CBER CMC BLA Review Memorandum

BLA STN 125738

Omisirge
(Omidubicel-olnv)

Reviewer/Title/Affiliation
Elizabeth Lessey-Morillon, Ph.D. | Biologist | CBER/OTP/OCTHT/DCT1/CTB1
Sukhanya Jayachandra, Ph.D. | Biologist | CBER/OTP/OCTHT/DCT1/CTB1
Archana Siddam, PhD | Biologist | CBER/OTP/OCTHT/DCT1/CTB1
Heba Degheidy, MD, PhD | Biologist | CBER/OTP/OCTHT/DCT1/CTTB

1. BLA#: STN 125738

2. APPPLICANT NAME AND LICENSE NUMBER
Gamida Cell Ltd., License # 2223

3. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Description:	*CF*: Allogeneic human umbilical cord blood derived hematopoietic CD34+ progenitor cells, ex-vivo expanded in the presence of nicotinamide and cytokines *NF*: Allogeneic human umbilical cord blood derived hematopoietic mature myeloid and lymphoid cells *IS*: diluent of 8% w/v HSA and 6.8% w/v Dextran.
Dosage Form:	Cell Suspension for Infusion
Strength/Potency:	*CF*: a minimum of 8.0 x 10^8 total number viable cells with a minimum of 8.7% CD34+ cells and a minimum of 9.2 x 10^7 CD34+ cells in 20 ml of cryopreservation solution containing 10% DMSO *NF*: a minimum of 4.0 x 10^8 total number viable cells and 2.4 x 10^7 CD3+ cells 10 mL of cryopreservation solution containing 10% DMSO
Route of Administration:	Intravenous Infusion
Indication:	(b) (4)

4. PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/Proper/USAN:	Omidubicel- onlv
Proprietary Name:	OMISIRGE (Formerly (b) (4) NiCord)
Company Code:	Cultured Fraction, CF Non-Cultured Fraction, NF Infusion Solution, IS
UNII Code:	Omidubicel-onlv, CF: ET4JC4S66E Omidubicel-onlv, NF: MAH7ZHD7ZJ
WHO Number:	11164
NDC Codes:	Omidubicel-onlv: 73441-100-01 Omidubicel-onlv, CF: 73441-200-01 Omidubicel-onlv, NF: 73441-200-01 Omidubicel-onlv, IS for CF: 73441-300-01 Omidubicel-onlv, IS for NF: 73441-400-01 Chimerism Testing Sample (CBU segment): (b) (4) Chimerism Testing Sample (NF sample): (b) (4)

5. MAJOR MILESTONES

Initial Non-Clinical Module Received	February 8, 2022
Module Clinical Received	March 4, 2022
Final Module (CMC and Labeling) Received	June 1, 2022
DSCSA Exemption Request	June 8, 2022
Proprietary Name Review Request	June 9, 2022
First Committee Meeting	June 22, 2022
Filing Meeting	July 13, 2022
Mid-Cycle Meeting	October 4, 2022
Major Amendment Determination	November 18, 2022
Late-Cycle Meeting	February 23, 2023
Target Date	April 17, 2023
PDUFA Action Date	May 1, 3022

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Elizabeth Lessey-Morillon, PhD BLA Chair/CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB1	Environmental Analysis, Labeling *Drug Substance [CF] and Drug Substance [NF]:* General information, Manufacture, Control of Drug Substance, Reference Standards or Materials *Drug Product [CF], Drug Product [NF] and Drug Product [IS]:* Description and Composition of the Drug Product, Pharmaceutical development, Manufacture, Control of Excipients, Control of Drug Product, Reference Standards or Materials Adventitious Agents Safety Evaluation Regional information
Archana Siddam, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB1	*Drug Product [CF], Drug Product [NF] and Drug Product [IS]:* Stability
Sukhanya Jayachandra, PhD CMC Reviewer CBER/OTP/OCTHT/ DCT1/CTB1	*Drug Substance [CF]:* Control of Materials
Heba Degheidy, MD, PhD CMC Reviewer CBER/OTP/OCTHT/ DCT1/CTTB	*Drug Substance [CF], Drug Substance [CF] and Drug Substance [NF]:* Analytical Procedures, Validation of Analytical Procedures
Wen Jun (Aaron) Seeto, PhD Consult reviewer CBER/OTP/OCTHT/DCT2/TEB2	Consult review of Container Closure System.
Andrey Sarafanov, PhD Consult reviewer CBER/OTP/OPPT/DH/HB2	Consult review of Toxicology Risk Assessment for the Container Closure
Jennifer Reed, PhD Consult reviewer CBER/OTP/OPPT/DPD/PDB2	Consult review of Toxicology Risk Assessment for the Container Closure

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
Rachel Lokanga (CDER/OPQ/OBP/DBRR3) Ian McWilliams (CDER/OPQ/OBP/DBRR3)	ICCR 00893424 - MF (b) (4)	Yes

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
8Feb2022	STN 125738 /0.1	Preclinical Module
28Feb2022	STN 125738 /0.2	Clinical Module
1Jun2022	STN 125738 /0.3	Quality Module and completed submission of rolling BLA
25Jul2022	STN 125738 /0.13	Response to CMC IR#1 dated 18Jul2022
2Sep2022	STN 125738 /0.20	CMC Late Minor Components
8Sep2022	STN 125738 /0.22	Response to CMC IR #2 dated 26Aug2022
22Sep2022	STN 125738 /0.25	Request for Proprietary name Review
26Sep2022	STN 125738 /0.26	Response To CMC IR #3, dated 14Sep2022
26Sep2022	STN 125738 /0.27	120-day Safety update report
12Oct2022	STN 125738 /0.31	Request for reconsideration of non-proprietary name
13Oct2022	STN 125738 /0.32	Response to CMC IR #4, dated 7Oct2022
3Nov2022	STN 125738 /0.33	Response to DHT IR #2, dated 28Oct2022
8Nov2022	STN 125738 /0.35	Response to CMC IR #3, DMPQ IR #3, and CMC IR #4, dated 14Sept2022, 22Sept 2022 and 7Oct2022 respectively
10Nov2022	STN 125738 /0.36	Response to CMC IR #5, dated 8Nov2022
15Nov2022	STN 125738 /0.37	Response to CMC IR #6, dated 9Nov2022
15Nov2022	STN 125738 /0.38	Major Amendment
17Nov2022	STN 125738/0.39	Suffixes for Non-Proprietary Name
30Nov2022	STN 125738/0.40	Response to teleconference dated 21Sept2022 and CMC IR #4 7Oct2022
8Dec2022	STN 125738/0.41	Response to CMC IR #7, dated 01Dec2022
12Dec2022	STN 125738/0.43	Response to DHT IR #4, dated 021Dec2022
10Jan2023	STN 125738/0.46	Response to CMC IR, dated 27Dec2022
20Jan2023	STN 125738/0.47	Response to CMC IR #8, dated 17Jan2023
30Jan2023	STN 125738/0.48	Response to CMC IR #9, dated 25Jan2023
21Feb2023	STN 125738/0.53	Response to CMC IR #10, dated 16Feb2023
8Mar2023	STN125738/.055	Response to CMC PMCs IR #1, dated 22Feb2023
16Mar2023	STN125738/.057	Response to CMC PMCs IR #1, dated 8Mar2023
23Mar2023	STN125738/.060	Finalized CMC PMC Agreement

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
BB MF (b) (4)	(b) (4)	(b) (4) Reagent	Letter dated 20Oct 202020 authorize for chemistry, manufacturing, control of (b) (4) reagent.	Information pertinent to (b) (4) selection process was reviewed, assessed, and documented in the memo by Sukhanya Jayachandra in *section 3.2.S.2.3 Control of Materials* [CF]
BB-MF (b) (4)		(b) (4)	Letter dated 4Nov2020 authorize reference to any and all information in the Master file	Information pertinent to cryopreservation media, assessed and documented in the memo by Sukhanya Jayachandra in *section 3.2.S.2.3 Control of Materials* [CF]

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Gamida Cell Ltd. (GC) submitted the biologics license application (BLA) 125738 to market omidubicel-onlv (OMISIRGE), an ex vivo expanded allogeneic human hematopoietic CD34+ progenitor cell therapy for the treatment of patients with hematologic malignancies in need of a hematopoietic stem cell transplant. Omidubicel contains two fractions from a single cord blood unit (CBU): (1) ex vivo cultured fraction (CF) of CD34+ cells that will engraft, and (2) a supportive non-cultured fraction (NF) of the non-selected CBU cells that is administered directly after the CF to support engraftment and improve clinical outcomes. The CF and NF drug products (DP) are individually cryopreserved in 10% DMSO until thawed for infusion. Each DP is diluted (b) (4) with Infusion solution (IS), of human serum albumin (HSA) and dextran, just before infusion by a closed port system. Each CF DP and NF DP has a corresponding IS DP bag for a total of two IS DP bags.

