

CBER CMC BLA Review Memorandum

BLA STN 125813

Aucatzyl

Obecabtagene Autoleucel (obe-cel)

Reviewers

Andrew Timmons, CMC Reviewer/Chair OTP/OGT/DGT2/GTB5

Jessica Chery, CMC Reviewer OTP/OGT/DGT2/GTB5

Timothy Kamaldinov, CMC Reviewer OTP/OGT/DGT2/GTB4

Anurag Sharma, CMC Reviewer OTP/OGT/DGT1/GTB2

1. BLA#: STN 125813**2. APPLICANT NAME AND LICENSE NUMBER**

Name: Autolus Inc.

License Number: 2339

3. PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/Proper Name/USAN: Obecabtagene autoleucel

Proprietary Name: Aucatzyl

Company Codename(s): Auto1 (Cellular DS/DP); (b) (4) (LVV DS)

UNII Code: 760HJB0YRD

NDC Code:

Infusion bag configurations	NDC Number
10×10 ⁶ CD19 CAR-positive viable T cells in one 50mL infusion bag	83047-010-10
100×10 ⁶ CD19 CAR-positive viable T cells in one or more 50mL infusion bags	83047-100-10
100×10 ⁶ CD19 CAR-positive viable T cells in one 250mL infusion bag	83047-100-30
300×10 ⁶ CD19 CAR-positive viable T cells in one or more 250mL infusion bags	83047-300-30

GENERAL DESCRIPTION OF THE FINAL PRODUCT

Pharmacological Category: CD19-directed genetically modified autologous T cell immunotherapy

Dosage Form: Cell suspension for Infusion

Strength/Potency: 410E6 CAR positive T cells

Route of Administration: Intravenous Infusion

Indication: Treatment of adult patients with relapsed or refractory B cell precursor acute lymphoblastic leukemia

MAJOR MILESTONES

Milestone	Date
Initial IND Submission (IND-19534)	March 16, 2020
Orphan drug designation granted	November 4, 2020
Regenerative Medicine Adv. Therapy Designation Granted	April 20, 2020
preBLA Meeting	September 28, 2023
BLA Submission	November 17, 2023
Combined First Committee Meeting/Filing Meeting	December 14, 2023
BLA Filed	January 16, 2024
Mid-cycle Meeting	May 18, 2024
Late-cycle Meeting	August 1, 2024
PDUFA Action Due Date	November 16, 2024

CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Andrew Timmons (AET) CBER/OTP/OGT/DGT2/GTB5	Obe-cel manufacturing process development, assay validation, specifications
Jessica Chery (JC) CBER/OTP/OGT/DGT2/GTB5	Obe-cel manufacturing process, process validation, obe-cel stability
Timothy Kamaldinov (TK) CBER/OTP/OGT/DGT2/GTB4	Obe-cel and (b) (4) control of materials and container closure systems. (b) (4) specifications and assay validations
Anurag Sharma (AS) CBER/OTP/OGT/DGT1/GTB2	(b) (4) manufacturing process, process validation, and (b) (4) stability

INTER-CENTER CONSULTS REQUESTED

Not Applicable

SUBMISSION(S) REVIEWED

Date Received	Amendment (125813.0.###)	Comments/ Status
17-Nov-23	0	Initial submission of complete BLA
18-Dec-23	5	Response to DMPQ IR in preparation for inspection
29-Dec-23	6	(b) (4) comparability report
5-Jan-24	8	Response to DBSQC IR, describing DP myco sampling
29-Jan-24	14	Response to CMC IR #1, requesting CSV files of data tables
31-Jan-24	16	Response to DBSQC IR #2, describing the mycoplasma sampling strategy for the (b) (4)
4-Mar-24	24	Response to CMC IR #2, requesting information on E/L
29-Mar-24	29	Response to CMC IR #3, requesting information on obe-cel analytical procedures
7-May-24	34	Response to CMC IR #4, requesting information on obe-cel labeling and handling
30-May-24	38	Response to CMC IR #5, providing the (b) (4) comparability report
19-Jul-24	44	Response to CMC IR #6, providing additional obe-cel stability data
8-Aug-24	49	Update to include all (b) (4) stability data available
21-Aug-24	54	Response to CMC IR #7, providing a counter proposal for release specifications
22-Aug-24	55	Response to CMC IR #7, part 2
23-Aug-24	56	Response to CMC IR #7, part 3
4-Sep-24	61	Update to include all available obe-cel stability data
5-Sep-24	62	Response to CMC IR #7 commitment, includes additional obe-cel validation data
6-Sep-24	63	Response to CMC IR #8
13-Sep-24	67	Response to CMC IR #5, and comprehensive editorial update of LVV module
23-Sep-24	70	Response to CMC IR #9, including additional information on IVAA testing for the (b) (4)
26-Sep-24	71	Response to CMC IR #11, including information on the (b) (4) testing strategy
30-Sep-24	75	Response to CMC IR #10
4-Oct-2024	78	Response to CMC IR #12, including information on the updated (b) (4) lot

Date Received	Amendment (125813.0.###)	Comments/ Status
11-Oct-2024	81	Response to CMC IR #13, including information on LVV specs and stability shelf life
16-Oct-2024	82	Response to labeling IR #3, which provides the final carton and container labels.
17-Oct-2024	83	BLA Module Updates part 1 of 2. Autolus provides comprehensive updates to components of Module 3 that have been updated throughout the review cycle.
23-Oct-2024	85	Response to CMC IR #14. This IR contained a single item and confirmed agreement on the specifications for the obe-cel stability study.
25-Oct-2024	86	Response to proposed PMRs and PMCs. Autolus agrees to all CMC PMCs.

REFERENCED REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder (1)	Referenced Item	Comments/Status (2)
(b) (4)	(b) (4)	Mfg. of (b) (4)	Active, supports other BLAs
(b) (4)	(b) (4)	Mfg. of (b) (4)	Active, supports other BLAs
(b) (4)	(b) (4)	Mfg. of (b) (4)	Active, supports other BLAs
(b) (4)	(b) (4)	Mfg. of (b) (4)	Active, supports other BLAs
(b) (4)	(b) (4)	Mfg. of (b) (4) PBS/EDTA Buffer	Active, supports other BLAs
(b) (4)	(b) (4)	Mfg. of (b) (4)	Active, supports other BLAs
(b) (4)	(b) (4)	(b) (4)	Active, supports other BLAs
(b) (4)	(b) (4)	(b) (4) Characterization and Final Product Testing	Active, supports other BLAs
<p>1) Letters of Authorization (LoAs) have been supplied for all master files, granting BLA-125813 referential rights to information contained within the master files</p> <p>2) In addition to currently supporting other BLAs, the status of each master file was confirmed by consulting each CMC reviewer individually during the review cycle.</p>			

**REVIEWER SUMMARY AND RECOMMENDATION
EXECUTIVE SUMMARY**

The FDA CMC review team concludes that the manufacturing process, test methods, and control measures in place for obecabtagene autoleucel (obe-cel; Aucatzyl) are sufficient to ensure the generation of autologous products with consistent quality attributes that are acceptable for commercialization of obe-cel under this BLA.


Obe-cel is a genetically modified T cell immunotherapy indicated for the treatment of adults with relapsed or refractory B cell acute lymphoblastic leukemia (r/r B-ALL). Obe-cel consists of autologous T cells that have been genetically modified via transduction with the (b) (4) lentiviral vector (LVV), which equips transduced cells with a constitutively expressed chimeric antigen receptor (CAR) construct that targets human

CD19. Upon recognition of CD19 on target cells, the CAR triggers a cytolytic response, resulting in killing of the CD19-expressing target cell. CD19 is a well-characterized marker of mature B cells, and elimination of CD19 expressing cells is an established therapeutic approach for the treatment of B cell lymphomas.

There are other approved CD19-directed CAR T cell immunotherapies (Yescarta, BLA-125643; Kymriah, BLA-125646; Tecartus, BLA-125703; Breyanzi, BLA-125714). Importantly, obe-cel utilizes a unique CD19 binding domain derived from the (b) (4) murine monoclonal antibody. The use of this unique binding domain imparts the obe-cel CAR with distinct binding kinetics relative to other CD19-directed CAR T cell products.

