

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. **APPLICANT 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 8.0×10^8 total number viable cells with a minimum of 8.7% CD34+ cells and a minimum of 9.2×10^7 CD34+ cells in 20 ml of cryopreservation solution containing 10% DMSO
NF: a minimum of 4.0×10^8 total number viable cells and 2.4×10^7 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- only

Proprietary Name: OMISIRGE (Formerly (b) (4) NiCord)

Company Code: Cultured Fraction, CF
Non-Cultured Fraction, NF
Infusion Solution, IS

UNII Code: Omidubicel-only, CF: ET4JC4S66E
Omidubicel-only, NF: MAH7ZHD7ZJ

WHO Number: 11164

NDC Codes: Omidubicel-only: 73441-100-01
Omidubicel-only, CF: 73441-200-01
Omidubicel-only, NF: 73441-200-01
Omidubicel-only, IS for CF: 73441-300-01
Omidubicel-only, 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, 2023

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 <i>Drug Substance [CF] and Drug Substance [NF]</i> : General information, Manufacture, Control of Drug Substance, Reference Standards or Materials <i>Drug Product [CF], Drug Product [NF] and Drug Product [IS]</i> : 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	<i>Drug Product [CF], Drug Product [NF] and Drug Product [IS]</i> : Stability
Sukhanya Jayachandra, PhD CMC Reviewer CBER/OTP/OCTHT/ DCT1/CTB1	<i>Drug Substance [CF]</i> : Control of Materials
Heba Degheidy, MD, PhD CMC Reviewer CBER/OTP/OCTHT/ DCT1/CTTB	<i>Drug Substance [CF], Drug Substance [CF] and Drug Substance [NF]</i> : 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 2020 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 <i>section 3.2.S.2.3 Control of Materials</i> [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 <i>section 3.2.S.2.3 Control of Materials</i> [CF]

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Gamida Cell Ltd. (GC) submitted the biologics license application (BLA) 125738 to market omidubicel-only (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 8.0×10^8 total number viable cells (TNVC) with a minimum of 9.2×10^7 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 $\leq -150^{\circ}\text{C}$.

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 $\leq -150^{\circ}\text{C}$ while the (b) (4) CF (b) (4) manufacturing is completed. The final NF DP contains at least 4.0×10^8 TNVC and 2.4×10^7 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 $\leq -150^{\circ}\text{C}$ for up to 12 weeks, the NF DP at $\leq -150^{\circ}\text{C}$ for up to 15 weeks, and the IS DP at $2-8^{\circ}\text{C}$ 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 $\leq -150^{\circ}\text{C}$ and the IS DP at $2-8^{\circ}\text{C}$. 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-only 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-only 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-only 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

Table of Contents

3.2.S DRUG SUBSTANCE [Cultured Fraction]	11
3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties	11
3.2.S.2 Manufacture	12
3.2.S.2.1 Manufacturer(s)	12
3.2.S.2.2 Description of Manufacturing Process	12
3.2.S.2.2.4 Manufacturing Process Flow Diagram	12
3.2.S.2.2.5 Manufacturing Process Description	13
3.2.S.2.2.3 Batches and Scale Definition	17
3.2.S.2.2.2 Manufacturing Process Control Strategy	18
3.2.S.2.2.6 and 3.2.S.2.2.7 In-Process Monitoring and In-Process Controls	18
Storage and Shipping	23
3.2.S.2.3 Control of Materials	23
Control of Raw Materials NOT of Biological Origin	23
Control of Raw Materials of Biological Origin	30
Control of Starting (i.e., Source) Material(s)	40
3.2.S.2.4 Controls of Critical Steps and Intermediates	41
3.2.S.2.5 Process Validation and/or Evaluation	42
3.2.S.2.6 Manufacturing Process Development	42
3.2.S.2.6.2 Control Strategy	43
3.2.S.2.6.3 Transfer to KGI site	48
3.2.S.3 Characterization	48
3.2.S.3.1 Elucidation of Structure and Other Characteristics	48
3.2.S.3.1.2 Phenotype Characterization	49
3.2.S.3.1.4 Biological Activity of the CF cell suspension	49
3.2.S.3.1.5 Mechanism of Action	50
3.2.S.3.2 Impurities	51
3.2.S.3.2.1 Product-Related Impurities	51
3.2.S.3.2.2 Product Related Sub-Populations	52
3.2.S.3.2.3 Process Related Impurities	52
3.2.S.4 Control of Drug Substance	62
3.2.S.4.1 and 3.2.S.4.5 Specification(s) and Justification of Specification(s)	62
3.2.S.4.2 and 3.2.S.4.3 Analytical Procedures and Validation of Analytical Procedures	62
3.2.S.4.4 Batch Analyses	62
3.2.S.5 Reference Standards or Materials	63
3.2.S.6 Container Closure System	63
3.2.S.7 Stability	63
3.2.S DRUG SUBSTANCE [Non-Cultured Fraction]	63
3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties	63
3.2.S.2 Manufacture	64
3.2.S.2.1 Manufacturer(s)	64
3.2.S.2.2 Description of Manufacturing Process	64
3.2.S.2.2.4 Manufacturing Process Flow Diagram	64

