytokine Release Syndrome	122 (46)	11 (4)
Neurologic Toxicity	95 (35)	31 (12)
Infections (includes febrile neutropenia)	121 (45)	52 (19)
Prolonged Cytopenias at Day 29	149 (56)	84 (31)
Infusion Reactions	3 (1.1)	0
Hypogammaglobulinemia*	85 (32)	0
Secondary malignancies	5 (1.9)	2 (0.7)
Tumor lysis syndrome	2 (0.7)	2 (0.7)

Source: FDA clinical reviewer analysis; Applicant response to information requests
**Hypogammaglobulinemia incidence based on adverse event reporting and laboratory testing*

Table 5 summarizes the most frequent nonlaboratory AEs by system organ class (SOC) and preferred or grouped terms (PTs or GTs) following BREYANZI infusion and is based on incidence of all grade AEs in ≥ 10% of subjects in Study 017001.

Table 5. Most frequent adverse events following BREYANZI infusion (N=268)

Body System Organ Class AE	**All Grades N (%)**	**Grades 3 or Higher N (%)**
Cardiac disorders		
Tachycardia*	66 (25)	0 (0)
Gastrointestinal disorders		
Nausea	89 (33)	4 (1.5)
Diarrhea	71 (26)	1 (0.4)
Constipation	62 (23)	0 (0)
Abdominal pain*	57 (21)	8 (3)
Vomiting	56 (21)	1 (0.4)
General disorders and administration site conditions		
Fatigue*	129 (48)	9 (3.4)
Pain*, #	76 (28)	4 (1.5)
Edema*, #	56 (21)	3 (1.1)
Fever	42 (16)	0 (0)
Chills	31 (12)	0 (0)
Immune system disorders		
Cytokine Release Syndrome	122 (46)	11 (4.1)
Hypogammaglobulinemia**	85 (32)	0 (0)
Infections and infestations		
Infections: pathogen unspecified	77 (29)	42 (16)
Bacterial infection*	35 (13)	14 (5)
Upper Respiratory Tract Infection*,#	34 (13)	2 (0.7)
Viral infection*	27 (10)	4 (1.5)
Metabolism and nutrition disorders		
Decreased appetite	76 (28)	7 (2.6)

Body System Organ Class AE	All Grades N (%)	Grades 3 or Higher N (%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	98 (37)	6 (2.2)
Motor dysfunction[#,*]	26 (10)	3 (1.1)
Nervous system disorders		
Headache*	81 (30)	3 (1.1)
Encephalopathy*[,#]	78 (29)	23 (9)
Dizziness*	65 (24)	7 (2.6)
Tremor*	43 (16)	0 (0)
Peripheral neuropathy*	29 (11)	0 (0)
Aphasia*	27 (10)	6 (2.2)
Psychiatric disorders		
Insomnia	36 (13)	1 (0.4)
Delirium*	28 (10)	6 (2.2)
Anxiety	27 (10)	0 (0)
Renal and urinary disorders		
Renal failure*	30 (11)	8 (3)
Respiratory, thoracic and mediastinal disorders		
Cough*	61 (23)	0 (0)
Dyspnea*	44 (16)	7 (2.6)
Skin and subcutaneous tissue disorders		
Rash[*,#]	36 (13)	1 (0.4)
Vascular disorders		
Hypotension*	69 (26)	9 (3.4)
Hypertension	37 (14)	12 (4.5)
Hemorrhage*	26 (10)	4 (1.5)

Source: FDA Analysis adae.xpt AE: adverse event. Based on all grade treatment emergent adverse event rate of ≥ 10%; excludes laboratory based adverse events
** Includes grouped terms as detailed in Appendix A of clinical review memo;*
 # Encompasses more than one system organ class
***Hypogammaglobulinemia incidence based on AE reporting and laboratory testing*

One hundred and fourteen of the 268 subjects in the DLBCL cohort of Study 017001 had died as of the primary data cutoff of April 12, 2019. Ninety-nine deaths were due to progressive disease, 3 from unknown causes and 3 from other causes. Nine deaths were adjudicated by the FDA to be related to the product and/or lymphodepleting chemotherapy which is part of the study. Five deaths attributed to the product and/or the study occurred within 30 days after BREYANZI administration. Fatal cases of CRS and NT occurred following BREYANZI administration.