Obe-cel is formulated at 10×10^6 cells/mL in PBS supplemented with (b) (4) HSA, (b) (4) EDTA, and 7.5% DMSO. The formulated cell suspension (i.e., the (b) (4) drug product) is filled into 3 distinct bag configurations and administered via a split dosing regimen. The total number of filled bags will vary between 3 and 5, depending on the frequency of CAR-positive cells present in each lot. Importantly, regardless of the frequency of CAR-positive cells in each lot, each bag configuration will deliver a specified number of CAR-positive cells (10×10^6 , 100×10^6 , and 300×10^6 , CAR positive cells, respectively) for a total cell dose of 410×10^6 CAR-positive cells. Following the filling procedure, the primary obe-cel container closure is sealed within a transparent overwrap, cryopreserved in a (b) (4), and then secured within a foam block held within a metal cassette and is then transferred to the vapor phase of liquid nitrogen. The metal cassette containing cryopreserved obe-cel is shipped frozen in a qualified liquid nitrogen shipper. After receipt at the administration site, obe-cel is stored in the vapor phase of liquid nitrogen until treatment, where it is thawed and infused within 1 hour of thawing.

(b) (4)



Obe-cel is generated from autologous apheresis material at the Nucleus, an Autolus-owned manufacturing facility located in Stevenage, UK. The apheresis material is

shipped to the Nucleus facility and processed within (b) (4) of collection. The obe-cel manufacturing process begins with (b) (4)

(b) (4) and then formulated to a target concentration (i.e., 10×10^6 cells/mL) using (b) (4) obe-cel drug product. The obe-cel drug product is filled into infusion bags and (b) (4) for quality control testing. (b) (4) and cryobags are cryopreserved in a (b) (4), and subsequently transferred to the vapor phase of liquid nitrogen for storage prior to shipment to an infusion site. The shelf life of obe-cel when stored in the vapor phase of liquid nitrogen was determined to be 6 months.

Autolus employs a multi-faceted control strategy to ensure the consistent generation of obe-cel. Raw materials, reagents, and manufacturing consumables each have defined quality attributes which must be confirmed prior to use in manufacturing. Raw materials derived from animal and human sources are appropriately controlled and tested (see **3.2.S.2.3 Control of Materials**) to ensure that reagents are free from microbial contamination.

To ensure manufacturing consistency, multiple in-process controls are used throughout the manufacturing process. Additionally, all lot release tests for the (b) (4) LVV and obe-cel DP are appropriately validated, and product specifications are adequate to ensure product quality and consistency. Autolus executed a comprehensive validation of the obe-cel manufacturing process, and also generated a substantial number of additional full-scale obe-cel lots as part of capacity demonstrations. The totality of data provided from process validation and capacity demonstrations ($n > (b) (4)$) indicate that Autolus can reliably generate obe-cel with consistent, predictable properties when using the manufacturing process outlined in the BLA.

RECOMMENDATION:

APPROVAL

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization strategy for obecabtagene autoleucel (obe-cel; AUCATZYL). The CMC review team has concluded that the manufacturing process, manufacturing controls, test methods, and stability data indicate that the proposed commercial manufacturing facility (i.e., the Nucleus) can produce obe-cel with consistent quality characteristics. This information, along with the post-marketing commitments (PMCs; below) satisfy the CMC requirements for biological product licensure per the provisions of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products. Further, based on the information provided in the BLA submission, and information gathered during the pre-license inspection of the Nucleus manufacturing facility, the CMC review team recommends approval of this BLA.

Post-Marketing Commitments (PMCs):

1. Autolus Limited commits to conducting an additional product-specific requalification of the LVV adventitious agents test using a sample withdrawn from the (b) (4). Final Study Report Submission: March 31, 2025
2. Autolus Limited commits to providing a supplemental assay validation of the obe-cel (b) (4) assay, which evaluates the accuracy and linearity of the (b) (4) assay at (b) (4) CD19 CAR frequencies. Final Study Report Submission: May 31, 2025
3. Autolus Limited commits to establishing a procedure for (b) (4) between “in-use” and “new” lots of the (b) (4) antibody lots used for the (b) (4) and (b) (4) (obe-cel) release assays. Protocol Submission: June 30, 2025
4. Autolus commits to providing a reassessment of the acceptance criterion for the (b) (4) assay following the manufacture of (b) (4) additional lots of commercial (b) (4) vector. Revision Submission: December 31, 2025
5. Autolus commits to providing a supplemental validation study report evaluating the robustness of the (b) (4) assay performed as part of the (b) (4) release test. Final Study Report Submission: March 31, 2025

SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Andrew Timmons CMC Reviewer/Chair OTP/OGT/DGT2/GTB5	I concur with this review	
Jessica Chery CMC Reviewer OTP/OGT/DGT2/GTB5	I concur with this review	
Timothy Kamalidinov CMC Reviewer OTP/OGT/DGT2/GTB4	I concur with this review	
Anurag Sharma CMC Reviewer OTP/OGT/DGT1/GTB2	I concur with this review	
Graeme Price Branch Chief OTP/OGT/DGT2/GTB5	I concur with this review	
Kimberly Schultz Division Director OTP/OGT/DGT2	I concur with this review	
Denise Gavin Office Director OTP/OGT	I concur with this review	

Review of CTD

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88 pages determined to be not releasable: (b)(4)

(b) (4)

3.2.P Obecabtagene Autoleucel (Obe-cel) Drug Product

3.2.P.1 Description and Composition of the Drug Product

This section reviewed by JC

Obe-cel is manufactured, formulated, and cryopreserved as a cell suspension at a target concentration of 10×10^6 total viable cells/mL filled in (b) (4) bags for intravenous (IV) infusion (**Table 52**).

Table 52 – Obe-cel suspension for Infusion Unit Composition per volume

Components	Supplier (Reagent)	Quantity/Amount per mL	Function
Total viable cells	Autolus	10×10^6 ^A	Active ingredient
CD19 CAR-positive viable T cells	Autolus	Variable based on (b) (4)	
Human Serum Albumin (HSA)	(b) (4)	(b) (4)	(b) (4)
Dimethyl Sulfoxide (DMSO)	(b) (4)	7.5% (v/v)	Cryoprotectant
Ethylenediaminetetraacetic Acid (EDTA)	(b) (4) PBS/EDTA)	(b) (4)	(b) (4) r
Phosphate Buffered Saline (PBS)	(b) (4) PBS/EDTA) and (b) (4)	(b) (4) (b) (4) (b) (4) (b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

^A Range is controlled per commercial process between (b) (4) cells/mL

The fill volume and amount of CD19 CAR-positive T cells is variable due to the transduction efficiency and the total viable cell concentration. The target dose, 410×10^6 CD19 CAR-positive viable T cells, is filled into three different bag configurations (**Table 53**) using (b) (4) freezing bag sizes: (b) (4), which has a fill volume of 10-20mL, and (b) (4), which has a fill volume of 30-70mL.

Table 53 – Obe-cel Infusion Bags Configuration

Bag	Infusion Bag Configuration	Bag Type	Maximum Number of CD19 CAR-positive Viable T cells per Bag	Fill Volume Per Bag
A	10×10^6 CD19 CAR-positive viable T cells	(b) (4)	(b) (4)	10 mL Contains overfill
B	100×10^6 CD19 CAR-positive viable T cells	(b) (4)		10 – 20 mL (b) (4) 30 – 70 mL (b) (4)
C	300×10^6 CD19 CAR-positive viable T cells	(b) (4)		30 – 70 mL No overfill

Bag configuration A contains an overfill of (b) (4), depending on the (b) (4) and viability of the obe-cel lot. In contrast to bag configurations B and C (which have no overfill), bag configuration A will be administered by drawing a defined volume into a syringe for infusion via a vascular access port. To mitigate the risk of overdosing, Autolus provides a dose schedule form and an infusion certificate to the treating physician, which outlines the appropriate volume to infuse. Further, to mitigate the risk of improper dosing in a commercial setting, Autolus has implemented a color-coding strategy for each infusion bag, and bag configuration A is conspicuously labeled to indicate the syringe administration procedure.

Reviewer Comment – During the initial review period the clinical reviewer (Najat Bouchkouj) requested a consult from the Division of Medication Error Prevention and Analysis (DMEPA) given that there were 3 instances in which treating physicians administered the entire 10mL within bag configuration A as opposed to administering the specified volume. In response to these errors, Autolus is implementing several mitigation strategies for commercial sale (color coding of bags, additional documentation,

conspicuous labeling). The DMEPA consult review considered these dosing error mitigation strategies to be sufficient.