3.2.S.2.2.5 Manufacturing Process Description.....	65
3.2.S.2.2.2 Manufacturing Process Control Strategy.....	66
3.2.S.2.2.6 Reprocessing	66
3.2.S.2.2.7 Analytical Methods used for IPC testing.....	66
3.2.S.2.2.3 Batch Numbering, Pooling and Scale Definition.....	66
Storage and Shipping	66
3.2.S.2.3 Control of Materials	66
3.2.S.2.4 Controls of Critical Steps and Intermediates	67
3.2.S.2.5 Process Validation and/or Evaluation.....	67
3.2.S.2.6 Manufacturing Process Development.....	67
3.2.S.2.6.2 Control Strategy	67
3.2.S.2.6.3 Transfer to KGI site	68
3.2.S.3 Characterization	68
3.2.S.3.1 Elucidation of Structure and Other Characteristics.....	68
3.2.S.3.1.2 Phenotype Characterization of the NF	68
3.2.S.3.1.3 Cell Viability.....	69
3.2.S.3.1.5 Microbiological Safety	69
3.2.S.3.1.6 Biological Activity of the NF Cell Suspension.....	69
3.2.S.3.1.7 General Mechanism of Action (MoA)	70
3.2.S.3.2 Impurities.....	70
3.2.S.3.2.1 Product-Related Impurities.....	70
3.2.S.3.2.2 Process-Related Impurities	70
3.2.S.4 Control of Drug Substance	71
3.2.S.4.1 and 3.2.S.4.5 Specification(s) and Justification of Specification(s).....	71
3.2.S.4.4 Batch Analyses.....	71
3.2.S.5 Reference Standards or Materials.....	71
3.2.S.6 Container Closure System.....	72
3.2.S.7 Stability.....	72
3.2.P DRUG PRODUCT [Cultured Fraction]	72
3.2.P.1 Description and Composition of the Drug Product.....	72
3.2.P.2.1 Components of the Drug Product.....	73
3.2.P.2.1.1 Drug Substance	73
3.2.P.2.1.2 Excipients.....	73
3.2.P.2 Pharmaceutical Development.....	73
3.2.P.2.2 Drug Product	73
3.2.P.2.2.1 Formulation Development	73
3.2.P.2.2.2 Overages	74
3.2.P.2.2.3 Physicochemical and Biological Properties.....	74
3.2.P.2.3 Manufacturing Process Development.....	74
3.2.P.2.3.1 Overview	74
3.2.P.2.3.2 Manufacturing Process Development	76
3.2.P.2.4 Container Closure System	80
3.2.P.2.5 Microbiological Attributes	80
3.2.P.2.6 Compatibility.....	80
3.2.P.3 Manufacture	80
3.2.P.3.1 Manufacturer(s).....	80

3.2.P.3.2 Batch Formula	80
3.2.P.3.3 Description of Manufacturing Process	80
3.2.P.3.3.2 Manufacturing Process Control Strategy	81
3.2.P.3.3.3 Batches and Scale Definition	81
3.2.P.3.3.4 Manufacturing Process Flow Diagram	81
3.2.P.3.3.5 Manufacturing Process Description	81
3.2.P.3.3.6 Process Parameters	83
3.2.P.3.3.7 Summary of the Traceability of the CF DS and CF DP	84
3.2.P.3.4 Controls of Critical Steps and Intermediates	89
3.2.P.3.5 Process Validation and/or Evaluation	89
3.2.P.3.5.1 Process Validation Overview	89
3.2.P.3.5.2 Process Qualification (PQ) Outline	90
3.2.P.3.5.3 Process Validation and/or Evaluation KGI Facility Results	90
3.2.P.3.5.4 Extractables and Leachables	95
3.2.P.3.5.5 Aseptic Process Simulation	95
3.2.P.3.5.6 Shipping Validation Studies	96
3.2.P.3.5.7 Production Capacity	97
3.2.P.3.5.8 Continued Process Verification	98
3.2.P.4 Control of Excipients	102
3.2.P.4.1 Specifications	102
3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures	102
3.2.P.4.4 Justification of Specifications	104
3.2.P.4.5 Excipients of Human or Animal Origin	104
3.2.P.4.6 Novel Excipient	104
3.2.P.5 Control of Drug Product	105
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)	105
3.2.P.5.1 Specifications	105
3.2.P.5.6 Justification of Specifications	106
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures	120
3.2.P.5.4 Batch Analyses	140
3.2.P.5.5 Characterization of Impurities	142
3.2.P.6 Reference Standards or Materials	142
3.2.P.7 Container Closure System	142
3.2.P.8 Stability	148
3.2.P.8.1 and 3.2.P.8.3 Stability Summary and Conclusion and Stability Data	148
3.2.P.8.1.2. Long-Term Stability Studies	149
3.2.P.8.1.2.2 In-Use Stability Study	151
3.2.P.8.1.3. Supportive In-Use Stability Study	153
3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment	155
3.2.P DRUG PRODUCT [Non-Cultured Fraction]	156
3.2.P.1 Description and Composition of the Drug Product	156
3.2.P.2 Pharmaceutical Development	156
3.2.P.2.1 Components of the Drug Product	156
3.2.P.2.1.1 Drug Product	156