Omidubicel is manufactured from a cryopreserved CBU in a Class (b) (4) biological safety cabinet (BSC) within a Class (b) (4) qualified room. The CBU is thawed and the cells undergo (b) (4) reagent using the (b) (4) instrument. The (b) (4) selected cells are then cultured at approximately (b) (4) (b) (4) in (b) (4) containing (b) (4) with (b) (4) (b) (4) Cell culturing with NAM allows the (b) (4) CD34+ cells to proliferate while retaining a progenitor phenotype for engraftment. Fresh culture (b) (4) the volume. After (b) (4) , the cultured cells are a mix of CD34+/(b) (4) progenitor cells as well as other immature (b) (4) progenitor cells. The other cells present are myeloid cell subsets at various stages of maturation, such as (b) (4) The cells are collected and washed using the (b) (4) The (b) (4) CF (b) (4) is (b) (4) of cryopreservation solution containing (b) (4) filtered across a (b) (4) filter directly into the attached cryopreservation bag to become the CF DP. The final CF DP contains at least 8.0 x 10^8 total number viable cells (TNVC) with a minimum of 9.2 x 10^7 CD34+ cells and a

minimum of 8.7% CD34+ cells. The CF DP is cryopreserved in a control rate freezer before being transferred to (b) (4) for storage at ≤-150°C.

The NF (b) (4) is manufactured from cells eluted during the CF (b) (4) selection. The NF (b) (4) is washed and the (b) (4) NF (b) (4) is (b) (4) of cryopreservation solution containing (b) (4) filtered across a (b) (4) filter directly into the attached cryopreservation bag to become the NF DP. The NF DP is cryopreserved in a control rate freezer before being transferred to (b) (4) for storage at ≤-150°C while the (b) (4) CF (b) (4) manufacturing is completed. The final NF DP contains at least 4.0 x 10^8 TNVC and 2.4 x 10^7 CD3+ cells.

After completion of manufacturing, the cryopreserved Omidubicel is released for shipping to the transplant center based on meeting the available in-process control testing. The NF DP and CF DP are shipped in a liquid nitrogen dry vapor shipper concurrently with the refrigerated shipping container containing the two IS bags. Omidubicel is shipped to be available for infusion as quickly as possible once the product is released for infusion. There is a serious risk for the patient if the treatment is delayed, therefore product may be released for infusion while the final sterility (b) (4) (b) (4) and (b) (4) results are pending because these tests take two to three weeks to obtain the results. Instead, CF DP is released for infusion after the rapid contamination culture and (b) (4) results are obtained. Then, the final CF DP release occurs after all release testing results are obtained. The Applicant's deviation reporting procedure outlines the action plan for any infused batches that fail final sterility or potency release testing and is appropriate. Release test methodology has been validated and release specifications reviewed and determined to be acceptable to ensure quality.

The CF DP is thawed at bedside and diluted (b) (4) with the corresponding IS DP bag via a closed port system. Then the NF DP is thawed, diluted (b) (4) with IS DP and administered within an hour of administration of the CF DP.

The commercial omidubicel product is to be manufactured at the GC Kiryat Gat (KGI) manufacturing facility. KGI is a (b) (4) facility and started manufacturing clinical batches of omidubicel in (b) (4) (b) (4) omidubicel was manufactured at (b) (4) and (b) (4) Jerusalem, Israel (b) (4).The firm was inspected on (b) (4) to (b) (4) No observations were identified during the prelicensure inspection (PLI).

The real time stability data from full scale batches supports storage of the CF at ≤-150°C for up to 12 weeks, the NF DP at ≤-150°C for up to15 weeks, and the IS DP at 2-8°C for five months. The NF and CF have a shelf-life of up to (b) (4) hours at room temperature after thawing and dilution with the IS DP. The extended storage of the CF DP and NF DP is intended to accommodate instances where administration of omidubicel is delayed based on the patient's medical condition. The product is stored in 510(k)-cleared cryopreservation bags for freezing cells. The bags are evaluated and tested, including for extractables and leachables, for both the cryopreservation and

storage of the CF DP and NF DP ≤-150°C and the IS DP at 2-8°C. The assessment of elemental extractables from all high-risk materials did not directly evaluate the cumulative elemental leachables. Therefore, we require the assessment of elemental leachables in a real process study or relevant simulated study as a PMC.

Omidubicel is manufactured in a mostly closed process system with appropriate controls to maintain product quality and safety. The raw materials, product contacting materials and reagent qualification programs are acceptable. Raw materials derived from animals and humans are controlled to ensure the absence of microbial contaminants and adventitious agents. The manufacturing process has been adequately validated. The Chain of Identity/Chain of Custody (COI/COC) is appropriate for a patient specific product and starts with the identification of the CBU and is maintained through the manufacturing and shipping process, until administration at the transplant center using product specific identifiers.

On November 15, 2022 (STN 125738/0.36), the Applicant provided a substantial amount of new clinical study data required for the FDA to independently adjudicate the primary endpoint, evaluate key secondary endpoints, and conduct a comprehensive review of the safety of the clinical data. Therefore, the Amendment was determined to be a major Amendment and the review timeline revised accordingly.

The following major CMC concerns were raised during the review of this submission and were resolved through information requests:

1. Insufficient donor eligibility documentation.
2. Insufficient information on the non-licensed CBU source material.
3. Change in number of cell culture bags processed during a single (b) (4) (b) (4) to reduce residual cell culture impurities in the CF DP.
4. Higher than anticipated residual (b) (4) impurities in the KGI PPQ batches.
5. Lack of identity and purity methodology information and incomplete identity and purity analytical methods validation assay.
6. Misleading proprietary name and non-proprietary name that initially did not includes both the CF DP and NF DPs.

The following CMC concerns were raised during review of this submission that require a post-marketing commitment (PMC):

1. A residual (b) (4) impurities study with the Omidubicel drug product to provide assurance that residual (b) (4) levels remain within the established manufacturing range of less than (b) (4) per batch.
2. An elemental leachables study to assess the elemental leachables in a real process study, or relevant simulated study, over its manufacturing and storage.
3. Agreement from the Applicant to notify the FDA when the MF (b) (4) (b) (4) Reagent) issues are adequately resolved.

The CMC review team recommends approval, with PMCs.

B. RECOMMENDATION

I. APPROVAL

Manufacturing facilities

The following manufacturing and testing facilities are used for manufacturing the CF DS and DP, NF DS and DP, and IS DP:

- GC Kiryat Gat Israel (KGI), (b) (4) Kiryat Gat, Israel

(b) (4)

Post-Marketing Commitments (PMCs)

1. Gamida Cell Ltd. commits to perform a residual (b) (4) impurities study on the omidubicel-onlv drug product to provide assurance that residual levels remain under the established limit of less than (b) (4) per batch, as informed by previous manufacturing experience. The study will include at least (b) (4) full scale batches, manufactured over the course of a year, that are representative of the commercial omidubicel-onlv drug product and include at least three batches for each number of (b) (4) used in manufacturing (i.e., (b) (4) (b) (4) Gamida Cell Ltd. also commits to submitting the (b) (4) impurities study protocol in a product correspondence supplement by June 30, 2023. Gamida Cell Ltd. will submit the final study report as a Postmarketing Commitment – Final Study Report by June 30, 2024.

   Final Study Report Submission: June 30, 2024

2. Gamida Cell Ltd. commits to execute a real process elemental leachables study of the final container closures for omidubicel-onlv to include the cultured fraction, non-cultured fraction, and infusion solution drug products over their manufacturing and storage periods. Given the complexity of the biological product, (b) (4) as Gamida Cell Ltd. performed for the assessment of organic leachables. Gamida Cell Ltd. will submit the final study report as a Postmarketing Commitment – Final Study Report by January 31, 2024.

   Final Study Report Submission: January 31, 2024

3. Gamida Cell Ltd. commits to notify the FDA when the master file (MF) (b) (4) holder has adequately resolved concerns with the MF. The notification will include a copy of a letter from the MF holder stating that they have received

notification from the FDA that MF (b) (4) concerns have been adequately resolved. Gamida Cell Ltd. will submit this information as a Postmarketing Commitment – Status Update by February 29, 2024.

Postmarketing Commitment - Status Update: February 29, 2024

CBER Lot release
Omidubicel is exempt from lot release.

II. COMPLETE RESPONSE (CR)

Not applicable.