Autolus uses the different bag configurations described in **Table 53** to accommodate a split dosing strategy. Briefly, the full dose of obe-cel (i.e., 410×10^6 viable CAR+ cells) will be administered in two infusion sessions separated by 10 days. The quantity of obe-cel received at each infusion session is driven by the patient's disease burden, which is determined with a bone marrow assessment (**Table 54**).

Table 54 – Obe-cel split dosing strategy

BM Blast (%)	Dosing Schedule	
	Dose 1 (Day 1)	Dose 2 (Day 10 ± 2)
≤ 20%	Entirety of Bag Configuration B (100×10^6 CD19 CAR-positive viable T cells)	10×10^6 CAR+ Cells from Configuration A Entirety of Bag Configuration C (310×10^6 CD19 CAR-positive viable T cells)
≥ 20%	10×10^6 CAR+ Cells from Configuration A	Entirety of Bag Configuration B Entirety of Bag Configuration C (400×10^6 CD19 CAR-positive viable T cells)

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

This section reviewed by JC

3.2.P.2.1.1 Drug Substance

Obe-cel manufacturing is a continuous process with no hold step between DS, (defined as (b) (4)) and DP formulation and fill.

The active component of obe-cel is autologous patient-derived T cells transduced with (b) (4) to express CD19 (CAR). Obe-cel also includes (b) (4)

excipients Table 55.

PBS is sourced from (b) (4) and (b) (4)

Dosing is determined based on CAR positive T cells.

3.2.P.2.1.2 Excipients

Table 55 – Obe-cel Suspension for Infusion Excipients

Excipient	Function
Human Serum Albumin (HSA)	(b) (4)
Dimethyl Sulfoxide (DMSO)	
EDTA	
Phosphate Buffer Saline (PBS)	
(b) (4)	

The total amount of different excipients in obe-cel in worst-case infusion volume of (b) (4) (based on (b) (4) CAR expression) Table 56.

Table 56 – Maximum levels of Excipients Relative to Recommended Levels

Excipient	Total amount in 133mL Obe-cel	Recommended daily dose via intravenous infusion
(b) (4) EDTA	(b) (4)	(b) (4)
HSA	(b) (4)	
DMSO	(b) (4)	

Reviewer Comment: Autolus calculates the total amount of excipients present in worse case infusion volumes to be well below the recommended maximum daily levels for therapeutic use, supporting an acceptable margin of safety. In addition, the excipients are not novel for formulation of CAR-T products. These are commonly used excipients in CAR-T product formulation with no strong record of high risks to product quality. Additional documentation, such as Certificates of Analysis, provided to support quality of excipients is reviewed in Control of Materials section. This is acceptable.

3.2.P.2.2 Drug Product

This section reviewed by JC

3.2.P.2.2.1 Formulation Development

Two formulations have been used throughout development: an initial formulation (b) (4) formulation) used by (b) (4) since 2013 for the cryopreservation of T cells for early clinical use, and Autolus (CGT) formulation Table 57. The (b) (4) formulation was used to cryopreserve obe-cel manufactured under Process (b) (4) for the ALLCAR19 and CARPALL studies. The Autolus formulation was used in Process (b) (4) manufacturing of product used in the FELIX study.

Table 57 – Formulations used in clinical studies

Clinical Study	Code	Facility	Formulation
ALLCAR19 CARPALL	(b) (4)	(b) (4)	(b) (4)
FELIX Phase Ib and Phase II	(b) (4)	Autolus (CGT)	(b) (4)

(b) (4)

CGT: Cell and Gene Therapy Catapult – Manufacturing Centre, Stevenage, UK.

Reviewer Comment – *The pivotal study intended to provide the primary evidence of efficacy (i.e., the FELIX study) was performed entirely with manufacturing process (b) (4). Therefore, a thorough review of comparability between the process (b) (4) formulation and process (b) (4) formulation is omitted for brevity. Data supporting the comparability of these different formulations was reviewed under IND-19534, amendment 367 and found acceptable.*

3.2.P.2.2.2 Overages

Reviewer Comment: Overages were reviewed in Section 3.2.P.1.

3.2.P.2.2.3 Physicochemical and Biological Properties

The physiochemical and biological properties of obe-cel are reviewed in Section 3.2.S.3.1, and the quality attributes are described in the Drug Product specifications in section 3.2.P.5.1.

3.2.P.2.3 Manufacturing Process Development

This section reviewed by JC

Obe-cel DS (defined as CD19 CAR-positive T cells at the (b) (4) is forward processed to manufacture the final DP with no hold step prior to Formulation and Final Fill. Autolus performed a number of process development studies to determine CPPs IPCs.

Formulation and final fill step starts by (b) (4)

The (b) (4) DP is then aseptically dispensed into 3 to 5 infusion bags via a fully closed transfer manifold. After formulation and final fill, the infusion bag is placed in an overwrap, sealed, and cryopreserved in a (b) (4) using a qualified freezing profile. Cryopreserved DP is then stored in liquid nitrogen (LN2) vapor phase at ≤ -150°C.

Autolus performed a Failure Modes and Effects Analysis (FMEA)-based risk assessment for formulation, final fill, cryopreservation, and storage steps to identify needed development studies. Failure modes classified as medium or high risk by FMEA were prioritized in study design. The studies evaluated the impact of different (b) (4) hold times, fill volumes (b) (4) bag), and viable cell concentrations on obe-cel cell viability (upon thaw) and potency by (b) (4) (CD19 CAR-positive function). The (b) (4) hold time is defined as the time from the addition of (b) (4) to the start of the (b) (4) protocol. In addition, the filling accuracy of the (b) (4) used in the formulation and final step was assessed with (b) (4). The results from these studies were used to establish control parameters such as PARs for formulation and final fill.

The study used split material from CD19 CAR-positive T cells manufactured using healthy donor (N=(b) (4)) and patient leukapheresis starting materials (N=(b) (4)). Justification was provided for the limits tested Table 58.

(b) (4)

(b) (4)

Reviewer Comment: All lots had (b) (4) cell viability upon thaw and (b) (4) CAR T cell specific killing for all the conditions tested. In addition, the statistical analysis performed by Autolus indicated no statistically significant (P (b) (4) impact on obe-cel viability upon thaw and CAR-T cell function or CD19 killing as evaluated by (b) (4) for the ranges or limits tested. Overall, the data support (b) (4) of hold time from addition of (b) (4) to the start of the (b) (4) freezing, fill volumes of 10-20mL for (b) (4) bag size, fill volumes of 30-70 for (b) (4) bag size, and a filling range of (b) (4) viable cell concentration.

Filling Accuracy

The formulation and final fill step uses a (b) (4) was used to perform an accuracy study with (b) (4) operators and (b) (4) bags with low, middle, and high target fill volumes. The (b) (4) of the filled bags was measured (b) (4), calibrated to (b) (4) accuracy. The results of the study are in **Table 59**.

(b) (4)

Reviewer Comment: The data indicate (b) (4) reproducibility for 10-70 mL volumes for the (b) (4) used in formulation and final fill. Autolus' analysis support higher accuracy (b) (4) reproducibility) at higher volumes (30-70 mL). Based on the results for the formulation and final fill development studies, Autolus implemented proven acceptable ranges of (b) (4) between addition of (b) (4) to the start of the (b) (4) cryopreservation protocol and 10-20 mL for (b) (4) DP fill, 30-70 mL for (b) (4) DP fill volume. The time for addition of freeze mix is classified as a CPP and the fill volumes for the (b) (4) bags are classified as IPCs. This is acceptable.

Cryopreservation and Storage

After filling the DP in (b) (4) bags, the filled bags are cryopreserved in a (b) (4) with a qualified freezing profile. FMEA was used to identify critical parameters for the cryopreservation and storage step that could impact obe-cel CQAs. This evaluation was done using (b) (4) studies from the (b) (4) study lots, with results indicating that the (b) (4) freezing profile and duration of transport (or exposure to room temperature) for cryopreserved product to cryoshipper and LN2 storage could be critical parameters. Therefore, acceptable ranges for these parameters were

established via development studies assessing qualification of the freezing profile, and time of transfer from (b) (4) to LN2 storage. The (b) (4) profile is shown in Table 60.