3.2.P.2.1.2 Excipients.....	156
3.2.P.2.2 Drug Product	156
3.2.P.2.2.1 Formulation Development	156
3.2.P.2.2.2 Overages	156
3.2.P.2.2.3 Physicochemical and Biological Properties.....	156
3.2.P.2.3 Manufacturing Process Development.....	156
3.2.P.2.3.1 Overview	157
3.2.P.2.3.2 Analytical Method Development.....	157
3.2.P.2.3.3 Manufacturing Process Development	157
3.2.P.2.4 Container Closure System	158
3.2.P.2.5 Microbiological Attributes	158
3.2.P.2.6 Compatibility	158
3.2.P.3 Manufacture	158
3.2.P.3.1 Manufacturer(s).....	158
3.2.P.3.2 Batch Formula.....	159
3.2.P.3.3 Description of Manufacturing Process.....	159
3.2.P.3.3.5 Manufacturing Process Description.....	159
3.2.P.3.3.6 Process Parameters.....	160
3.2.P.3.3.7 Traceability.....	161
3.2.P.3.4 Controls of Critical Steps and Intermediates	161
3.2.P.3.5 Process Validation and/or Evaluation.....	161
3.2.P.4 Control of Excipients	163
3.2.P.5 Control of Drug Product.....	163
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s).....	163
3.2.P.5.1 Specifications.....	163
3.2.P.5.6 Justification of Specifications	163
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures	166
3.2.P.5.4 Batch Analyses.....	167
3.2.P.5.5 Characterization of Impurities.....	167
3.2.P.6 Reference Standards or Materials.....	168
3.2.P.7 Container Closure System.....	168
3.2.P.8 Stability.....	168
3.2.P.8.1 and 3.2.P.8.3 Stability Summary and Conclusion and Stability Data.....	168
3.2.P.8.1.2.1 Long-Term Stability Studies	169
3.2.P.8.1.2.2 In-use Stability Study	170
3.2.P.8.1.4 Supportive In-use Stability Study	171
3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment	172
3.2.P DRUG PRODUCT [Infusion Solution]	173
3.2.P.1 Description and Composition of the Drug Product.....	173
3.2.P.2 Pharmaceutical Development.....	173
3.2.P.2.1 Components of the Drug Product.....	173
3.2.P.2.1.1 Drug Substance	173
3.2.P.2.1.2 Excipients.....	173
3.2.P.2.2 Drug Product	174
3.2.P.2.2.1 Formulation Development	174

3.2.P.2.2.2 Overages	174
3.2.P.2.2.3 Physicochemical and Biological Properties	174
3.2.P.2.3 Manufacturing Process Development	174
3.2.P.2.3.1 Manufacturing Process Development	174
3.2.P.2.3.2 Analytical Method Development	174
3.2.P.2.3.3 Control Strategy	175
3.2.P.2.3.4 Thawing of the CF DP and NF DP	176
3.2.P.2.3.5 Analytical Comparability Study of Manufacturing Sites: (b) (4)	176
3.2.P.2.3.6 Comparability Study of Manufacturing Sites: (b) (4)	176
3.2.P.2.4 Container Closure System	176
3.2.P.2.5 Microbiological Attributes	176
3.2.P.2.6 Compatibility	176
3.2.P.3 Manufacture	177
3.2.P.3.1 Manufacturer(s)	177
3.2.P.3.2 Batch Formula	177
3.2.P.3.3 Description of Manufacturing Process	177
3.2.P.3.4 Controls of Critical Steps and Intermediates	180
3.2.P.3.5 Process Validation and/or Evaluation	180
3.2.P.3.5.2 Process Qualification Outline	180
3.2.P.3.5.3. Extractable and Leachables	181
3.2.P.3.5.4 Aseptic Process Simulation	183
3.2.P.3.5.5 Shipping Validation Studies	183
3.2.P.3.5.6 Production Capacity	184
3.2.P.3.5.7 Continued Process Verification	184
3.2.P.4 Control of Excipients	184
3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures	184
3.2.P.4.4 Justification of Specifications	185
3.2.P.4.5 Excipients of Human or Animal Origin	185
3.2.P.4.6 Novel Excipient	185
3.2.P.5 Control of Drug Product	185
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)	185
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures	186
3.2.P.5.4 Batch Analyses	188
3.2.P.5.5 Characterization of Impurities	189
3.2.P.6 Reference Standards or Materials	189
3.2.P.7 Container Closure System	189
3.2.P.8 Stability	194
3.2.P.8.1 and 3.2.P.8.3 Stability Summary and Conclusion and Stability Data	194
3.2.P.8.1.2.2 Photostability Studies	194
3.2.P.8.1.2.3 Sub-visible Particulate Study	195
3.2.P.8.1.2.4 Long-term Stability Studies	196
3.2.P.8.1.2.5 Long-term Stability Studies with PPQ Batches	198
3.2.P.8.1.2.6 In-use Container Integrity Study	199
3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment	199

3.2.A APPENDICES.....	200
3.2.A.1 Facilities and Equipment	200
3.2.A.2 Adventitious Agents Safety Evaluation	200
3.2.A.2.1 Summary	200
3.2.R Regional Information (USA).....	205
Other eCTD Modules.....	205
Module 1.....	205