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Elizabeth Lessey-Morillon, PhD BLA Chair; CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB1	Concur	
Archana Siddam, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB1	Concur	
Sukhanya Jayachandra, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB1	Concur	
Heba Degheidy, MD, PhD CMC Reviewer CBER/OTP/OTP/OCTHT/DCT1/CTTB	Concur	
Melanie Eacho, PhD Branch Chief CBER/OTP/OCTHT/DCT1/CTB1	Concur	
Steven Oh, PhD Acting Division Director CBER/OTP/OCTHT/DCT1	Concur	

Review of CTD

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TABLE OF FIGURES

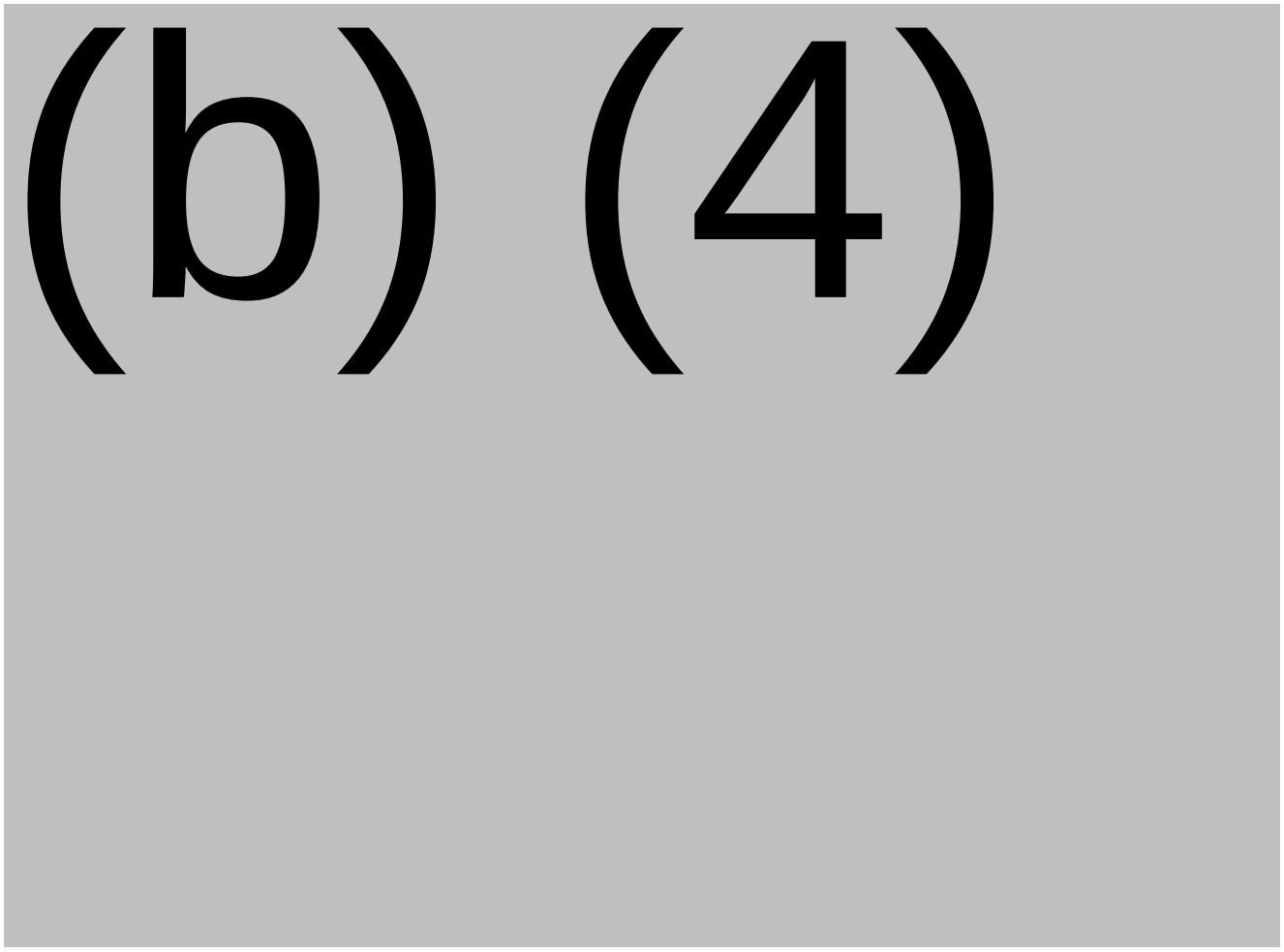
TABLES

Module 3

3.2.S DRUG SUBSTANCE [CULTURED FRACTION]

(b) (4)

60 pages have been determined to be not releasable: (b)(4)



3.2.P DRUG PRODUCT [CULTURED FRACTION]
3.2.P.1 Description and Composition of the Drug Product
This section is reviewed by EL.
Proprietary name: OMISIRGE-onlv, Cultured Fraction (CF)
Reviewer Comment: The Applicant's proposed proprietary name in the initial BLA submission, (b) (4) *is not acceptable. The name invokes* (b) (4) *stem cells. This is misleading for a "multipotent" cell product. On 7Sept2022, the Applicant was notified the proprietary name is unacceptable. In response, the Applicant submitted Omisirge for review in Amendment 24 on 22Sep2022. APLB accepted the name on December 12, 2022. There are no CMC objections to accepting the name Omisirge.*

Non-Proprietary name: Omidubicel-onlv
The CF DP is an allogeneic, ex vivo expanded, hematopoietic CD34+ progenitor cell product. CF DP contains at least $8.0x10^8$ TNVC with a minimum of 8.7% CD34+ cells and a minimum of $9.2x10^7$ CD34+ cells suspended in approximately 20 mL of cryopreservation solution, filtered through a (b) (4) filter during transfer into a cryopreservation bag. The product is formulated as a single dose cell suspension for infusion.

3.2.P.2.1 COMPONENTS OF THE DRUG PRODUCT

3.2.P.2.1.1 Drug Substance

CF is made of allogeneic, hematopoietic CD34+ progenitor cells that are ex vivo expanded in the presence of NAM and cytokines. The CF DP also contains a small (b) (4) population of myeloid cell subsets at various maturation stages and the less differentiated early progenitor (b) (4) cells. At the end of the (b) (4) culture, the cultured cells are suspended in cryopreservation solution, filtered into the cryopreservation bag, and stored at ≤150°C. (b) (4)

3.2.P.2.1.2 Excipients

(b) (4)

3.2.P.2 Pharmaceutical Development

This section is reviewed by EL.

3.2.P.2.2 DRUG PRODUCT

This section is reviewed by EL.

3.2.P.2.2.1 Formulation Development

(b) (4)

(b) (4)

3.2.P.2.2.2 Overages
This section is not applicable to the CF DP.

3.2.P.2.2.3 Physicochemical and Biological Properties
This section is reviewed by EL.
The biological properties of the CF DP are reviewed with CF DS in 3.2.S.3.1.4 Biological Activity of the CF cell suspension [CF] of this memo.

Overall Reviewer's Assessment of Section 3.2.P.2:
Information provided is acceptable, with no deficiencies identified.

3.2.P.2.3 MANUFACTURING PROCESS DEVELOPMENT
3.2.P.2.3.1 Overview

(b) (4)

5 pages have been determined to be not releasable: (b)(4)

(b) (4)

3.2.P.3 Manufacture

This section is reviewed by EL.

3.2.P.3.1 MANUFACTURER(S)

The CF DP is manufactured at GC KGI and testing conducted at KGI and (b) (4) (b) (4) as listed in Table 49.

Table 49. CF DP Manufacture and In-Process Testing Sites

Site Name	Address	FEI	Responsibility
GC Kiryat Gat Israel (KGI)	Leshem 12 8258412 Kiryat Gat, Israel	3017482905	Manufacturing, packaging and labeling Release and Stability testing (Appearance, Identity and Potency tests)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

3.2.P.3.2 BATCH FORMULA

The CF DP is formulated as a single dose cell suspension for intravenous infusion. It contains 1-2 mL of ≥9.2x10^7 CD34+ cells and ≥8.7% CD34+ cells with 20 mL of cryopreservation solution with 10% DMSO. The total volume is approximately (b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

Information provided is acceptable, with no deficiencies identified.

3.2.P.3.3 DESCRIPTION OF MANUFACTURING PROCESS

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

(b) (4)

- **3.2.P.3.3.5.2 Shipment**
  - The CF DP batches are shipped at temperatures ≤-150°C in liquid nitrogen dry vapor shippers
  - The liquid nitrogen dry vapor shipper containing the CF and NF bags is shipped concurrently with the refrigerated shipping container containing the two IS bags

- **3.2.P.3.3.5.3 Product Release and Infusion Procedure**

(b) (4)

13 pages have been determined to be not releasable: (b)(4)

3.2.P.3.5.6 Shipping Validation Studies

A shipping validation study was conducted by (b) (4) simulated shipments of omidubicel products (CF and NF) and IS to the TC. The NF and CF were shipped in liquid nitrogen dry vapor shipper with a refrigerated shipping container containing the two IS bags, the same as the commercial product. The shipment was from KGI to (b) (4) (b) (4) to represent maximum storage of size days and a worst-case route including supplementary wait times. Testing was conducted at KGI, on the shipped and reconstituted omidubicel CF and NF using the shipped IS. The NF DP shipping validation data are discussed in 3.2.P.3.5 Process Validation and/or Evaluation [NF] of this memo, and the IS shipping validation data are discussed in 3.2.P.3.5.5 Shipping Validation Studies [IS] of this memo.