(b) (4)

(b) (4)

Reviewer Comment: The representative profiles indicate consistent freezing profiles or temperatures as reported from the (b) (4) different probes. The consistency in freezing rate between the probes provides support for the reliability of the (b) (4) probe. The freezing rates and profiles for the different fill volumes (10, 20, 30, 70mL) and bag sizes (b) (4) support similar freezing rate for the different DP filling or bag configurations. Overall, the data support suitability of the (b) (4) profile proposed for obe-cel cryopreservation. The (b) (4) was qualified and validated. This is acceptable.

Time of Transfer from (b) (4) to Liquid Nitrogen (LN2) Storage

Autolus performed a study to determine the maximum time frozen obe-cel can be exposed to room temperature during transfer from (b) (4) to LN2 storage in the manufacturing facility and transportation transfers until the LN2 storage in the administration centers. Autolus measured the time it took to warm the frozen (b) (4) bags from (b) (4) to room temperature Table 61.

(b) (4)

Based on this study Autolus proposes to limit exposure of frozen bags to room temperature to within (b) (4) during the following transfer operations:

- (b) (4)

Reviewer Comment: The warming rates and times to reach temperatures critical for viability (b) (4) indicate slightly longer times (b) (4) to reach (b) (4) as the fill

volume increases. The time to reach (b) (4) indicate similar times for fill volumes 10, 20, 30mL and about twice the time for the 70mL filled bags to reach (b) (4). The shortest time to reach (b) (4). Based on this data, keeping the transfer time for frozen bags within (b) (4) should avoid inappropriate warming of frozen DP during transfer from (b) (4) to Liquid Nitrogen (LN2) Storage. This is acceptable.

3.2.P.2.4 Container Closure System

Reviewed in Section 3.2.P.7 Container Closure System (CCS)

3.2.P.2.5 Microbiological Attributes

This section reviewed by JC

Obe-cel is manufactured under aseptic conditions using a functionally closed manufacturing system. DP samples are withdrawn from the final container closure for sterility and endotoxin lot release testing. The DP is cryopreserved in a buffered solution supplemented with a cryoprotectant (DMSO) in the vapor phase of liquid nitrogen.

Container closure integrity was evaluated on both the (b) (4) bags to confirm that the container closures maintain a sterile barrier and prevents the ingress of microbial contamination. Briefly, (b) (4)

(b) (4)

Reviewer assessment: Results from the CCIT are acceptable to demonstrate microbiological suitability of the CCS.

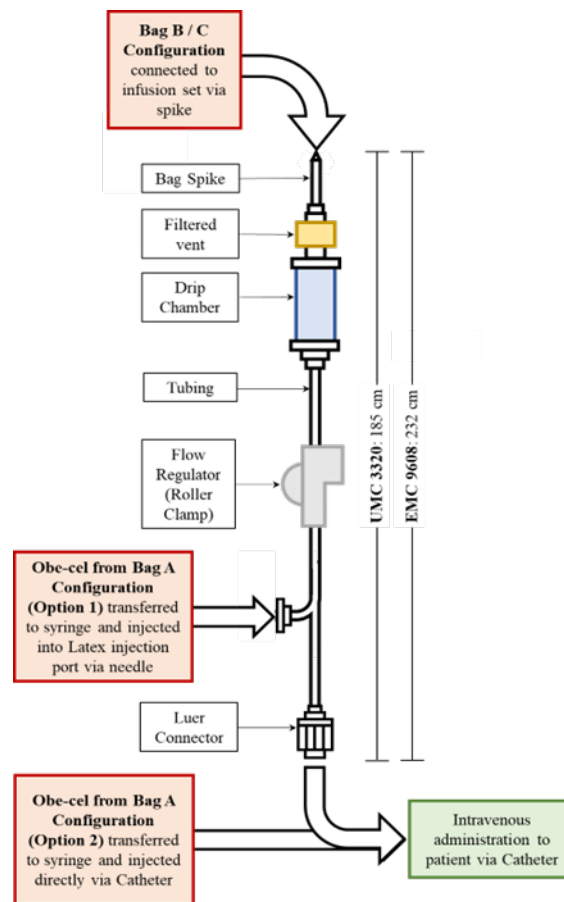
3.2.P.2.6 Compatibility

This section reviewed by JC

Autolus performed a number of studies to support the compatibility of obe-cel DP with the container closure, administration procedure, and administration components. The obe-cel final Drug Product target dose of 410×10^6 CD19 CAR-positive viable T cells is filled into (b) (4) bags with (b) (4) different numbers of CD19 CAR-positive viable T cells to allow Autolus to meet a split dosing regimen (see **Table 53**). Because bag configuration A is infused with a syringe, the administration and infusion sets are diagramed in Figure 28, and their associated materials of construction are denoted in Table 62.

Reviewer Comment: The suitability of the administration with syringe injection into latex injection port of the infusion set is further reviewed in the DMEPA consult review.

Figure 28 – Schematic of Infusion Sets Used for administration of obe-cel



(b) (4)

Autolus performed a FMEA assessment of the thawing and infusion process to determine what delivery process parameters could present risks that could affect obe-cel CQAs or

administration. Based on the FMEA assessment, Autolus designed the compatibility studies to focus on DP handling prior to administration, dosing accuracy, and infusion times.

Drug product handling prior to administration

To assess DP compatibility with administration components, Autolus evaluated the procedures for handling prior to administration. For these studies Autolus assessed the impact of some parameters such as hold time during thaw on certain obo-cel attributes, in-use stability, and sterility during administration.

Hold time during thaw

Clinical sites used either a water bath or (b) (4) to thaw the DP in the FELIX Phlb/II Study. DP handling compatibility studies used process development lots manufactured from healthy donor or patient leukapheresis starting material and (b) (4) bags filled with (b) (4) as a substitute for DP. Thawing times were measured for (b) (4) bags filled with different volumes when thawed in a water bath (FELIX Phlb/II lots at clinical sites) or (b) (4) (process development lots).

Reviewer Comment: A matrix approach was used to assess the impact of thawing method and fill volume on thaw time due to the limited cell numbers to fill all bag configurations in multiple units. Based on the data, thawing takes (b) (4). In response to CMC IR6 received July 19, 2024, Autolus clarified the rationale for the “N/D=Not Determined” and “N/A=Not Applicable” results in Table 4 of Section 3.2.P.2.6. According to Autolus, “Not Determined” is reported in cases where samples were not available to measure the thaw time as this is a cell-based product with limited material availability. “Not applicable” refers to cases where the number of bags available and subsequently thawed of each specific fill volume was N^{(b) (4)}, and therefore, the standard deviation could not be determined. Given a matrix approach for testing is needed due to limited material, this is acceptable. In addition, the times and volumes seem to cover conditions proposed for the commercial thawing.

(b) (4)


Reviewer Comment: Thawing time data indicate obe-cel thaws more rapidly than formulation (b) (4). In addition, the larger bag configuration (b) (4) takes longer (approximately (b) (4) to thaw than the (b) (4) bag. Thawing time for both equipment (b) (4), waterbath) is similar across each bag configuration (b) (4). This data supports suitability of (b) (4) and waterbath to thaw product bags. *Additional studies indicate that thaw time increases with larger fill volumes for formulation without cells using either (b) (4) or waterbath. However, thaw times for the different fill volumes (10, 20, 30 mL) of obe-cel are similar between thawing procedures. In addition, the data indicates lower variability (b) (4) for thawing time for obe-cel versus (b) (4). This is acceptable.*

(b) (4)

(b) (4)

(b) (4)

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The redaction covers approximately five lines of text and a table header. The text "(b) (4)" is visible in the top left corner of this redacted area.

(b) (4)

Reviewer Comment: The infusion studies support the recommended parameters.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

This section reviewed by JC

Obe-cel manufacturing, fill, finish, packaging, storage, all release testing, and stability testing are performed at Autolus Limited facility referred to as The Nucleus.

Table 65 – Obe-cel Drug Product Manufacturers

Address	Responsibility
Autolus Limited (referred to as The Nucleus) Marshgate, Stevenage, SG1 1FR United Kingdom FEI: 3015674982; DUNS: 229442484	Obe-cel Manufacture, Fill and Finish, Packaging and Storage Obe-cel Quality Control Obe-cel Release Testing Obe-cel Stability and Stability Testing

3.2.P.3.2 Batch Formula

This section reviewed by JC

Each batch of obe-cel is manufactured for an individual patient and filled at a target concentration of 10×10^6 total viable cells/mL (range (b) (4) cells/mL). Fill volume and the amount of CD19 CAR-positive T cells is variable based on the (b) (4) and the total viable cell concentration, with a typical batch formula shown in **Table 66**.