TABLE OF FIGURES

Figure 1. CF DS Manufacturing Diagram (Step 1 and 2).....	13
Figure 2. CF DS Manufacturing Diagram (Step 2 to 6).....	15
Figure 3. Control Chart of (b) (4) Total Number of Viable Cells ($\times 10^5$) Post (b) (4)	
Figure 4. Control Chart of Viability (%) Post-(b) (4)	21
Figure 5. Control chart of TNVC Yield (%) Post-(b) (4)	21
Figure 6. Control Chart of (b) (4) Cells Post-(b) (4)	22
Figure 7. Control Chart of CD34+ (%) Cells Post-(b) (4)	22
Figure 8. Control Chart of CFU/1000 Cells (Average).....	23
Figure 9. Process Parameter Decision Matrix	46
Figure 10. Comparison of estimated (b) (4) impurities in Omidubicel during Phase 3 by incidence of AE (Fever, and/or Hypotension).....	56
Figure 11. NF Drug Substance Manufacturing Process Flow Diagram	65
Figure 12. Overview of the CF DP Manufacturing Process	81
Figure 13. Traceability and Chain of Identity Flow Diagram from CBU Selection to CF DP Labels.....	85
Figure 14. Summary of COI/COC	86
Figure 15. Linear Regression Analysis of Impurity Concentration to Number of Bags Per LOVO Run.....	94
Figure 16. Control Chart of TNVC	113
Figure 17. Control Chart of Percent Viability of TNC.....	114
Figure 18. Control Chart of Percent CD34+ Cells	114
Figure 19. Chart of Number of CD34+ Cells ($\times 10^8$)	115
Figure 20. Control Chart of Number of (b) (4) cells.....	116
Figure 21. Control Chart for Total CD34+ Cells Fold Increase.....	116
Figure 22. Control Chart for Total CFU ($\times 10^6$).....	117
Figure 23. Control Chart of Percent Viability of CD34+ Cells	117
Figure 24. Log CFU on (b) (4).....	119
Figure 25. Linear Regression CFU (b) (4) and CFU Harvest Day	119
Figure 26. Example of Initial Gating CF DS.....	129
Figure 27. Example of Gating for CD34+ Cells	129
Figure 28. Example of (b) (4) gating	130
Figure 29. Summary of Assay Validation Results	131
Figure 30. Example of Gaiting for all Live Nuclear Cells	133
Figure 31. Example of (b) (4) Gating Strategy	135
Figure 32. Example of (b) (4) Dot Plot.....	135
Figure 33. Example of (b) (4) (b) (4) Dot Plot	135
Figure 34. Example of (b) (4) (b) (4) Dot Plot.....	136
Figure 35. Photographic image and schematic view of the (b) (4) filling assembly and overwrap bag	143
Figure 36. CF DP in the Storage Cassette. Schematic view (L) and Photographic image (R)	144
Figure 37. Photographic image and schematic view of the (b) (4)	145

Figure 38. NF DP in the Storage Cassette. Schematic view (L) and Photographic image (R).....	145
Figure 39. Liquid nitrogen dry vapor shipper	147
Figure 40. Metal cassette rack.	147
Figure 41. Overview of the NF DP Manufacturing Process	159
Figure 42. Total Number of Viable Cells.....	165
Figure 43. Control Chart of % Viability of TNC	165
Figure 44. Control Chart for Number of (b) (4) Cells.....	166
Figure 45. IS Manufacturing Process Flow Diagram	178
Figure 46. Excipients used in the manufacturing of the IS	184
Figure 47. Infusion Solution Freezing Bag and Sterile Secondary Bag.....	190
Figure 48. The Infusion Solution Validated Shipping Container.	192
Figure 49. Allocation of IS batches for Long-Term Stability Study Testing.....	196
Figure 50. Location of CF DP Labels on Primary and Tertiary Packaging	207
Figure 51. CF DP Patient Specific Label and Fixed Data Label	207
Figure 52. IS for CF DP Label	208
Figure 53. Location of NF DP Labels on Primary and Tertiary Packaging	208
Figure 54. NF DP Patient Specific Label and Fixed Data Label	209
Figure 55. IS for NF DP Label	209
Figure 56. Chimerism Testing Sample	210
Figure 57. Image of omidubicel Shipping Labels.....	210

TABLES

Table 1. Omidubicel Manufacture and CF DS In-Process Testing Sites	12
Table 2. Number of Cell Culture Bags and (b) (4)	17
Table 3: In-Process Controls (IPC) and In-Process Monitoring in the Manufacturing of the CF DS	18
Table 4. Statistical Process Control Analysis Results for CF DS IPCs.....	20
Table 5. Compendial Reagents and Media Components	24
Table 6. Non-Compendial Reagents and Media Components	26
Table 7. (b) (4) Tests and Acceptance Criteria.....	27
Table 8. (b) (4) Tests and Acceptance Criteria	27
Table 9. (b) (4) Tests and Acceptance Criteria	28
Table 10. (b) (4) Tests and Acceptance Criteria ...	28
Table 11. (b) (4) Tests and Acceptance Criteria	29
Table 12. (b) (4) Specification Tests and Acceptance Criteria.....	29
Table 13. Reagents and Media Components of Biological Origin Used to Manufacture the Cultured Fraction.....	30
Table 14. (b) (4) Irradiated Tests and Acceptance Criteria	32
Table 15. (b) (4) Tests and Acceptance Criteria	33
Table 16. (b) (4) Tests and Acceptance Criteria.....	34
Table 17. (b) (4) Tests and Acceptance Criteria	34