Median time to CRS onset was 5 days (range 1 to 15 days). CRS resolved in the majority of subjects (119 of 122, 98%) with a median time to resolution of 5 days (range 1 to 17 days). One subject had fatal CRS and 2 subjects had CRS ongoing at death. The median duration of CRS in all subjects, including those who died from CRS or had CRS ongoing at the time of death was 5 days (range 1 to 30 days). The most common manifestations of CRS included fever, hypotension, tachycardia, chills, hypoxia, fatigue

and headache. Other serious events associated with CRS included acute kidney injury, cardiac arrhythmias including atrial fibrillation, AV block, bradycardia, elevated hepatic aminotransferases, and respiratory failure (including failure due to diffuse alveolar damage). Twenty-three percent (61/268) received tocilizumab and/or corticosteroids for CRS management.

The median time to onset of neurologic toxicity was 8 days (range 1 to 46 days). Neurologic toxicities resolved in 85% of subjects with a median time to resolution of 12 days (range 1 to 87 days). Of the 3 fatal neurotoxicity events, two were attributed to study product and one was thought to be more likely due to Fludarabine in the context of sepsis. Median duration of neurologic toxicity was 15 days (range 1 to 785 days) in all subjects, including those with ongoing neurologic adverse events at time of death or data cutoff. The most common neurologic toxicities included encephalopathy, tremor, aphasia, delirium, headache, ataxia and dizziness. Encephalopathy was attributed to fludarabine in 2 subjects. Other serious neurologic adverse events included seizures, cerebellar syndrome and cerebral edema. Neurologic toxicities were managed with corticosteroids and antiseizure medications, either as prophylaxis or treatment, and supportive care.

Acquired hypogammaglobulinemia due to the loss of normal B cells after treatment with BREYANZI was observed. Subjects received immunoglobulin replacement therapy based on physician discretion.

Additional secondary malignancies beyond the treatment-emergent period were reported. None of the hematologic malignancies tested for the CAR transgene were deemed to be related to the product. However, risk of insertional mutagenesis and secondary malignancy remains a concern.

Grade 3 or 4 laboratory abnormalities occurring in ≥ 10% of subjects include neutropenia (76%), thrombocytopenia (39%), anemia (23%), hypofibrinogenemia (15%) and hypophosphatemia (13%).

BREYANZI was administered in the inpatient and outpatient setting. However, 91% of subjects received product in the inpatient setting. Eighteen of 25 subjects who received product in the outpatient setting were subsequently hospitalized. For hospitalizations recorded through end of study, median total days of hospitalization for all subjects was 17 days (range 2-116 days) with 12% intensive care unit (ICU) admissions and median ICU stay of 7 days (range 1-56 days). Although BREYANZI was administered in a substantial proportion of subjects in the inpatient setting and a substantial proportion of subjects receiving the product in the outpatient setting required hospitalization, implementation of the REMS program and labelling requirements to ensure daily monitoring of patients is expected to facilitate early diagnosis and management of CRS and neurologic toxicity.

The safety database of 268 subjects is sufficient to assess the acute toxicities of BREYANZI, and severity of CRS and neurologic toxicity warrant marketing authorization

under the REMS program. The long-term adverse reactions require post-marketing study to evaluate the risks of secondary malignancies, particularly those associated with insertional mutagenesis.

Risk Evaluation and Mitigation Strategies (REMS)

FDA determined that a REMS is necessary to ensure that the benefits of BREYANZI outweigh the serious risks of cytokine release syndrome (CRS) and neurologic toxicities (NT). The REMS includes the following Elements to Assure Safe Use (ETASU) to mitigate these risks:

- Health care settings that dispense BREYANZI are specially certified.
- BREYANZI is dispensed to patients only in certain health care settings.