Table 66 – Obe-cel Batch Size

Ingredient	Quantity/Amount per mL	Amount per Typical Batch ^a
Total viable cells	10 × 10 ⁶ ^b	(b) (4)
CD19 CAR-positive viable T cells	Variable based on (b) (4)	
Human Serum Albumin (HSA)	(b) (4)	
Dimethyl Sulfoxide (DMSO)	7.5% (v/v)	
Ethylenediaminetetraacetic Acid (EDTA)	(b) (4)	
Phosphate Buffer Saline (PBS)		
(b) (4)		
^a Typical batch - example from (b) (4) with CD19 CAR Expression (b) (4) of (b) (4) and total pre-fill volume of (b) (4).		
^b The range is controlled per commercial process between (b) (4) cells/mL		

3.2.P.3.3 Description of Manufacturing Process

This section reviewed by JC

The obe-cel DP manufacturing process includes formulation and final fill as well as cryopreservation and storage. This process, including CPPs and IPCs, is described in Table 39.

Batch Number

Each obe-cel batch manufactured at The Nucleus is assigned a unique batch number composed of an alphanumeric code derived from a unique patient identifier, but not containing any patient identifiable information. The same batch number is assigned to the leukapheresis starting material on receipt at The Nucleus. This batch number is used to trace and identify the patient-specific batch from leukapheresis collection throughout manufacturing.

Formulation and Final Fill

The cell suspension is (b) (4) to a target concentration of (b) (4) cells/mL with (b) (4). The cell suspension is then (b) (4) with cryopreservation buffer (b) (4) containing HSA and DMSO to a target concentration of 10×10^6 (b) (4) total viable cells/mL, (b) (4) HSA and 7.5% DMSO.

Formulated DP is filled using a closed system into the final container closure:

(b) (4) (10 – 20 mL) and (b) (4) (30 – 70 mL) cryobags based on

transduction efficiency and number of CD19 CAR-positive T cells to meet dose. Controls for formulation and fill are outlined Table 39.

Cryopreservation and Storage

After formulation, cryobags filled with DP are overwrapped, sealed, and cryopreserved in a qualified (b) (4). Frozen cryobags containing DP are stored in vapor phase LN2 ($\leq -150^{\circ}\text{C}$). Obe-cel DP bags are transported to clinical sites at $\leq -150^{\circ}\text{C}$ in a validated liquid nitrogen dry shipper (cryoshipper) by a courier experienced in medicinal product transportation.

Reviewer Comment: Drug product packaging is reviewed in section 3.2.P.7; and DP shipping validation is reviewed in section 3.2.P.3.5.

3.2.P.3.4 Controls of Critical Steps and Intermediates

This section written by JC

CPPs and IPCs used to ensure consistency of the obe-cel DP manufacturing process and product quality according to the established commercial specifications are outlined in Table 67. These CPPs and IPCs were established based on clinical manufacturing experience, process characterization, and PPQ studies. Deviations are raised for excursions of a CPP outside its proven acceptable range or for an IPC outside of its acceptance criterion, according to Autolus.

(b) (4)

3.2.P.3.5 Process Validation and/or Evaluation

This section reviewed by JC

Obe-cel process validation was conducted in 3 stages: Process Design, Process Qualification, and Continued Process Verification. Process Design is focused on designing a commercial manufacturing process that consistently produces product of desired quality. This includes setting controls for the process, such as proven acceptable ranges (PAR) for process parameters and controls, to ensure the Obe-cel product meets established critical quality attributes (CQA). In the process qualification stage, the process design was tested for reproducible manufacturing. The process qualification included qualification of equipment and utilities as well as the manufacturing process, such as production capacity at the facility (The Nucleus), chain of identity/chain of custody, aseptic process simulation, extractables and leachables, drug product transport.

16 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.4 Control of Excipients

This section reviewed by AET

The final formulation of obe-cel includes four excipients (see **3.2.P.3.2 Batch Formula**). Of these excipients, two are (b) (4) standards and/or approved products (i.e., DMSO and (b) (4) HSA) and two are (b) (4), and PBS supplemented with EDTA). The measures taken to ensure quality of the (b) (4) excipients are described below.

(b) (4) is used as an excipient to ensure an (b) (4) for obe-cel. While (b) (4) itself is not a (b) (4) material, all underlying components of (b) (4) are (b) (4) materials (e.g., (b) (4)). The quality of each lot of (b) (4) is confirmed at the Nucleus manufacturing facility by CoA inspection and additional testing. Briefly, Autolus performs supplemental assessments to confirm the concentration of (b) (4) assays. Additionally, full independent testing of (b) (4) lots of (b) (4) was performed as part of initial supplier qualification.

Reviewer Comment – The quality of (b) (4) is acceptable, and the ongoing control strategy for (b) (4) is acceptable.

PBS supplemented with EDTA (b) (4) (PBS/EDTA Buffer) is also used as an excipient to ensure an (b) (4) carrier solution. EDTA is supplemented (b) (4) to chelate divalent cations, which enhances the stability of human cells in culture. Similar to (b) (4), all constituent components of the PBS-EDTA solution are themselves (b) (4) materials (including EDTA). The quality of each lot of PBS-EDTA is confirmed at the Nucleus manufacturing facility by CoA inspection and additional testing is performed. Briefly, the concentration of (b) (4) is confirmed using (b) (4) assays. Further, the concentration of EDTA is verified using an independent (b) (4) assay which reports the extent of (b) (4).

Reviewer Comment – The quality of PBS-EDTA is acceptable, and the ongoing control strategy for PBS-EDTA is acceptable.

3.2.P.4.1 Specifications

For information regarding incoming testing of excipients, please refer to **Control of Raw Materials NOT of Biological Origin**.

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

This section reviewed by TK

The information on analytical methods used to qualify excipients for use in obe-cel formulation are described in **Table 77**.

Table 77 – The analytical procedures used in incoming testing of obe-cel excipients

Excipient	Analytical Method Description and Method Validation/Qualification
(b) (4)	(b) (4)
(b) (4) PBS/EDTA	

Excipient	Analytical Method Description and Method Validation/Qualification
Human Serum Albumin	(b) (4)
DMSO	

Reviewer Comment – The analytical methods and method validations are acceptable for its intended purpose. The excipients and methods are either (b) (4) or based on (b) (4) material and methods and thus do not require validations.

3.2.P.4.4 Justification of Specifications

Reviewer Comment – The specifications are acceptable for its intended purpose.

3.2.P.4.5 Excipients of Human or Animal Origin

This section reviewed by JC

Human Serum Albumin (HSA) (b) (4) is the only reported excipient of human or animal origin used in the DP final formulation. According to Autolus, plasma donations used to manufacture the HSA are individually tested and tested in mini-pools.

Reviewer Comment – HSA is a FDA licensed product (NDC = 68982-633-02).

3.2.P.4.6 Novel Excipients

Obe-cel formulation does not contain novel excipients.

Reviewer's Overall Summary of Module 3.2.P.4 – The information provided on the excipients is acceptable to support their use in the final formulation for obe-cel.

3.2.P.5 Control of Drug Product

This section reviewed by AET

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Release specifications for commercial obe-cel are outlined in **Table 78**. For a graphical depiction of each specification relative to clinical experience, see **3.2.P.5.4 Batch Analyses**.