Table 18.	(b) (4)	Tests and Acceptance Criteria	35
Table 19.	(b) (4)	Reagent – Tests and Acceptance Criteria.....	37
Table 20.		Buffers, and Stock Solutions Used in Manufacturing of CF	38
Table 21.		Product-Contacting Materials	39
Table 22.		Source Material Acceptance Criteria	40
Table 23.		Critical Steps the Manufacturing the CF DS	41
Table 24.		CQAs for CF	43
Table 25.		Non-CQA for CF DP	43
Table 26.		Rating Score for Process Risk Assessment	44
Table 27.		Summary of High and Medium Risks Identified.....	44
Table 28.		Process Parameters in the Manufacturing of the CF DS	46
Table 29.		Phenotype Characterization of the CF During Manufacturing	49
Table 30.		Correlation and regression Analysis Demonstrating CF Attributes Correlated to Time to Engraftment (TtE).....	50
Table 31.		Phenotype Characterization of CF Pre-Freeze and Post-Thaw.....	52
Table 32.		Summary of studies evaluating impurities following washing during harvest	53
Table 33.	(b) (4)	Level Based on Manufacturing Experience	55
Table 34.		Study Design PMC Study to Monitor Residual (b) (4) in Omidubicel	57
Table 35.		Summary of safety Margin Data for (b) (4) Impurities	58
Table 36.		Summary of Risk from Other Cell Culture Impurities.....	60
Table 37.		Process Related in the CF DP.....	61
Table 38.		NF DS Manufacture.....	64
Table 39.		Process Parameters in the Manufacturing of the NF DS	66
Table 40.		CQAs for NF	67
Table 41.		Non-CQA for NF	67
Table 42.		Phenotype Characterization of NF Pre-Freeze and Post-Thaw.....	68
Table 43.		Risk Assessment for Manufacturing Residual Impurities in the NF DS	71
Table 44.		CF DP Analytical Method Development Summary	75
Table 45.		Comparison of Cell Density of the CF DP and QC Sample	77
Table 46.		Comparison of Phenotype Characterization of the Cells Before and After Filtration of the CF Product Sample and CF DP Bags.....	77
Table 47.		Summary of the Processing Design for (b) (4)	78
Table 48.		Statistical Assessment (TOST) for Comparability of KGI (b) (4) Confirmation Batches and Phase 3 Clinical Batches and ITT Phase 3 Clinical Batches.....	79
Table 49.		CF DP Manufacture and In-Process Testing Sites.....	80
Table 50.		Process Parameters in the Manufacturing of CF DP	84
Table 51.		COI Initiation and COC Tracking Systems	87
Table 52.		Summary of Systems and COI and COC	87
Table 53.		IPC for CF DP	89
Table 54.		CF IPC and Final CF DP Test Results	91
Table 55.		Critical Process and Key Process Parameters for CF	91
Table 56.		Summary Results for Cell Expansion in Different Bags for Intra-Batch Comparison	92
Table 57.		Impurities Clearance Study Design	93
Table 58.		Summary of Residual Levels (b) (4)	94
Table 59.		Summary of Residual Levels (b) (4)	94