The CF DP release acceptance criteria in the shipping study report was based on the product acceptance criteria at the time the study was completed. Since completion of the shipping study, the release acceptance criteria has tightened, as discussed in 3.2.P.5.6 Justification of Specifications of this memo. The data from the shipped product also meets the current acceptance criteria provided in Table 41.

Shipping Validation Study Results

The test parameters used are the same as the stability protocol reviewed in 3.2.P.8 Stability [CF] of this memo. The analytical test methods are the same as the release testing and are reviewed with CF DP in 3.2.P.5 Control of Drug Product[CF] of this memo. The temperature records demonstrate that all lots had a mean and maximum temperature below -150°C during shipping. A visual inspection confirmed all labels remained adhered. There were two deviations, one related in sealing overwrap and one related timing of appearance test. Both these deviations were reviewed and found to be acceptable

Table 61. Results for the CF Tests Prior Cryopreservation and Post-thaw

8 pages have been determined to be not releasable: (b)(4)

See 3.2.S.2.3 Control of Materials[CF] of this memo for additional review of the reagents including the COAs and vendor qualification program.
Information provided is acceptable, with no deficiencies identified.

3.2.P.5 Control of Drug Product
3.2.P.5.1 AND 3.2.P.5.6 SPECIFICATION(S) AND JUSTIFICATION OF SPECIFICATION(S)
This section is reviewed by EL.
3.2.P.5.1 Specifications
The release specifications for the CF DP are listed in Table 68. The Applicant's selection of attributes is reviewed in 3.2.S.2.2.6 and 3.2.S.2.2.7 In-Process Monitoring and In-Process Controls [CF] of this memo. The Applicant initially considered unmanipulated cord blood attributes to evaluate the CF DP. The CQAs and relevant specifications were refined and determined by experience from product development and clinical batches. TNVC, viable TNC, viability CD34+, and CFU parameters are commonly attributes for HSCTs and licensed minimally manipulated HPC, Cord Blood, release testing. The additional identity and potency parameters for the CF DP are total CD34+ cells, percent CD34+ cells, (b) (4) (b) (4) and CD34+ (b) (4) These measurements are designed to control for the CD34+ expansion process and ensure the CD34+ cells at the end of culture have expanded enough for successful HSCT.. Identity is also established by product traceability, as discussed in 3.2.P.3.3.7 Summary of the Traceability of the CF DS and CF DP [CF] of this memo.
Table 68. Quality Control Specifications for CF DP

Attribute	Analytical procedure	Sample	Final acceptance criteria	Testing facility
Appearance	(b) (4)	DP	Yellowish suspension, essentially free of visible white clumps and foreign particulates	(b) (4)
TNVC (Potency)	(b) (4)	QC sample	≥8.0x10^8	
% Viability of TNC (Potency)		QC sample	(b) (4)	
% CD34+ cells (Potency and Identity)		QC sample	≥8.7	
% Viability of CD34+ cells (Identity)		QC sample	(b) (4)	
No. of CD34+ cells (Potency and Identity)		QC sample	≥9.2x10^7	
(b) (4)		(b) (4)	(b) (4)	
Rapid contamination test		QC sample	Not detected	
Sterility[1]		QC sample	No growth	
Mycoplasma content		Cell culture medium	Not detected	
Endotoxin content (b) (4) (b) (4)		QC sample	(b) (4)	

Adapted from Table 1 in eCTD section 3.2.S.5.1 [CF] of the submission
[1] results available after Infusion for Final Release.

Reviewer Comment: The potency assay matrix was agreed to prior to the BLA submission in IND 14459.

3.2.P.5.6 Justification of Specifications

Table 69 includes the summary of the justification of the specifications.
The justification for the Appearance, Rapid contamination test, Sterility, Mycoplasma content, and Endotoxin specifications are based on established safety limits from compendial methodology. Not all release testing results will be available when the product is infused. The product is cryopreserved and stable to be allowed for release of the product after all testing is available. However, because of medical need, the product will be available for infusion before obtaining the final sterility results, and Harvest Day CFU results. There is a surrogate measurement for these attributes available for infusion, rapid contamination test, and (b) (4) CFU test, respectively. For sterility, the product will be released for infusion before obtaining final sterility culture results. The product will be release based on overnight culture test, which is a rapid contamination test. The final release process includes an action plan in case of positive microbiological test result or failure in CFU evaluation post release. In such cases, an investigation will be initiated as defined in the internal procedure for deviation reporting. The Biological

Product Deviation Reporting (SOP 03.023GC) includes specification instruction for reporting failed final sterility tests that include notification to the FDA within 45 days, physician notification through the GC Assist Platform, identification of the strain, if possible, investigation and follow-up. The Applicant states this release and infusion procedure is in line with (b) (4)

Reviewer Comment: The use of the RCT was discussed with the OCBQ reviewer, Simleen Kaur, on 14July2022. The LOD sensitivity for the RCT test did not meet (b) (4) (b) (4) *requirement for most of the microorganism tested. It does not have the same sensitivity of the final sterility testing but is more robust than a* (b) (4) *method. The rapid contamination test performed on CF samples was validated in accordance with* (b) (4) *by demonstrating the tested product is suitable for the intended test method. It is suitable for a preliminary testing for gross final product contamination, in combination with the final sterility culture and the preliminary IPC sterility from culture day* (b) (4) *which is evaluated* (b) (4) *until the final* (b) (4) *compliant sterility results. Additionally, the final sterility culture will be used to identify the contaminate in the case of a post-infusion sterility failure to assist the patient treatment plan. The Biological Product Deviation Reporting (SOP#03.023GC) was also reviewed as part of the PLI and found acceptable.*

The identity and potency matrix acceptance criteria are informed by current HPC, Cord Blood, standards. To support the identity and potency matrix acceptance criteria, the Applicant used two statistical approaches: (1) the correlation analysis of CF to TtE, discussed in 3.2.S.3.1.4.1 Correlation Analysis of CF Quality Attributes and Engraftment [CF] of this memo; (2) SPC analysis. The Applicant considered the results of both analyses in setting the final commercial acceptance criteria.

40 pages have been determined to be not releasable: (b)(4)

3.2.P.8.1.2. Long-Term Stability Studies

3.2.P.8.1.2.1 Long-Term Stability Protocol for CF DP at T1 (6 weeks) and T2 (12 weeks)

The long-term stability plan evaluated (b) (4) batches stored at ≤ -150°C. To provide sufficient material for stability testing, (b) (4) were evaluated pre-freeze and six weeks (T1) and (b) (4) were evaluated pre-freeze and 12 weeks (T2) is detailed below in Table 83. Because of limited testing material per batch, the Applicant is unable to test multiple timepoints per final product bag. Each batch is tested at one time point in addition to QC samples at time point zero. For the long-term stability study, CF DP was stored upright in the same 250 mL cryopreservation bag, filled with the same volume (20ml) as the commercial product. Before testing, the CF DP bag is thawed and reconstituted (b) (4) with IS following the same procedure used at the TC. The CF DP is tested immediately after thawing and reconstitution. All test methods are the same as previously described in 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures [CF]. The results summarized for T1 in Table 84and T2 in Table 85 from the Stability Data submitted in eCTD section 3.2.P.8.3 Stability Data [CF]. The results summarized for T2 in Table 85 from the Stability Data submitted in eCTD section 3.2.P.8.3 Stability Data [CF], submitted in Amendment 19, on 02Sept2022.

Reviewer Comment: The approach to long term stability is acceptable.

Table 83. Long-Term Stability Studies for CF DP

Test	Method	Acceptance criteria	T0	T1	T2
Appearance	(b) (4)		X	X	X
TNVC			X	X	X
% Viability of TNC			X	X	X
Viability of CD34+ cells			X	X	X
No. of CD34+ viable cells			X	X	X
%CD34+ cells			X	X	X
(b) (4)			X	X	X
(b) (4)			X	X	X
Total No. of CFU Harvest Day			X	X	X
Sterility			X	X	X

Reproduced from Table 2 of Section 3.2.P.8.1 [CF] of the submission.

6 pages have been determined to be not releasable: (b)(4)

(b) (4)

3.2.P DRUG PRODUCT [NON-CULTURED FRACTION]
3.2.P.1 Description and Composition of the Drug Product
Proprietary name: OMISIRGE, Non-cultured Fraction
Non-Proprietary name: N/A for the Non-cultured Fraction, included in description of omidubicel-onlv
Reviewer Comment: The non-proprietary name for the CF is Omidubicel. This name did not include the NF fraction but does include a description of the NF. The NF DP is supportive to the CF DP which engrafts. This is acceptable.