Table 78 – Release specifications for obe-cel

Analytical Procedure	Acceptance Criteria	Justification (A)
Appearance by Visual Inspection for Color	Colorless to pale yellow	Established by Autolus based on a representative sample of n=(b) (4) aliquots from the FELIX registrational study
Appearance by Visual Inspection for Clarity	Very opalescent	Established by Autolus based on a representative sample of n=(b) (4) aliquots from the FELIX registrational study
Appearance by Visual Inspection for Visible Particles	Essentially free from visible foreign particles	Established by Autolus to ensure DP is free from visible foreign particulates. Note that term “essentially free” is derived from (b) (4) and FDA guidance
CD19 CAR Expression by (b) (4)	Detected	Established by Autolus to confirm DP consists of T cells transduced with the intended CD19 CAR vector. The identity is established by the integrated (b) (4) procedure.
Number of CD19 CAR-positive T cells by (b) (4)	410 × 10 ⁶ (b) (4)	Established to confirm Obe-cel DP contains the intended number of CAR-positive T cells. Obe-cel is administered as a flat dose of 410E6 cells regardless of patient weight;

Analytical Procedure	Acceptance Criteria	Justification (A)
		specification was established to ensure this dose target was met.
Cell Viability upon thaw by (b) (4)	(b) (4)	Defined objectively based on data from (b) (4) individual DP. A mean (b) (4) SD approach was used on logit-transformed data, resulting in a range of (b) (4). No upper limit of viability was established.
Cell Phenotype by (b) (4)	(b) (4)	Defined objectively based on data from (b) (4) individual measurements from (b) (4) obe-cel lots (N=(b) (4) clinical lots and N=(b) (4) GMP lots). A mean (b) (4) SD approach was used on logit-transformed data, resulting in a range of (b) (4). No upper limit of cell purity was established.
(b) (4)	(b) (4)	Defined objectively based on (b) (4) individual measurements from (b) (4) obe-cel lots (N=(b) (4) clinical lots and N=(b) (4) healthy donor lots). A mean (b) (4) SD approach was used on normally distributed data.
CD19 CAR Expression by (b) (4)	(b) (4)	Defined objectively based on (b) (4) individual measurements from (b) (4) obe-cel lots (N=(b) (4) clinical lots and N=(b) (4) healthy donor lots). Importantly, during the FELIX study all data were obtained using (b) (4) samples, whereas commercially this value will be obtained with the integrated (b) (4) procedure performed on formulated DP. The analytical comparability of these two assays was evaluated and found to be equivalent. A mean (b) (4) SD approach was used on untransformed data, despite not being normally distributed (B). This range was chosen based on the graphical distribution of data and the occurrence of multiple CRs at (b) (4) CAR+ frequencies. The calculated range was (b) (4).
Obe-cel Functionality by (b) (4)	(b) (4)	Defined objectively based on testing of retained patient material (N=(b) (4) and healthy donor runs (N=(b) (4) performed to validate the Nucleus facility. A (b) (4) confidence/ (b) (4) tolerance interval was used to establish the specification. Importantly, the (b) (4) interval determined a range of (b) (4). The lower range was increased by Autolus to (b) (4) based on analytical procedure capabilities and clinical experience.
Sterility by (b) (4)	No growth	Defined objectively by Autolus to ensure DP is free from microbial contamination
Endotoxin Detection by (b) (4)	(b) (4)	Defined mathematically based on worst-case product characteristics and thresholds for endotoxin exposure. Specifically, this threshold was chosen such that a (b) (4).
Mycoplasma Detection by (b) (4)	Negative	Defined objectively by Autolus to ensure DP is free from mycoplasma contamination
RCL Detection by (b) (4)	(b) (4)	Defined objectively by Autolus to ensure DP is free from RCL.

Analytical Procedure	Acceptance Criteria	Justification (A)
<p>A. Multiple statistical methods were used based on the distribution of data. For example, a mean \pm n SD was used for viability given that there was a significant amount of viability data, and the data could be normalized with a log transform. In contrast, a tolerance interval was used for the potency data, given that they had a smaller amount of data, and given that the tolerance interval computed an acceptable specification that fit the data distribution.</p> <p>B. The acceptance criterion for CAR expression was computed based on a mean (b) (4) range despite the data not being normally distributed. Importantly, the application of a logit transformation did not result in normally distributed data, so data from non-transformed data were evaluated.</p> <p>C. These acceptance criteria were altered during the review period. The updated acceptance criteria were agreed to by Autolus in SN-0054 submitted 21-Aug-2024.</p> <p>D. These assays utilize an obe-cel positive control sample as an internal system suitability criterion. Composition and manufacture of the obe-cel positive control is described in 3.2.P.6 Reference Standards or Materials</p>		

Justification of Target Dose Variance

In addition to providing justifications for the specifications proposed for the obe-cel DP, Autolus has also provided a justification for the proposed obe-cel dose range. Specifically, Autolus has applied an acceptable range of (b) (4) around the intended dose of 410E6 total cells (resulting in a total acceptable range of (b) (4)). This dose range was calculated by propagating the uncertainty (i.e., intermediate precision) in the dose determining assays (i.e., CAR expression and viable cell concentration) as well as the uncertainty in fill volume, as determined in a series of dedicated filling accuracy studies outlined in Module 3.2.P.2 of the OS BLA.

Importantly, the proposed commercial dose range of (b) (4) matches the dosing range used during Phase 1 and Phase 2 clinical studies to establish obe-cel safety and efficacy and is within the range of dosing experience obtained during the clinical study.

Reviewer Assessment for Modules 3.2.P.5.1 and 3.2.P.5.6: The specifications in place for obe-cel are adequate and appropriately ensure drug product quality.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Reviewer Comment – Analytical procedures and associated method validations for CAR DP lot release tests shown in Table 78 are described in dedicated subsections below. However, a number of release tests were reviewed by DBSQC. For a detailed description of release assays not described below, please refer to the DBSQC review memo for this BLA. Importantly, all DBSQC-reviewed assays and associated validations were determined to be acceptable. Multiple assays were either updated close to completion of the registrational study or were updated following completion of the registrational study. Analytical bridging data are provided to support consistency between the clinical and commercial assays.

CD19 CAR Expression (Identity)

Analytical Procedure

Obe-cel identity is established via detection of the CD19 CAR by (b) (4). Commercial release of obe-cel will use the same (b) (4) assay to

23 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

Reviewer's Overall Summary of Module 3.2.P.5.4 – The batch analysis information provided acceptably demonstrates that Autolus can consistently generate obe-cel with the intended critical quality attributes.

3.2.P.5.5 Characterization of Impurities

This section written by JC

Process and product related impurities are reviewed in Section 3.2.S.3.2. because the manufacturing process from DS to DP is continuous.

3.2.P.6 Reference Standards or Materials

This section reviewed by JC

No reference standard is used for obe-cel to compute reportable values for release assays. However, Autolus uses a positive control (PC) manufactured from healthy donor material as part of system suitability criteria for a number of assays (see **Table 78**).

Autolus justifies the use of healthy donor material given that patient apheresis material is highly variable and is more complex to reliably obtain.

The same manufacturing process steps were used to produce obe-cel PC lots starting from FELIX Study Phase Ib through the preparation of commercialization (Process (b) (4)). and future PC lots will be manufactured according to the obe-cel manufacturing process described in Section 3.2.S.2.2 [CD19 CAR-positive T cells].

***Reviewer Comment:** In response to CMCIR6 received July 19, 2024, Autolus provided details about the manufacturing process used to produce Obe-cel positive control (PC). Autolus also provided a comparison of the manufacturing process for obe-cel PC used in the FELIX studies and clinical/commercial lots; this information indicates minimal differences. This is acceptable.*

PC lots are (b) (4) filled to (b) (4). The same analytical procedures were used to characterize obe-cel PC lots used in the FELIX Phase Ib and II studies, except for (b) (4) which was performed according to the method described in Section 3.2.S.2.6.4 [CD19 CAR-positive T cells] Table 87. The methods were updated to the commercial method and comparability studies are provided in Section 3.2.S.2.6.4 [CD19 CAR-positive T cells].

(b) (4)

(b) (4)

Reviewer Comment: Overall, the characterization data indicate that obe-cel PC lots used in the FELIX Phase I and II studies through preparation for commercialization are similar in quality.

Autolus has performed stability studies with (b) (4) obe-cel PC lots stored at $\leq -150^{\circ}\text{C}$ for (b) (4), evaluating Cell Viability, CAR Expression, and Cell Phenotype pre-cryopreservation and (b) (4) post-cryopreservation. AC were set based on the specifications at the time.

Reviewer Comment: Stability data for (b) (4) obe-cel PC lots stored at $\leq -150^{\circ}\text{C}$ was reported. %Cell viability decreased about (b) (4) (ranging from (b) (4) from T=0 months (pre-cryopreservation) to (b) (4) post-cryopreservation. Other product attributes (%CAR Expression, (b) (4) remained similar over time (t=0 months versus t=(b) (4) months). This data indicates obe-cel PC lots were stable up to (b) (4) months at $\leq -150^{\circ}\text{C}$.