Table 60. Cell Loss During Impurities Clearance Study (Report #RP131)	95
Table 61. Results for the CF Tests Prior Cryopreservation and Post-thaw	96
Table 62. Example of Omidubicel Manufacturing Schedule in one suite per one month	97
Table 63. Yearly Product Capacity Scale up	97
Table 64. CF In-Process and Release Test Results	99
Table 65. In-Process Monitoring in the Manufacturing of the CF DS	101
Table 66. (b) (4) Conditions for the (b) (4)	103
Table 67. Summary of Assay by (b) (4) Method Qualification Studies and Results	104
Table 68. Quality Control Specifications for CF DP	105
Table 69. Summary of Justification of Acceptance Criteria	108
Table 70. Potency Matrix Specifications Summary Data from Phase 3 study	109
Table 71. Statistical Process Control Analysis Results for CF DP	112
Table 72. Control Chart of the Number of (b) (4) Cells	118
Table 73. Summary of Validation Parameters	121
Table 74. Study Design of Automated Cell Count Assay Validation	123
Table 75. Summary of the Automated Cell Count Assay Validation Study Results	126
Table 76. Summary of Assay Validation Study Data	134
Table 77. Validation Parameters, Design and Acceptance Criteria	137
Table 78. Acceptance Criteria for CFU Assay Validation Study	138
Table 79. Summary CFU Assay Validation	139
Table 80. Details of storage cassette, tertiary packaging for CF and NF	144
Table 81. Manufacturers Specifications of the (b) (4) Freezing Bags	144
Table 82. Summary of CF DP Stability Studies	148
Table 83. Long-Term Stability Studies for CF DP	149
Table 84. Summary of Long-Term Stability Data for CF DP at Timepoint 6 weeks	150
Table 85. Summary of Long-Term Stability Data for CF DP at Timepoint 12 Weeks	151
Table 86. In-Use Stability Protocol for CF DP for 1h and 2 h at Room Temp	152
Table 87. Summary of In-Use Stability Data for CF DP	153
Table 88. In-Use Stability Protocol for CF Supportive Stability Study	154
Table 89. Summary of Supportive In-Use Stability Data for CF DP for (b) (4) days	155
Table 90. NF DP Manufacture and Testing Sites	158
Table 91. Process Parameters in the Manufacturing of NF DP	161
Table 92. IPC for NF DP	161
Table 93. Summary of NF PPQ Results	161
Table 94. Summary of the Results for the NF Shipping Validation Studies	162
Table 95. Quality Control Specifications for NF DP	163
Table 96. Justification of Specifications for NF DP Release Testing	164
Table 97. Summary of the SPC Analysis Using Phase 3 and KGI Batches	164
Table 98. Summary of Validation Parameters for the NF DP	166
Table 99. Stability Studies for NF DP	168
Table 100. Long-Term Stability Protocol for NF DP at T1 (Nine Weeks) and T2 (15 Weeks)	169
Table 101. Summary Long Term Stability Data for NF DP at 9 weeks	169
Table 102. Summary Long Term Stability Data for NF DP at 15 Weeks	170

Table 103. In-use Stability Protocol for NF DP for PPQ and Stability Batches following Storage for 9 weeks (T1) and 15 weeks (T2) at room temperature	170
Table 104. Summary of In-use Stability Data for NF DP Batches	171
Table 105. In-use Stability Protocol for NF Supportive Stability Study	172
Table 106. Summary of Supportive In-Use Stability Data for NF DP Stored for (b) (4) days	172
Table 107. IS Excipients.....	173
Table 108. IS DP Manufacturing Process Development Summary	174
Table 109. IS DP Analytical Method Development Summary	174
Table 110. Critical Quality Attributes for IS.....	175
Table 111. Key Process Parameters for IS	175
Table 112. CF DP Manufacture and In-Process Testing Sites	177
Table 113. IPC during IS Manufacturing	179
Table 114. Process Parameters for Manufacturing of IS.....	179
Table 115. IS Product-Contact Materials.....	180
Table 117. IS DP PPQ Results	181
Table 118. Shipping Validation Results.....	183
Table 119. IS DP Release Specifications.....	185
Table 116. Summary of Validation Parameters	188
Table 120. Summary of IS DP Batch Data Analysis.....	188
Table 121. Secondary Packaging Details for the IS.	190
Table 122 Information on the Refrigerated Shipping Container.	193
Table 123. Photostability Protocol for IS DP Batches	195
Table 124. Particulate Matter Stability of the Infusion Solution	196
Table 125. Table 30: Long-Term Stability Protocol for IS DP.....	197
Table 126. Long-Term (2-8°C) Stability Protocol for IS PPQ Batches.....	199
Table 127. Viral Risk Assessment for omidubicel	201
Table 128. Labels for Omidubicel and Their Location	206

Module 3

3.2.S DRUG SUBSTANCE [CULTURED FRACTION]

(b) (4)

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

(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-only, 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-only

The CF DP is an allogeneic, ex vivo expanded, hematopoietic CD34+ progenitor cell product. CF DP contains at least 8.0×10^8 TNVC with a minimum of 8.7% CD34+ cells and a minimum of 9.2×10^7 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 $\leq 150^{\circ}\text{C}$. (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) 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 $\geq 9.2 \times 10^7$ CD34+ cells and $\geq 8.7\%$ 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 $\leq -150^{\circ}\text{C}$ 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	$\geq 8.0 \times 10^8$	(b) (4)
% 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	$\geq 9.2 \times 10^7$	
(b) (4)	(b) (4)	(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)		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 $\leq -150^{\circ}\text{C}$. 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 84 and 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-only

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 4.0×10^8 TNVC and 2.4×10^7 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 $\leq -150^\circ\text{C}$.

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	$\geq 4.0 \times 10^8$	
Viability TNC		QC Sample	(b) (4)	
No. of CD3+ cells		QC Sample	$\geq 2.4 \times 10^7$	
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 Analyses 3.2.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 $\leq -150^{\circ}\text{C}$. 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 $\leq -150^{\circ}\text{C}$ three weeks longer and required a longer shelf life to ensure stability through 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 \pm 3 days	0	0, 1h, (b) (4)
	Long-Term/In-use	9 weeks \pm 3 days	0	0, 1h, (b) (4)
	Long-Term/In-use	9 weeks \pm 3 days	0	0, 1h, (b) (4)
	Long-Term/In-use	9 weeks \pm 3 days	0	0, 1h, (b) (4)
	Long-Term/In-use	15 weeks (b) (4)	0	0, 1h, (b) (4)
	Long-Term/In-use	15 weeks (b) (4)	0	0, 1h, (b) (4)
	Long-Term/In-use	15 weeks (b) (4)	0	0, 1h, (b) (4)
	Long-Term/In-use	15 weeks (b) (4)	0	0, 1h, (b) (4)
	Supportive In-use	7-14 days	0, (b) (4)	
	Supportive In-use	7-14 days	0, (b) (4)	
	Supportive In-use	7-14 days	0, (b) (4)	
	Supportive In-use	7-14 days	0, (b) (4)	