The NF is composed of allogeneic, non-expanded, hematopoietic mature myeloid and lymphoid cells. The NF DP contains at least $4.0x10^8$ TNVC and $2.4 x10^7$ CD3+ cells in 10 mL of cryopreservation solution, filtered through a (b) (4) filter during transfer into a cryopreservation bag. The product is formulated as a single dose cell suspension for infusion for intravenous use. The NF DP suspension has a reddish appearance.

3.2.P.2 Pharmaceutical Development
3.2.P.2.1 COMPONENTS OF THE DRUG PRODUCT
3.2.P.2.1.1 Drug Product
The NF contains allogeneic, non-expanded, hematopoietic mature myeloid and lymphoid cells, such as monocytes, granulocytes, B cells, T-cells, and NK cells. The NF DP is manufactured from the eluted negative fraction of CBU cells during the (b) (4) positive selection of (b) (4) cells. The cells are collected and then washed and suspended in the cryopreservation solution containing (b) (4) The NF DP is filtered into the cryopreservation bag for storage at ≤-150°C.

3.2.P.2.1.2 Excipients
Same as CF DP and reviewed in 3.2.P.2.1.2 Excipients [CF] of this memo.

3.2.P.2.2 DRUG PRODUCT
3.2.P.2.2.1 Formulation Development
(b) (4)

6 pages have been determined to be not releasable: (b)(4)

Overall Reviewer's Assessment of Section 3.2.P.3.5:
Information provided is acceptable, with no deficiencies identified

3.2.P.4 Control of Excipients
This section is reviewed by EL.
Same as CF DP.

3.2.P.5 Control of Drug Product
This section is reviewed by EL.
3.2.P.5.1 AND 3.2.P.5.6 SPECIFICATION(S) AND JUSTIFICATION OF SPECIFICATION(S)
3.2.P.5.1 Specifications
Table 95 is the release specifications for the NF DP. All results for the NF DP will be available before shipping the product. Identity is also established by product traceability, as discussed in 3.2.P.3.3.7 Summary of the Traceability of the CF DS and CF DP [CF].
Table 95. Quality Control Specifications for NF DP

Attribute	Analytical procedure	Sample	Final acceptance criteria	Testing facility
Appearance	(b) (4)	DP	Reddish suspension, essentially free of visible clumps and foreign particulates	(b) (4)
TNVC		QC Sample	≥4.0x10^8	
Viability TNC		QC Sample	(b) (4)	
No. of CD3+ cells		QC Sample	≥2.4x10^7	
Sterility		QC Sample	No growth	
Endotoxin content (b) (4)		QC Sample	(b) (4)	

3.2.P.5.6 Justification of Specifications
Table 96 summarizes the Applicant's justification of the NF release specifications. The justification for the Appearance, Sterility, and Endotoxin specifications are based on established safety limits from compendial methodology.

4 pages have been determined to be not releasable: (b)(4)

See 3.2.P.5.4 Batch Analyses3.2.P.5.4 Batch Analyses [CF] for IRs sent to Applicant regarding batch records analysis. See 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s) [NF] for the analyses of the batch records. Information provided is acceptable, with no deficiencies identified.

3.2.P.6 Reference Standards or Materials

Reference Standards or Materials used during assay controls and system suitability controls used in individual test methods are reviewed in 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures [CF] of this memo.

3.2.P.7 Container Closure System

This section is reviewed by consult reviewer Aaron Seeto Wen (CBER/OTP/OCTHT/DCT2).

Reviewed with CF DP in 3.2.P.7 Container Closure System [CF] of this memo.

Overall Reviewer's Assessment of Section 3.2.P.7:

Same as CF DP.

3.2.P.8 Stability

This section is reviewed by AS.

3.2.P.8.1 AND 3.2.P.8.3 STABILITY SUMMARY AND CONCLUSION AND STABILITY DATA

The stability studies of NF DP were conducted to demonstrate physical, chemical, biological, and microbiological stability through the proposed shelf-life of 15 weeks, when stored at ≤-150°C. Timepoint T1 representing nine weeks of stability data submitted as part of the BLA submission, and timepoint T2 representing 15 weeks of stability data from the stability batches are submitted under Amendment 19. Each batch omidubicel has the same expiry date for the NF and CF DP. NF DP is cryopreserved at Day 0, thus, is stored at ≤-150°C three weeks longer and required a longer shelf life to ensure stability though the CF DP shelf life. The Applicant uses the same stability testing approach for the NF DP as the CF DP and reviewed in 3.2.P.8 Stability [CF] of this memo. A summary of the NF stability studies is presented in Table 99.

Table 99. Stability Studies for NF DP

Batch number	Study	Study length (NF DP)	Holding time[1]	Holding time[2]
(b) (4)	Long-Term/In-use	9 weeks ± 3 days	0	0, 1h, (b) (4)
	Long-Term/In-use	9 weeks ± 3 days	0	0, 1h,
	Long-Term/In-use	9 weeks ± 3 days	0	0, 1h,
	Long-Term/In-use	9 weeks ± 3 days	0	0, 1h,
	Long-Term/In-use	15 weeks (b) (4)	0	0, 1h,
	Long-Term/In-use	15 weeks (b) (4)	0	0, 1h,
	Long-Term/In-use	15 weeks (b) (4)	0	0, 1h,
	Long-Term/In-use	15 weeks (b) (4)	0	0, 1h,
	Supportive In-use	7-14 days	0, (b) (4)	
	Supportive In-use	7-14 days	0,	
	Supportive In-use	7-14 days	0,	
	Supportive In-use	7-14 days	0,	

[1] Holding time for Long-Term Stability Studies
[2] Holding time for In-Use Stability Studies

3.2.P.8.1.2.1 Long-Term Stability Studies

Long-Term (≤-150°C) Stability Protocol for NF DP at T1 (Nine Weeks) and T2 (15 Weeks)

The long-term stability plan used for the (b) (4) batches stored at ≤-150°C for 9 weeks (T1) and 15 weeks (T2) is detailed in Table 100. The Applicant uses the same long term stability testing approach as the CF DP and reviewed in 3.2.P.8.1.2. Long-Term Stability Studies [CF] of this memo. The only change is the NF is stored for three weeks longer. The long-term stability data provided by the Applicant in eCTD section 3.2.P.8.3 Stability Data [CF] are summarized in Table 101 for T1 (nine weeks) and Table 102 for T2 (15 weeks).

Table 100. Long-Term Stability Protocol for NF DP at T1 (Nine Weeks) and T2 (15 Weeks)

Test	Method	Acceptance criteria	T0	T1	T2
Appearance	(b) (4)	Reddish cloudy suspension, essentially free of visible clumps and foreign particulates	X	X	X
TNVC		T0: ≥ $4.0x10^8$ T1/T2: (b) (4)	X	X	X
% Viability of TNC		(b) (4)	X	X	X
No. of CD3+ viable cells		T0: ≥ $2.4x10^7$ T1/T2: (b) (4)	X	X	X
Sterility		No growth	X	X	X

Reproduced from Figure 2 of Section 3.2.P.5.6 [NF] of the submission.

(b) (4)

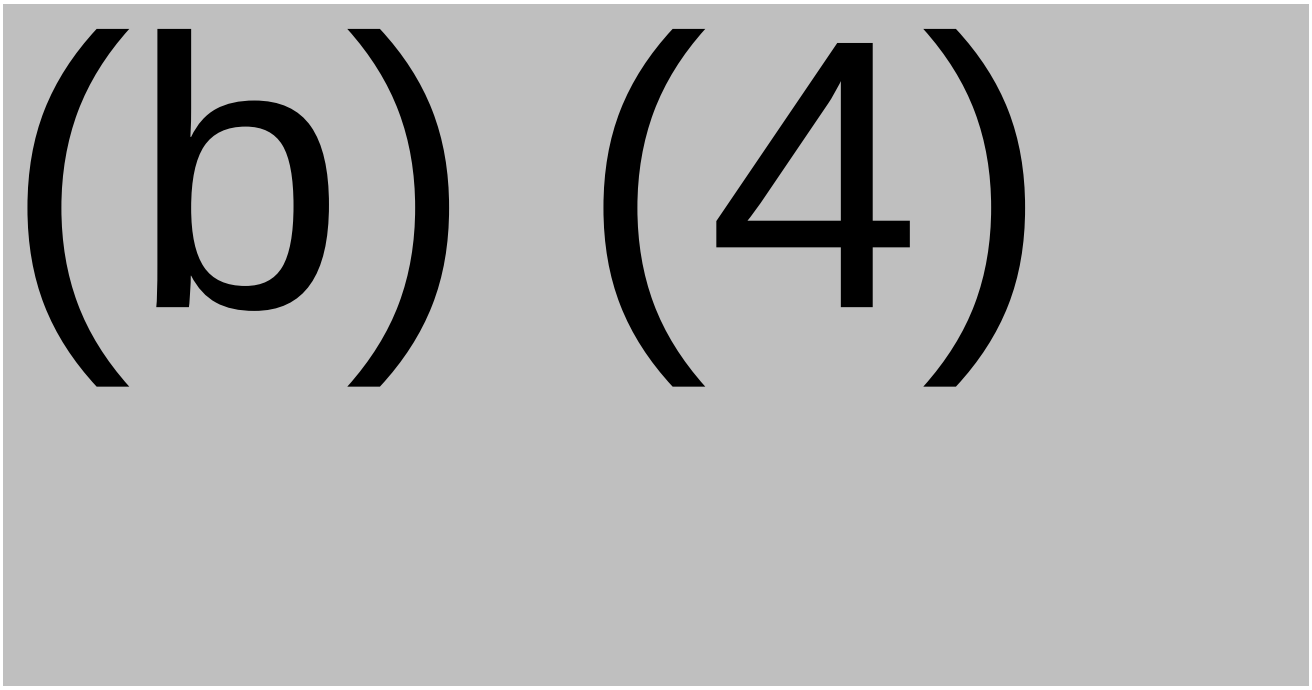
3 pages have been determined to be not releasable: (b)(4)