Stability of obe-cel PC at (b) (4) (after removal from -150°C storage) was evaluated over 28 days to support QC lab operations. For these short-term studies, CD19 CAR Expression and Cell Phenotype was assessed at 7, 14, 28 days alongside the same PC lot that has been stored at $\leq -150^{\circ}\text{C}$. AC were based on the mean (b) (4) of PC stored at $\leq -150^{\circ}\text{C}$ at each timepoint, with the mean of the PC stored at (b) (4) compared to these AC.

Reviewer Comment: Data for obe-cel PC lots stored at (b) (4) indicates similar quality from Day 7 to Day 28, supporting stability of obe-cel PC lots for up to 28 days at (b) (4).

According to Autolus, future obe-cel PC will be manufactured according to the process described in Section 6.1.1 and released according to the proposed specification for obe-cel (Section 3.2.P.5.1) and trends will be monitored. Autolus states that obe-cel lots used in purity and potency analytical methods will be tested in replicates. Autolus commits to placing future obe-cel PC lots manufacturing by the commercial process on stability to establish a (b) (4) shelf life. Stability specifications will be the same as commercial specifications.

Reviewer Comment: Autolus intends to report obe-cel PC lot testing on lot-specific certificate of testing. The stability protocol includes sample size, test intervals including a zero-time point, storage conditions, specifications that evaluate purity/identity, potency, sterility. This is acceptable.

Standards are used for analytical methods and acquired from external vendors **Table 88**.

Table 88 – Analytical Standards and Controls “copied from submission”

Analytical Procedure	Standard or Control	Supplier	Qualification
Endotoxin Detection by (b) (4) Section 3.2.P.5.2.12	Control Standard Endotoxin (CSE)	(b) (4)	No internal qualification performed. CSE prepared as per CoA provided by supplier
Mycoplasma Detection by (b) (4) Section 3.2.P.5.2.13	Positive Control	(b) (4)	CoAs provided by supplier
	Internal Control		

Analytical Procedure	Standard or Control	Supplier	Qualification
Replication Competent Lentivirus Detection by (b) (4) Section 3.2.P.5.2.14	(b) (4)	Autolus – in-house	Each lot is qualified by Autolus QC. (b) (4) lot to be qualified. The analytical procedure is executed as per Section 3.2.P.5.2.14 . Qualification is deemed successful based on the system suitability and samples acceptance criteria being met.
Appearance by Visual Inspection for Color Section 3.2.P.5.2.01	Color EP Standards	(b) (4)	No internal qualification performed. Material released as per CoA provided by supplier.
Appearance by Visual Inspection for Clarity Section 3.2.P.5.2.02	Primary Opalescent Suspension	(b) (4)	No internal qualification performed. Material released as per CoA provided by supplier.

Reviewer Comment: No concerns are identified with the standards proposed.

3.2.P.7 Container Closure System (CCS)

This section reviewed by TK

The primary packaging for obe-cel is (b) (4) and/or (b) (4) Freezing Bags as shown in **Figure 43**. (b) (4) Freezing Bags are 510(k) cleared devices ((b) (4) manufactured by (b) (4). Each freezing bag is supplied with an overwrap bag. The freezing/overwrap bags are sterilized using (b) (4) by the supplier. All bag components are made of (b) (4) tubular film. The specifications for CCS are provided in **Table 89**.

(b) (4)

(b) (4)

Filled bags are placed into a secondary CCS which consists of an aluminum cassette from (b) (4) to hold one primary CCS. When (b) (4) bag is used, a U-shaped felt insert made of matted fabric (b) (4) is inserted into the secondary container closure to prevent primary CCS from movement inside the secondary CCS. Specifications for CCS are shown in **Table 90**.

(b) (4)

(b) (4)

The tertiary packaging is (b) (4) which consists of a (b) (4) material) sleeve with separate four compartmental inserts for each secondary CCS. The (b) (4) was validated by third-party laboratory using (b) (4) tests in the (b) (4) shipper according to (b) (4) and 49 CFR 173.199. (b) (4) specifications are shown in **Table 91**. The (b) (4) is placed into an (b) (4) Smart Shipper pre-charged with LN2 for transportation of obe-cel to clinical sites. The shipper has an (b) (4) which absorbs LN2 after charging creating a dry payload atmosphere. (b) (4) cryoshipper lid is equipped with temperature monitor, GPS, and communication electronics.

Table 91 – Specifications for Drug Product Tertiary packaging.

Test	Acceptance criteria
Supplier Testing	
(b) (4)	Satisfies
(b) (4)	Satisfies
Incoming Material Testing	
Visual inspection	Practically free of visible particles, tears and structural issues

Reviewer comment: For information related to Container Closure Integrity (CCIT) assessment, please refer to DMPQ memo, For additional information related to CCS, see Section 3.2.P.2.6 Compatibility and Drug Product Shipping Qualification in Section 3.2.P.3.5 Process Validation and/or Evaluation.

Reviewer's Overall Summary of Module 3.2.P.7 – Obe-cel container closure system is acceptable for commercial manufacturing and distribution.

3.2.P.8 Stability

This section reviewed by JC

Obe-cel has a shelf life of 6 months when stored at $\leq -150^{\circ}\text{C}$ in the commercial container closure (b) (4) bags).

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

Obe-cel DP is cryopreserved, stored, and transported at $\leq -150^{\circ}\text{C}$ (vapor phase, liquid nitrogen) from the manufacturing site to the administration site where the DP is thawed for infusion. The lots used to generate the stability data included those manufactured with the proposed commercial process and tested with the proposed commercial analytical procedures (unless stated otherwise) with acceptance criteria valid at time of testing. Color and clarity were evaluated for characterization only because of a lack of data. Autolus provided 6 stability studies to support a proposed 6-month shelf-life **Table 92**. Ongoing stability studies for obe-cel include (b) (4) Confirmatory runs, (b) (4) Registrational runs, and (b) (4) Technology Transfer runs **Table 93**; these studies cover the proposed bag configurations needed to meet dose.

1 page determined to be not releasable: (b)(4)

(b) (4)

Reviewer Comment: Of the 6 stability studies, the 3 on-going studies (confirmatory, registrational, technology transfer/supportive) compose the registrational data while the other 3 studies are supportive. The 3 on-going stability studies provide sufficient data to cover the proposed shelf-life of 6 months and cover the bag configurations needed to meet dose for the commercial process. Data in the 3 on-going studies also includes paired data which is not available in some of the other supportive studies. Hence it is acceptable to focus on the 3 on-going stability studies to determine if the stability data provided support a 6-month shelf-life with the specifications proposed. Data for supportive studies 2,3,4 are summarized below, and the 3 on-going studies are reviewed after that.

Supportive Stability Studies 2,3,4

Supportive Stability 2 study used a single healthy donor lot (lot (b) (4)) described in **Table 92** and 6 months of results is reported in **Table 94**

Table 94 – Supportive Stability 2: Data for Long-Term Storage at $\leq -150^{\circ}\text{C}$ Lot (b) (4)

Analytical Procedure	Acceptance Criteria	Container Closure ^a	Time Points (Months)			
			0	1	3	6
(b) (4)						

^a(b) (4) with 20 mL fill
NT: Not Tested

- (b) (4)

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

Autolus makes no post-approval commitment for drug product stability. Rather Autolus will use the stability data generated to date with cryopreservation storage conditions for long-term stability. Autolus states they commit to completing the ongoing long-term stability studies (Registrational, Confirmatory, Technology Transfer).

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

A pre-license inspection (PLI) of the Nucleus manufacturing facility, located at Marshgate, Stevenage was conducted by CBER/DMPQ and CBER/OGT inspectors between 22-Apr-2024 and 30-Apr-2024 to support approval of BLA-125813. A form FDA 483 was issued at the end of the inspection, which annotated three 483 observations. The firm adequately responded to the observations noted. All inspectional issues were resolved, and the inspection was classified as voluntary action indicated. Details are provided in the Establishment Inspection Report (EIR).

The lentiviral vector manufacturing facility (b) (4) was not inspected as part of the review of BLA-125813. This facility was recently inspected for another BLA (b) (4), so the inspection requirement for BLA-125813 was waived.