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 ($\leq -150^{\circ}\text{C}$) 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 $\leq -150^{\circ}\text{C}$ 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: $\geq 4.0 \times 10^8$ T1/T2: (b) (4)	X	X	X
% Viability of TNC		(b) (4)	X	X	X
No. of CD3+ viable cells		T0: $\geq 2.4 \times 10^7$ 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-only

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

(b) (4)

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)

(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)	(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.

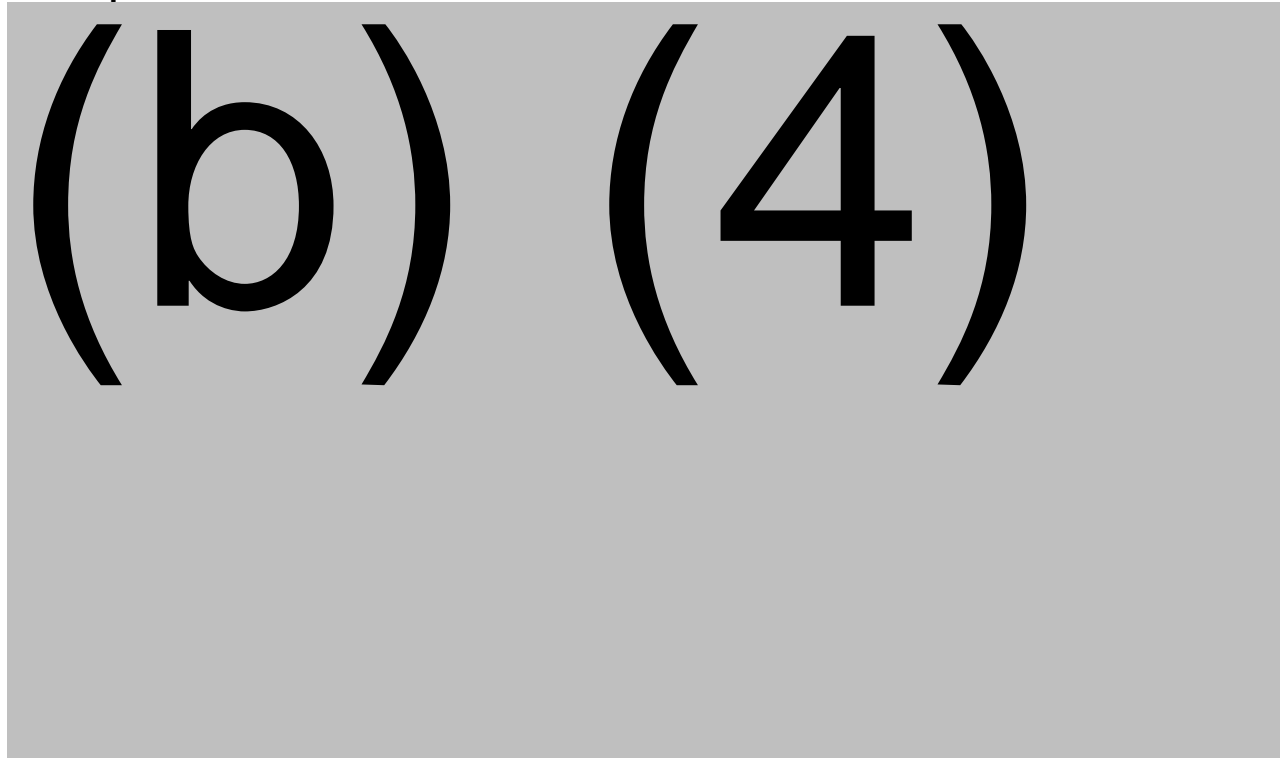
No reference standard is used in the testing and release of the IS DP.

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)

(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 Omisurge 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

 NDC 73441-100-01 omidubicel Nampluri™ Rx Only Cultured Fraction 1 Administer First FOR DESIGNATED RECIPIENT ONLY Name: Jack L. Smith DOB: DD-MMM-CCYY Batch: 1234567890 EXP: DD-MMM-CCYY Manufactured using CBU: ABC1234567890 Gamida Cell Patient ID: 12345678901 Hospital Patient ID: 0123456789012345 Mfd. by Gamida Cell Ltd. Jerusalem 91340, Israel (Kiryat Gat site) Distributed by Gamida Cell Inc. Boston, MA 02116, U.S. License #xxxxx Phone: (844) 477-7478 PK000106-2	omidubicel Nampluri™ Rx Only Allogeneic ex vivo expanded hematopoietic CD34+ progenitor cells Cultured Fraction Suspension for IV Infusion Dosage: See prescribing information. Infused FIRST, before the Non-cultured Fraction. Contents: One sterile bag for infusion. A minimum of 8.0×10^8 total viable cells with a minimum of 8.7% CD34+ cells and a minimum of 9.2×10^7 CD34+ cells cryopreserved in 10% DMSO Cultured Fraction total volume: ~20mL Ship and Store in Vapor Phase Liquid Nitrogen $\leq -150^\circ\text{C}$ Thaw Immediately Before Use To be DILUTED with INFUSION SOLUTION for Cultured Fraction. Total volume once diluted: ~100mL Complete infusion within 2 HOURS from end of dilution Do Not Use a Leukodepleting Filter Do Not Irradiate No Preservative, No US Standard of Potency Manufactured with gentamicin PK000105-2
--	--