The REMS ETASU requires Juno Therapeutics, Inc. to ensure that:

- Hospitals and their associated clinics are enrolled in the BREYANZI REMS Program and certified through a live training program and knowledge assessments.
- Certified sites report serious cases of CRS and NT.
- Juno Therapeutics, Inc. maintains documentation that processes and procedures are followed for the BREYANZI REMS Program.
- Juno Therapeutics, Inc. conducts audits to ensure that training processes and procedures are in place.
- Sites verify that a minimum of two doses of tocilizumab are available on site prior to BREYANZI infusion.

Materials provided as part of the BREYANZI REMS Program include:

- Hospital Enrollment Form
- Patient Wallet Card
- Live Training Program
- Knowledge Assessment
- BREYANZI REMS Program Website

Postmarketing requirement (PMR) study

Long-term safety after treatment with BREYANZI, particularly for the risk of insertional mutagenesis-related secondary malignancies, remains a concern due to the limited follow-up duration. Therefore, a safety postmarketing requirement (PMR) study is warranted under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA). The applicant is required to conduct a postmarketing, prospective, multi-center, observational study to assess the long-term safety of BREYANZI and the risk of secondary malignancies occurring after treatment with BREYANZI. The PMR study will include at least 1500 adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy; patients will be followed for 15 years after their BREYANZI infusion. The primary endpoint will be evaluation for secondary malignancy, which will include the collection and analysis of blood and/or biopsy specimens of certain malignancies for evaluation of insertional mutagenesis.

The PMR study milestones are as follows:
Final protocol submission: February 28, 2021
Study completion: April 30, 2041
Final report submission: July 31, 2042

8. ADVISORY COMMITTEE MEETING

BREYANZI is similar to other CD-19-directed genetically modified autologous T cell immunotherapies and did not raise new or unique scientific or regulatory issues; as a result, an advisory committee meeting was deemed not necessary.

9. OTHER RELEVANT REGULATORY ISSUES

None.

10. LABELING

The proposed proprietary name, BREYANZI, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on February 10, 2020 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on February 18, 2020.

The APLB reviewed the proposed prescribing information (PI), package and container labeling on August 4, 2020, and found them acceptable from a promotional and comprehension perspective.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review team recommends regular approval of BREYANZI for the treatment of patients with relapsed or refractory (R/R) DLBCL after at least two or more lines of systemic therapy, 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.

b) Risk/ Benefit Assessment

BREYANZI has demonstrated favorable ORR and CR rates and DOR in subjects with R/R DLBCL after at least two or more lines of systemic therapy. The safety results demonstrate an acceptable safety profile when implemented with Risk Evaluation and Mitigation Strategies (REMS) with Elements to Assure Safe Use (ETASU) for the

management of CRS and NT, which represent life-threatening adverse reactions. However, given the life-threatening nature of the disease in the indicated population, these adverse reactions, if managed appropriately, represent toxicities that are acceptable from a benefit-risk perspective. Thus, the overall benefit-risk profile favors regular approval of BREYANZI in patients with R/R large B-cell lymphoma.

c) Recommendation for Postmarketing Activities

1. Registry study: Marketing approval should include a postmarketing requirement (PMR) that the Applicant conduct a multicenter, prospective, observational safety study to assess the long-term safety of BREYANZI and the risk of secondary malignancies. The study will use a registry design and will include 1500 adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy; patients will be followed for 15 years after their BREYANZI infusion. This study is observational and focuses on short-term toxicity, documenting adverse events, and long-term follow-up for evaluation of secondary malignancies, which will include tissue work-up for these events.

The timetable for the PMR study is:

Final protocol submission: February 28, 2021
Study completion: April 30, 2041
Final report submission: July 31, 2042

The applicant agreed to the following postmarketing commitment (PMC):

1. Juno Therapeutics, Inc. commits to prospectively validate the [redacted] per protocol [redacted] and will provide the validation report.

   Final Study Report Submission: September 30, 2021