As the stability data presented covers the proposed shelf life and are derived from real-time, real storage conditions with three representative batches, produced by the commercial manufacturing process, the Applicant states that a routine annual stability study post-BLA approval will not be performed. However, in case significant changes to the manufacturing process or analytical methods for the NF are introduced after licensing, the Applicant plans to reevaluate stability, and data will be submitted as a supplement to the BLA.

Overall Reviewer's Assessment of Section 3.2.P.8:
In Amendment 19, received 2Sept2022, the Applicant submitted the final 15 weeks stability data. This information has been reviewed and no deficiencies identified.
The Applicant has demonstrated the NF DP is stable for 15 weeks and (b) (4) hours post-thaw and dilution with the IS DP.
There are no remaining provided on the information provided in this section.

3.2.P DRUG PRODUCT [INFUSION SOLUTION]
3.2.P.1 Description and Composition of the Drug Product
This section is reviewed by EL.
Proprietary name: OMISIRGE, Infusion solution (IS)
Non-Proprietary name: N/A for the IS, included in description of omidubicel-onlv
Description: The IS DP is added to final CF DP and NF DP formulation as a diluent via closed port system. As an excipient, the IS helps maintain cell stability during infusion. The IS DP is composed of 8% w/v HSA and 6.8% w/v Dextran.

3.2.P.2 Pharmaceutical Development
This section is reviewed by EL.
3.2.P.2.1 COMPONENTS OF THE DRUG PRODUCT



3.2.P.2.2 DRUG PRODUCT

3.2.P.2.2.1 Formulation Development

The optimal HSA and Dextran concentrations was identified before initiation of the clinical studies using the cryopreserved formulation of omidubicel. The identification of the optimal IS composition is reviewed with NF DP in 3.2.P.2.3.3.3 Impact of Thawing Procedure and IS Formulation on Cell Recovery [NF] of this memo. The Applicant established the concentration of 8% w/v HSA + 6.8% w/v Dextran 40 (b) (4)

3.2.P.2.2.2 Overages

This section is not applicable.

3.2.P.2.2.3 Physicochemical and Biological Properties

The final formulation provides a suitable (b) (4) that are for the intravenous administration of CF and NF. The IS does not have biological properties as the solution is used as a vehicle for suspension of the CF and NF before administration to the patient.

3.2.P.2.3 MANUFACTURING PROCESS DEVELOPMENT

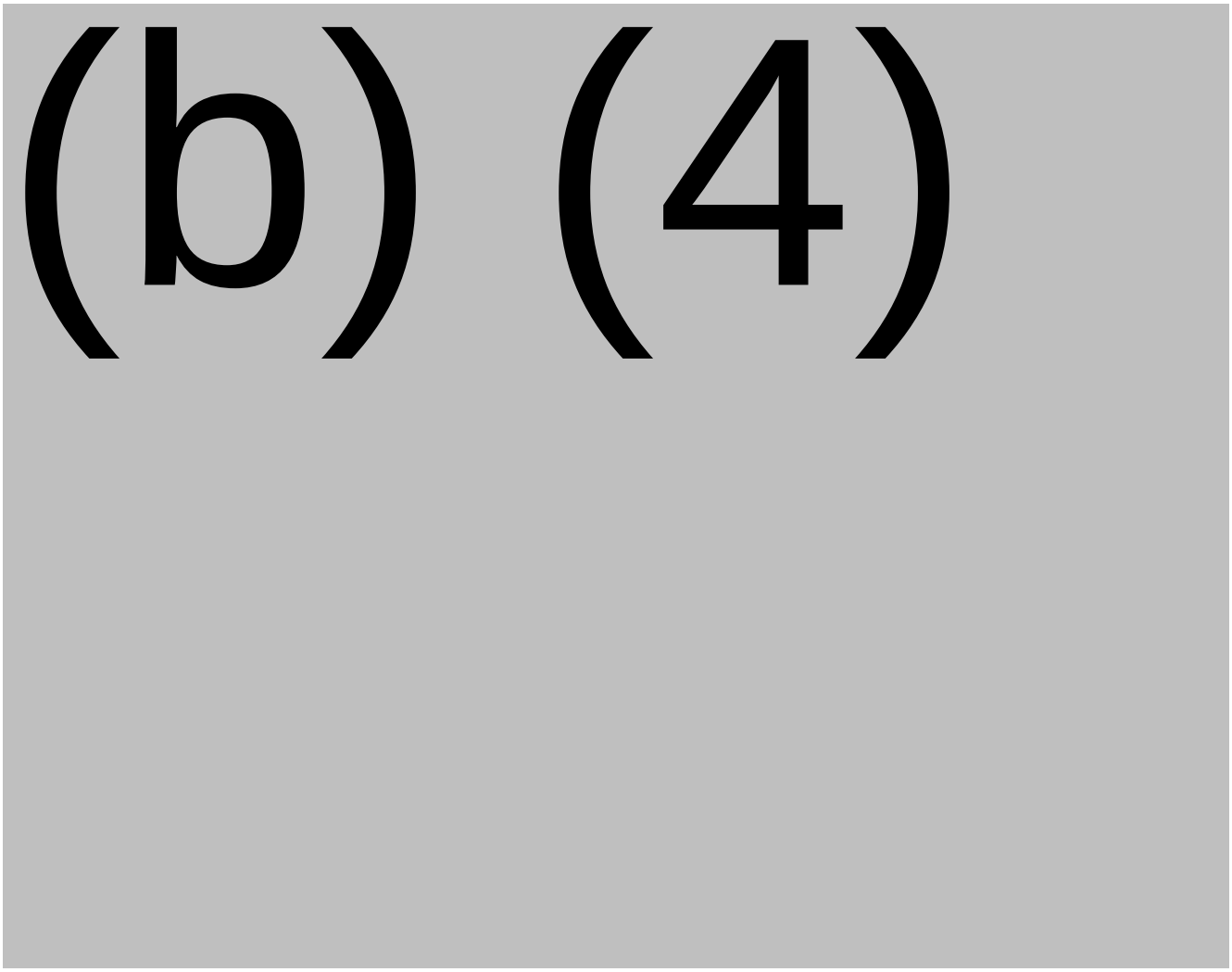
3.2.P.2.3.1 Manufacturing Process Development

Table 108 provides the manufacturing process development for the IS DP.

Table 108. IS DP Manufacturing Process Development Summary

(b) (4)

10 pages have been determined to be not releasable: (b)(4)



3.2.P.5 Control of Drug Product

3.2.P.5.1 AND 3.2.P.5.6 SPECIFICATION(S) AND JUSTIFICATION OF SPECIFICATION(S)

This section is reviewed by EL.

The release specifications for the IS DP are listed in Table 119. All results are available before the release for shipping.

Table 118. IS DP Release Specifications

Attribute	Analytical procedure	Sample	Final acceptance criteria	Testing facility
Appearance	(b) (4)			
Particulate matter (Sub-visible particulates)				
(b) (4)				
Osmolality				
HSA				
HSA				
Dextran				
HSA concentration				
(b) (4)				
Total related substances of HSA in the IS				
Sterility				
Endotoxin content (b) (4)				

Reproduced from Figure 1 of Section 3.2.P.5.1 [IS] of the submission.

Assessment of the IS test methods and assay validation is deferred to DMPQ.

(b) (4)

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

3.2.P.5.5 CHARACTERIZATION OF IMPURITIES
This section is reviewed by EL.
The IS DP is a combination of Dextran 40 and HSA. No other excipients are added during the manufacturing of the IS. Potential extractable/leachable impurities are discussed in 3.2.P.3.5 Process Validation and/or Evaluation [IS] of this memo.
(b) (4) -based quantitative methods is used as part of lot release to control for impurities. The acceptance criteria at release for the individual related substances is no more than (b) (4) (w/v) relative to the IS.

Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:
Information provided is acceptable, with no deficiencies identified.

3.2.P.6 Reference Standards or Materials
This section is reviewed by EL.
No reference standard is used in the testing and release of the IS DP.

3.2.P.7 Container Closure System
This section is copied from consult review by Aaron Seeto Wen (CBER/OTP/OCTHT/DCT2).
Description

(b) (4)

4 pages have been determined to be releasable: (b)(4)

(b) (4)

3.2.P.8 Stability

This section is reviewed by AS.

3.2.P.8.1 AND 3.2.P.8.3 STABILITY SUMMARY AND CONCLUSION AND STABILITY DATA

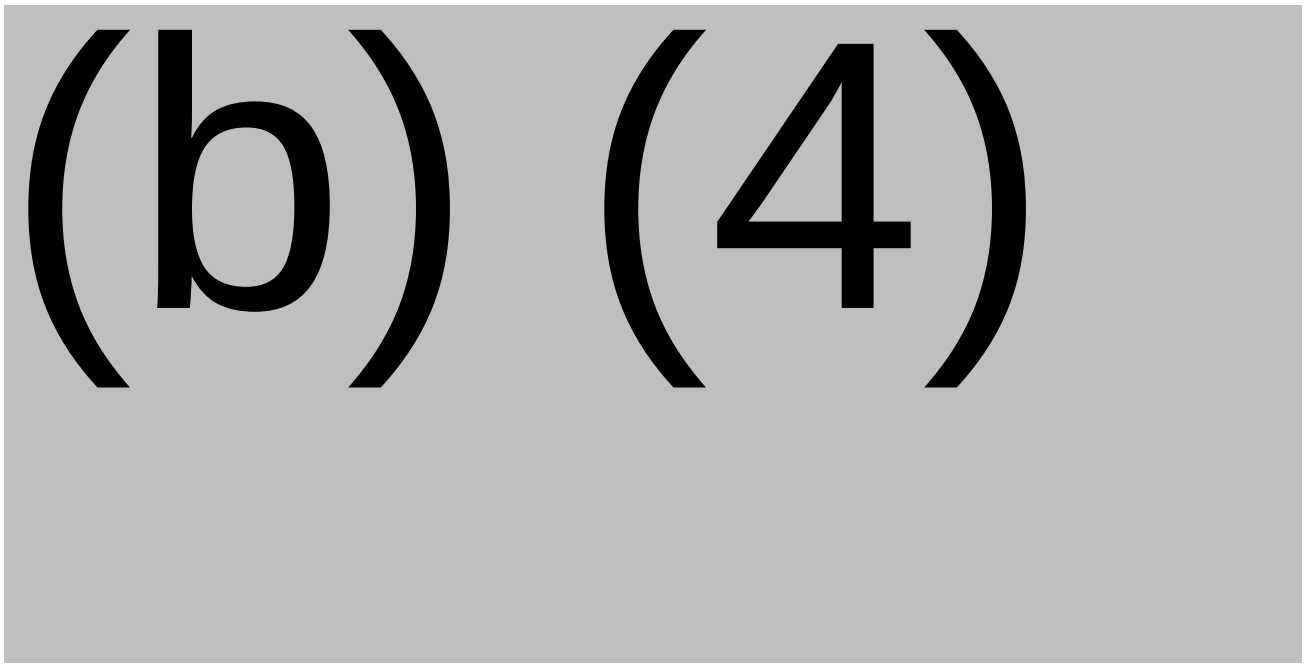
The IS DP stability studies were conducted to demonstrate physical, chemical, biological, and microbiological stability through the proposed shelf-life of five months when stored at the intended long-term storage condition of 2-8°C. For the long-term studies, (b) (4) batches of IS each consisting of (b) (4) IS lots (total of (b) (4) lots) were used. Each lot of IS consists of (b) (4) bags and (b) (4) bags for dilution of NF and CF, respectively. Therefore, each IS batch represents (b) (4) IS lots for one stability study. All IS stability studies conducted were performed in both (b) (4) (b) (4) As part of the original BLA submission, stability data from the interim timepoints (T1, T2, and T3) for the PPQ batches are included and the final stability data for T4 and T5 PPQ studies was submitted before the mid-cycle review meeting under Amendment 19.

Reviewer Comment: In response to CMC IR # 10, the Applicant clarified in Amendment 53 that for all stability studies the freezer bags were within the manufacturing expiration date for the entire duration of all stability studies.

3.2.P.8.1.2.2 Photostability Studies

(b) (4)

5 pages have been determined to be not releasable: (b)(4)



3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Assessment of the facilities and equipment is deferred to DMPQ. Please refer to the review memo by Rabia Ballica.

3.2.A.2 Adventitious Agents Safety Evaluation

This section is reviewed by EL.

3.2.A.2.1 SUMMARY

The mitigation measures include:

- Control of starting material, raw materials, and excipients:
- Risk mitigation activities during the manufacturing process
- Risk mitigation activities through environmental monitoring
- Risk of transmission of a viral infection and bacterial infection prophylaxis

4 pages have been determined to be not releasable: (b)(4)

3.2.R REGIONAL INFORMATION (USA)
This section contains analytical assay validation reports for assay validation and all PPQ validation reports. All validation reports found in the regional information section are discussed under the relevant section.

Comparability Protocols
Comparability protocols are discussed in 3.2.P.2.3 Manufacturing Process Development [CF] and 3.2.P.2.3.3 Manufacturing Process Development [NF] of this memo.

Other eCTD Modules
MODULE 1

- **Environmental Assessment or Claim of Categorical Exclusion**

This section is reviewed by EL.
The Applicant requests that Omisirge be granted a categorical exclusion under the provision of the 21 CFR Part 25.31(a). The requested action is in compliance with the categorical exclusion criteria. To the Applicant's knowledge, no extraordinary circumstances exist that require submission of an Environmental Assessment.
Reviewer Comment: A claim of categorical exclusion has been submitted under 21 CFR 25.31(c). FDA concludes that this product occurs naturally in the environment, and approval of this BLA does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment, and no extraordinary circumstances exist. The categorical exclusion claim is accepted.

- **Labeling Review**

This section is reviewed by EL.
Carton and Container Label:
The primary container for the CF and NF DP consists of the container closure bags that are directly labeling and then placed in a metal cassette which contains the same label. The primary container for the IS DP consists of the container closure bags.

Summary of Labels for omidubicel.

Table 128. Labels for Omidubicel and Their Location

Component	Document number	Label name	Label location	Duplicate label location
Cultured Fraction (CF)	PK000105	CF Fixed Data	CF bag, on top of label pouch	Front of CF cassette
	PK000106	CF Patient Specific label	CF bag, adjacent to first label	Front of CF cassette
Non-cultured Fraction (NF)	PK000103	NF Fixed Data	NF bag, on top of label pouch	Front of NF cassette
	PK000104	NF Patient Specific label	Back of NF bag	Front of NF cassette
Infusion Solution (IS) for CF	PK000107	Infusion Solution for CF (Patient Specific)	IS bag label pouch	NA
IS for NF	PK000108	Infusion Solution for NF (Patient Specific)	IS bag label pouch	NA
Liquid Nitrogen (LN) Dry Vapor Shipper	PK000113	Shipping Label: LN dry shipper	Label pouch on shipper	NA
Refrigerated Shipping Container	PK000112	Shipping Label Refrigerated Container	Label pouch on container	NA
Chimerism Testing Sample (b) (4)	PK000111	Chimerism Label: Segment(s)	Segment	Segment(s) sterile bag
	PK000110	Chimerism Label: Cassette with Segment(s)	Cassette	NA
	PK000109	Chimerism Label: NF sample + sterile bag	Sample vial	Vial's sterile bag

CF and NF Labels

Fixed Data labels: All text in the Fixed Data labels (omidubicel Label: CF Fixed Data and omidubicel Label: NF Fixed Data) is pre-printed, is not batch or patient specific and includes the following information: The product name, information, instructions, directions, and warnings , Important warning information and directions regarding administration, based on clinical experience with the product, and Document number and version number

Patient Specific labels: The Patient Specific labels (omidubicel Label: CF Patient Specific label and omidubicel Label: NF Patient Specific label) include some fixed pre-printed text and the following patient specific identifiers that are printed by the manufacturing site onto the pre-printed label template:, Patient first name, middle initial (where applicable) and last name, Patient Date of Birth, Omidubicel batch number, Omidubicel batch expiration date, CBU ID, GC Patient ID, Hospital Patient ID and A 2D data matrix containing the omidubicel batch number.
The label printing software (b) (4) receives the batch and patient specific data via integration with the Priority ERP system and prints this information onto the patient specific labels for a specific batch in the blank unprinted section.