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

Rx Only  NDC 73441-300-01	
omidubiceL Nampluri™	
Infusion Solution for Cultured Fraction	
Contents: 8% w/v HSA, 6.8% w/v Dextran 40 Dosage: See prescribing information. Solution volume: ~80mL	
FOR DESIGNATED RECIPIENT ONLY	
Name: Jack L. Smith DOB: DD-MMM-CCYY 	
Batch: 1234567890	
EXP: DD-MMM-CCYY	
Gamida Cell Patient ID: 123456789012 Hospital Patient ID: 0123456789012345	
Ship and store at 2-8°C	
Mfd. by Gamida Cell Ltd. Jerusalem 91340, Israel (Kiryat Gat site) Distributed by Gamida Cell Inc. Boston, MA 02116, U.S. License #xxxxx Phone: (844) 477-7478	
PK000107-2	

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

 NDC 73441-200-01 omidubicel Nampluri™ Rx Only Non-cultured Fraction 2 Administer Second FOR DESIGNATED RECIPIENT ONLY Name: Jack L. Smith DOB: DD-MMM-CCYY Batch: 1234567890 EXP: DD-MMM-CCYY Manufactured using CBU: ABC123 45 6789 Gamida Cell Patient ID: 123456789 Hospital Patient ID: 012345678 Mfd. by Gamida Cell Ltd. Jerusalem 91340, Israel (Kiryat Gat site) Distributed by Gamida Cell Inc. Boston, MA 02116, U.S. License #xxxxx Phone: (844) 477-7478 PK000104-2		omidubicel Nampluri™ Rx Only Allogeneic non-expanded cells Non-cultured Fraction Suspension for IV Infusion Dosage: See prescribing information. Infused SECOND, after the Cultured Fraction. Contents: One sterile bag for infusion. A minimum of 4.0×10^8 total viable cells with a minimum of 2.4×10^7 CD3+ cells cryopreserved in 10% DMSO Non-cultured Fraction total volume: ~10mL Ship and Store in Vapor Phase Liquid Nitrogen $\leq -150^\circ\text{C}$ Thaw Immediately Before Use To be DILUTED with INFUSION SOLUTION for Non-cultured Fraction. Total volume once diluted: ~50mL Complete infusion within 1 HOUR from end of dilution Do Not Use a Leukodepleting Filter Do Not Irradiate No Preservative, No US Standard of Potency PK000103-2
---	--	--

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

Figure 55. IS for NF DP Label

Rx Only  NDC 73441-400-01 omidubicel Nampluri™ Infusion Solution for Non-cultured Fraction Contents: 8% w/v HSA, 6.8% w/v Dextran 40 Dosage: See prescribing information. Solution volume: ~40mL FOR DESIGNATED RECIPIENT ONLY Name: Jack L. Smith DOB: DD-MMM-CCYY Batch: 1234567890 EXP: DD-MMM-CCYY Gamida Cell Patient ID: 123456789012 Hospital Patient ID: 0123456789012345 Ship and store at 2-8°C Mfd. by Gamida Cell Ltd. Jerusalem 91340, Israel (Kiryat Gat site) Distributed by Gamida Cell Inc. Boston, MA 02116, U.S. License #xxxxx Phone: (844) 477-7478 PK000108-2
--



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

 NDC 73441-100-01 Gamida Cell Patient ID: 123456789 Hospital Patient ID: 123456789 Batch: 1234567890	 NDC 73441-200-01 Gamida Cell Patient ID: 123456789 Hospital Patient ID: 123456789 Batch: 1234567890
omidubicel Nampluri™ Rx Only Container 1 of 2	omidubicel Nampluri™ Rx Only Container 2 of 2
Cultured Fraction Non-cultured Fraction	Infusion Solution for Cultured Fraction Infusion Solution for Non-cultured Fraction
SHIP TO: Transplant Center Name: Insert Name Address: Insert Address Telephone Number: Insert Number Receiver Name(s): List Names Product of Israel Manufactured For and Distributed By: Gamida Cell, Inc. Boston, MA, 02116 Telephone Number: (844) 477-7478	SHIP TO: Transplant Center Name: Insert Name Address: Insert Address Telephone Number: Insert Number Receiver Name(s): List Names Product of Israel Manufactured For and Distributed By: Gamida Cell, Inc. Boston, MA, 02116 Telephone Number: (844) 477-7478
Ship and Store in Vapor Phase Liquid Nitrogen ≤ -150°C DO NOT X-RAY Exempt Human Specimen	Ship and store at 2-8°C DO NOT X-RAY Exempt Human Specimen

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.