3.2.A.2 Adventitious Agents Safety Evaluation

Autolus employs complimentary control strategies to minimize the risk of introducing adventitious agents and microbial contamination into the manufacturing stream. Adventitious agents and microbial contamination are controlled by dedicated testing of biological precursor materials (i.e., (b) (4) MCBs used in (b) (4) manufacture, incoming leukapheresis material), testing and source control of raw materials, and comprehensive release testing of obe-cel. For details on the quality control

strategy for biological precursor materials and source control of raw materials, please see **Control of Materials – Leukapheresis Starting Material** and **Control of Raw Materials of Biological Origin**, respectively.

In addition to the control of materials, Autolus employs several manufacturing controls to mitigate the risk of introducing adventitious agents and microbial contamination during the manufacturing process. Specifically, obe-cel is manufactured in a GMP-compliant facility, within a grade (b) (4) environment. Further, the manufacturing process of obe-cel is completed in a fully closed system using semi-automated equipment (i.e., the (b) (4)).

At the conclusion of manufacture, Autolus aseptically fills infusion bags for patient use, and (b) (4) for quality control testing purposes. Autolus performs a comprehensive evaluation of microbial contamination as part of the obe-cel lot release process. This involves the testing of obe-cel with (b) (4) (or (b) (4) -equivalent) sterility, endotoxin, and mycoplasma assays.

Reviewer comment: The adventitious agent safety evaluation performed by Autolus is acceptable. Descriptions of the control strategy are integrated into 3.2.S.2.3 Control of Materials and 3.2.S.4 Control of Drug Substance. The adventitious agent testing and control strategy for obe-cel is acceptable for commercial manufacture.

Viral Clearance Studies

Viral clearance studies were not performed on the (b) (4) LVV or the obe-cel DP.

3.2.A.3 Novel Excipients

Not applicable, no novel excipients are used in the terminal formulation of the obe-cel DP

3.2.R Regional Information (USA)

Executed Batch Records

Autolus has provided unexecuted master batch records (MBRs) for both the (b) (4) lentiviral vector and the obe-cel CAR T product. Additionally, Autolus has provided executed MBRs for all process performance qualification (PPQ) runs performed in support of the BLA, including the lentiviral vector and obe-cel CAR T product.

Reviewer Comment – These MBRs were reviewed as part of BLA review, as well as part of the pre-licensing inspection (PLI) performed on the Nucleus manufacturing facility. No concerns were identified.

Method Validation Packages

Autolus has provided method validation reports for the quality control assays performed for the release of the (b) (4) LVV and obe-cel DP. These quality control assay methods and associated validations are described in **3.2.P.5 Control of Drug Product**.

Combination Products

Not applicable. Obe-cel is not regulated as a combination product.

Comparability Protocols

Not applicable. No comparability protocol is provided

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

The applicant is claiming a categorical exemption from the requirement to prepare an environmental assessment per 21 CFR 25.31(e). Obe-cel consists of human cells that have been genetically modified with a lentiviral vector to express a chimeric human protein. Importantly, the manufacturing of obe-cel involves the use of (b) (4), which minimize the amount of residual infectious lentiviral vector present within the final drug product. Further, the cells constituting obe-cel cannot survive outside the human body and rapidly decay into naturally occurring biological substances.

Reviewer Comment – Autolus has provided adequate justification to support waiving the requirement to prepare an environmental assessment.

B. Reference Product Designation Request

Autolus has requested a 12-year exclusivity period for the licensure of obe-cel. Based on an anticipated date of licensure of 17-Nov-2024, the exclusivity period will extend to 17-Nov-2036.

C. Labeling Review

Full Prescribing Information (PI):

During the BLA review period the PI was reviewed in part by the CMC team. Specifically, CMC reviewed Section 2 (Dose and Administration), Section 3 (Dosage forms and Strengths), Section 11 (Description), and Section 16 (How Supplied/Storage and Handling). The PI provided a sufficiently detailed description of obe-cel design, its mechanism of action, and the infusion procedures.

Carton and Container Label:

Obe-cel will be administered via a split dose, meaning that each patient-specific treatment course will contain several infusion bags. Infusion bags and associated cassettes will be affixed with product-specific labels and patient-specific labels. Bags will be shipped to infusion sites within metal cassettes, packaged within a tertiary packaging unit (i.e., a (b) (4)). Up to four infusion bags are packaged within a (b) (4). Representative labels are shown below, and all labels contain the required text.

Figure 60 – AUCATZYL Patient-specific label

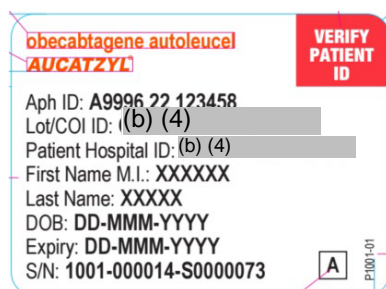


Figure 61 – AUCATZYL Product-specific label (Bag Configuration A)



Figure 62 – AUCATZYL Product-specific label (Bag Configuration B)

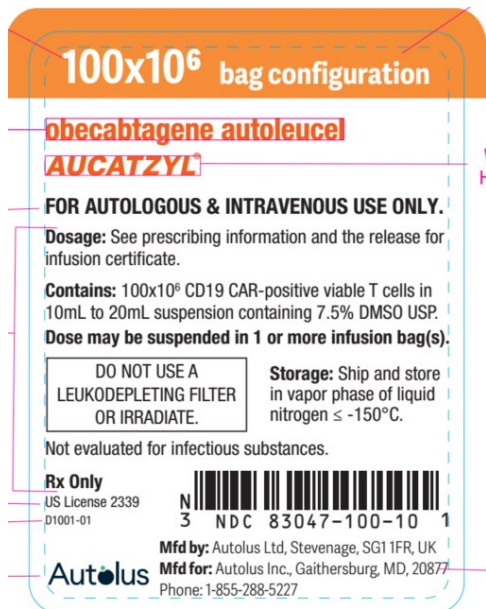


Figure 63 – AUCATZYL Product-specific label (Bag Configuration C)

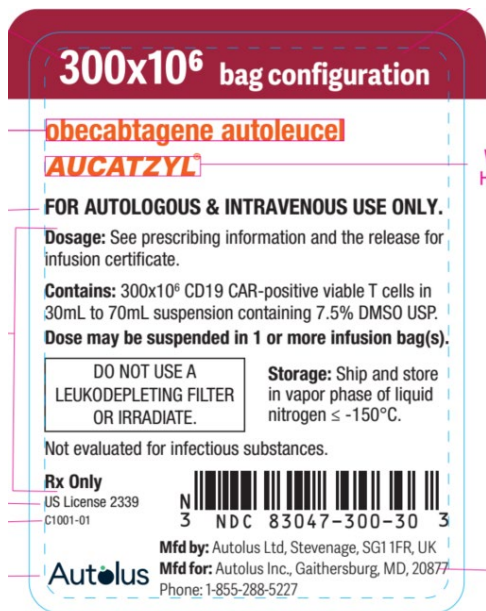
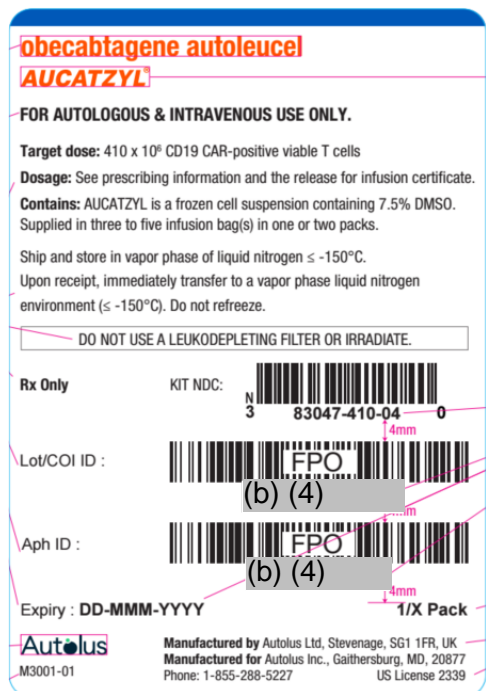


Figure 64 – AUCATZYL (b) (4) label



Modules 4 and 5

A total of (b) (4) analytical methods were performed to support the clinical efficacy and safety of obe-cel during the FELIX phase II study. These analytical methods are tabulated in Table 103, and are summarized in dedicated subsections.