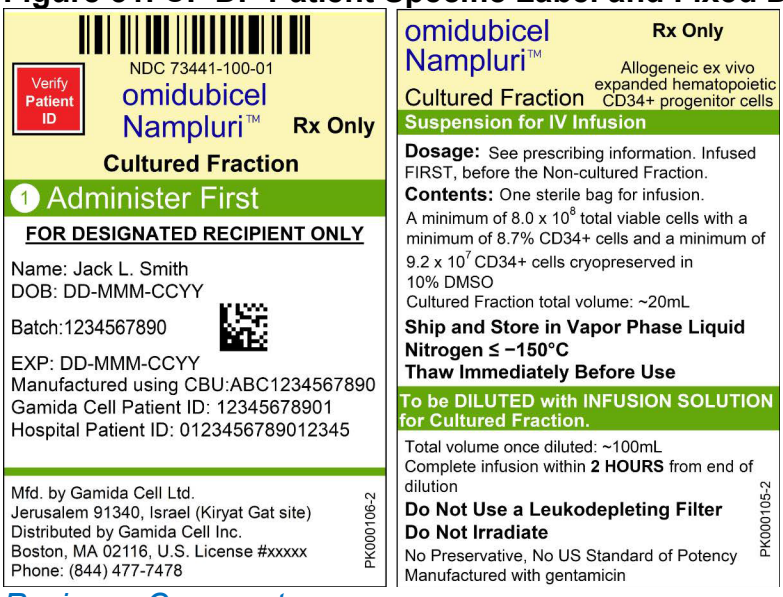
The pre-printed text on the CF and NF patient specific labels includes the following fixed information: The product name, the specific fraction's NDC number and its associated, linear barcode, warning to verify patient ID, color banding, order of infusions, manufacturer information, Document number and version number, and No images or tables.

Cultured Fraction (CF) Label

The primary label and the package label are the same labels. The patient specific and fixed data labels will always appear next to each other. The primary labeling is attached to the product (left side of Figure 50) above the product. The product is housed within the metal cassette (right side of Figure 50). The primary label bags are visible though the metal cassette opening and have duplicate primary labels attached. Additional "Do NOT open" cassette sticker (red sticker in Figure 50) will be used. If the donor is CMV positive, the "CMV positive" label is affixed onto the CF and NF's primary packaging.

Figure 50. Location of CF DP Labels on Primary and Tertiary Packaging

Figure 51. CF DP Patient Specific Label and Fixed Data Label



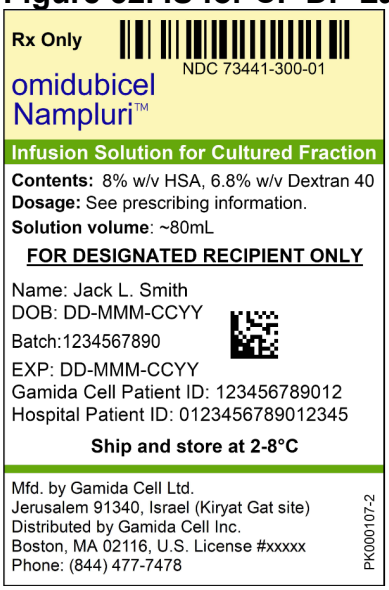
Reviewer Comment:

- *The PI includes a warning about product being manufactured with bovine reagents and antibiotics. The label only includes the product is manufactured with gentamicin but did not include that bovine material is used in manufacturing.*

In response to CMC IR # 10, Applicant agreed in Amendment 53 to revise the labeling to include "Manufactured with gentamicin and bovine product" to be in line with the PI. This is acceptable.

- *The Applicant's Drug Supply Chain Security Act exemption request was granted. The packaging does contain lot specific information, expiration date and IS*
- *The labels are not in conflict of compliance with 21 CFR 610 subpart G.*

Figure 52. IS for CF DP Label

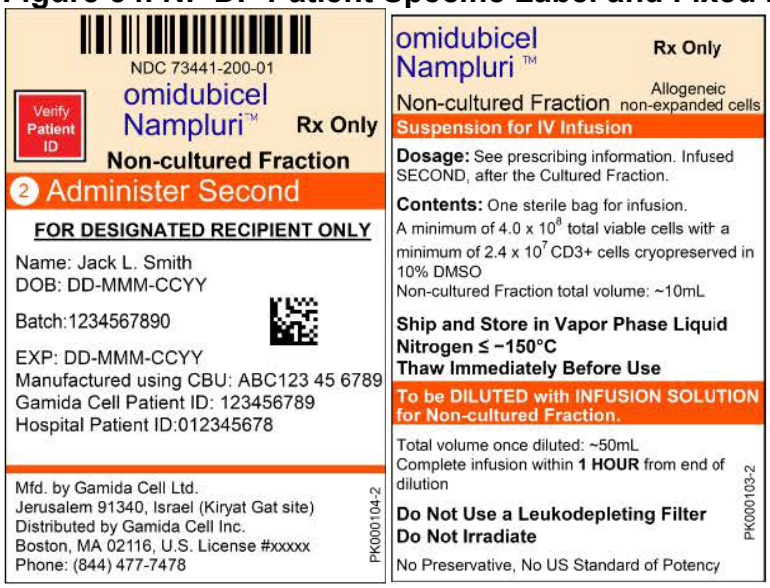


Non-Cultured Fraction (NF) Label

Figure 53. Location of NF DP Labels on Primary and Tertiary Packaging

Reviewer Comment: The full length and width of product in the container is visible. The label pouch for front does not extent across the container.

Figure 54. NF DP Patient Specific Label and Fixed Data Label



The IS label for the 50 ml IS bag is in figure 55.

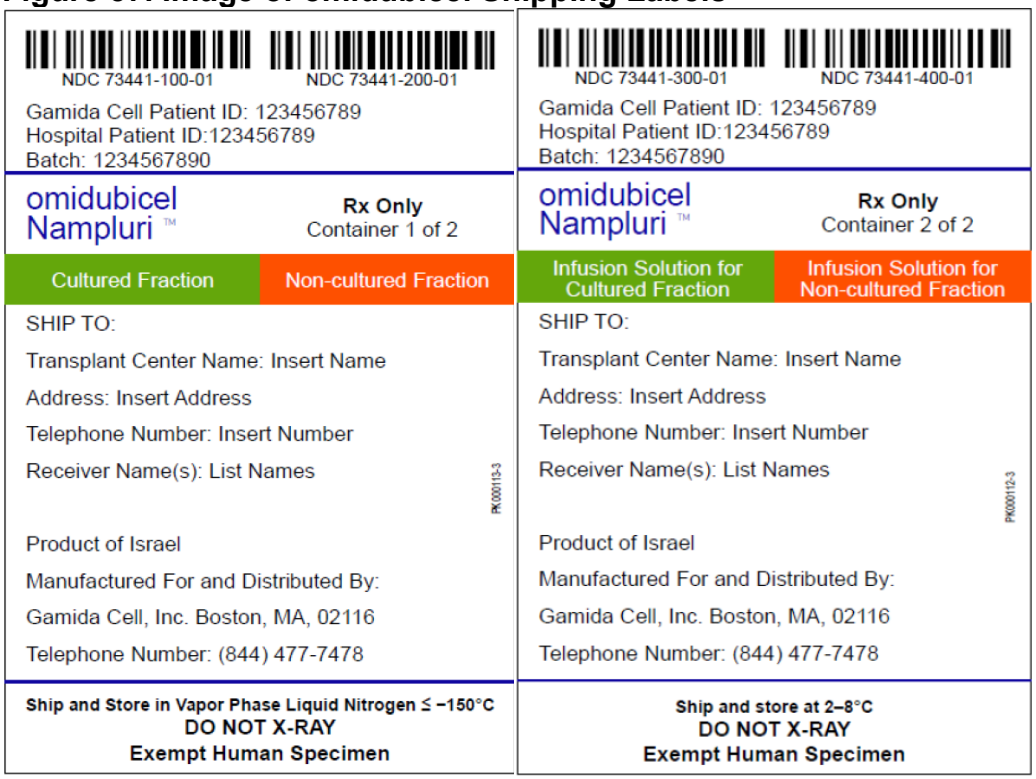
Figure 55. IS for NF DP Label

Reviewer Comment: The IS has only one patient specific label. Same as CF IS.

There are two options for the chimerism test sample: CBU segment, or NF sample. Figure 56 shows the CBU segment with the cassette open (left), CBU segment next to close cassette (middle), and the NF sample as chimerism test sample. This sample is not for infusion but made available to the transplant physician for confirmatory testing or post engraftment studies.

Figure 56. Chimerism Testing Sample

Figure 57. Image of omidubicel Shipping Labels



Reviewer Comment: Initially the product shipping label stated, "container 1/2" instead of "1 of 2". The "1/2" could be misinterpreted as one half instead of one of two. In Amendment 56, in response to CMC IR # 11, the Applicant provided revised label replacing "of" for "/". This is acceptable.