Summary Basis for Regulatory Action

Date:	April 17, 2023
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BLA STN:	BLA 125738/0
Applicant:	Gamida Cell Ltd.
Submission Receipt Date:	June 1, 2022
Action Due Date:	May 1, 2023
Proper Name:	omidubicel-onlv
Proprietary Name:	OMISIRGE
Indication:	Indicated for use in adults and pediatric patients 12 years and older with hematologic malignancies who are planned for umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection.

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

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Acting Director, Office of Clinical Evaluation

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Director, Office of Compliance and Biologics Quality

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Table of Contents

1. Introduction 4
2. Background 5
3. Chemistry, Manufacturing and Controls (CMC) 6
    a. Product Quality 6
    b. Testing Specifications 9
    c. CBER Lot Release 10
    d. Facilities Review / Inspection 11
    e. Container/Closure System 12
    f. Environmental Assessment 13
4. Nonclinical Pharmacology/Toxicology 13
5. Clinical Pharmacology 13
6. Clinical/Statistical 15
    a. Clinical Program 15
    b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance 16
    c. Pediatrics 16
    d. Other Special Populations 17
7. Safety and Pharmacovigilance 17
8. Labeling 19
9. Advisory Committee Meeting 19
10. Other Relevant Regulatory Issues 19
11. Recommendations and Benefit/Risk Assessment 19
    a. Recommended Regulatory Action 20

b. Benefit/Risk Assessment 20
c. Recommendation for Postmarketing Activities..... 20

1. Introduction

Gamida Cell Ltd. submitted the biologics license application (BLA) 125738 to market omidubicel-onlv (OMISIRGE), an ex vivo expanded allogeneic human hematopoietic CD34+ progenitor cell therapy indicated for use in adults and pediatric patients 12 years and older with hematologic malignancies who are planned for umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection.

OMISIRGE is comprised of two components 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. The CF drug product (DP) contains at least 8.0 x 10^8 total number viable cells (TNVC) and at least 9.2 x 10^7 CD34+ cells with a minimum of 8.7% CD34+ cells suspended in approximately 20 mL of cryopreservation solution. The NF DP contains at least 4.0 x 10^8 TNVC and at least 2.4 x 10^7 CD3+ cells in 10 mL of cryopreservation solution. The CF DP and NF DP are individually cryopreserved until thawed for infusion and administered sequentially. 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.

This document summarizes the basis for regular approval of OMISIRGE. A single clinical trial, Study GC P#05.01.020 (referred to as Study P0501 henceforth), provides the primary evidence of safety and effectiveness for the BLA submission. Study P0501 is a randomized, open-label, multicenter, Phase 3 study comparing transplantation of OMISIRGE to transplantation of one or two unmanipulated unrelated umbilical cord blood units (UCBUs) in subjects 12 to 65 years old with hematologic malignancies who underwent myeloablative conditioning.

The recommendation for approval is based on the reduction in time to neutrophil recovery and the incidence of infection in adult and adolescent subjects 12 years and older who received OMISIRGE compared to those who received UCBU. The median time to neutrophil recovery was 12 days versus 22 days, respectively. The incidence of BMT CTN Grade 2/3 bacterial or Grade 3 fungal infection through Day 100 following transplantation was 39% versus 60%, respectively. The safety profile was consistent with the known toxicities following allogeneic hematopoietic stem cell transplantation (HSCT). The review team concludes that the Applicant has provided substantial evidence of effectiveness and safety based on a single adequate and well controlled trial with confirmatory evidence.

The review team recommends regular approval of this BLA with the following Chemistry, Manufacturing, and Control (CMC) Postmarketing Commitments (PMCs):

- Gamida Cell Ltd. commits to perform a residual (b) (4) impurities study with the OMISIRGE to provide assurance that residual (b) (4) levels remain within the established manufacturing range of less than (b) (4) per batch.

- Gamida Cell Ltd. commits to execute a real process (b) (4) study of the final container closures for OMISIRGE to include CF, NF and IS for (b) (4) (b) (4) over its manufacturing and storage.
- Gamida Cell Ltd. commits to notify the FDA when contacted by the master file (MF) holder that the MF (b) (4) concerns are adequately resolved.

2. Background

Allogeneic HSCT is a well-established treatment for hematologic diseases that cannot be cured with conventional treatments. Successful blood and marrow transplantation requires the infusion of a sufficient number of hematopoietic stem/progenitor cells capable of both homing to the bone marrow and regenerating a full array of hematopoietic cell lineages. Although several options for a stem cell donor for transplantation exist, each option has limitations; therefore, these patients still have a serious unmet medical need.

HLA-matched donors, whether related or unrelated, are often not available or are difficult to procure in a timely manner, especially for diverse ethnic/racial groups. Alternative donor sources, including mismatched unrelated donors, haploidentical (haplo)–related donors, and umbilical cord blood transplantation (UCBT), are partially HLA-mismatched. UCBT has been used clinically and matching requirements are less stringent than those from unrelated donors, leading to a greater probability for finding a match. However, an important limitation of UCBT being used as the source for HSCT is the low number of HSPCs in each unit, leading to a prolonged time to engraftment and, thus, a higher rate of post-transplant complications, including infections, longer hospitalization time, and an increase in transplant-related mortality.

There are currently no marketed products that are designed to be used as HSCT graft sources that are indicated to reduce the time to neutrophil recovery or reduce the incidence of bacterial and fungal infections in patients with hematologic malignancies planned for UCBT following myeloablative conditioning.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting (PTS# PS000984)	February 18, 2010
2. IND submission (IND 14459)	August 5, 2010
3. IND allowed to proceed	September 3, 2010
4. Breakthrough Therapy designation granted	October 7, 2016
5. Orphan Drug designation granted (ODD # DRU-2018-6375)	May 23, 2018 and amended August 28, 2018 (designation date remains May 23, 2018)
6. Pre-BLA meeting	November 9, 2021
7. BLA 125738/0 submission – final module of rolling BLA received	June 1, 2022
8. BLA filed	July 28, 2022
9. Mid-Cycle communication	October 3, 2022
10. Pre-license Inspection	October 18 – 25, 2022
11. Major Amendment	November 15, 2022
12. Late-Cycle Meeting	February 23, 2023
13. Action Due Date	May 1, 2023

3. Chemistry, Manufacturing and Controls (CMC)

a. Product Quality

The review team concludes that the OMISIRGE manufacturing process and controls can yield a product with consistent quality attributes, and the CMC review team recommends approval.

Product Description
OMISIRGE contains two cell fractions from the same allogeneic CBU. The CF is a yellowish suspension of (b) (4) selected hematopoietic CD34+ progenitor cells ex vivo cultured with nicotinamide (NAM). In addition to the CD34+ progenitor cells, the CF consists of other cell populations, including lineage committed myelomonocytic cells, dendritic cells and granulocytes. The NF is a reddish suspension consisting of allogeneic, hematopoietic mature myeloid and lymphoid cells collected from the (b) (4) non-selected cells. Two IS bags are provided for diluting each fraction after thawing, one specifically for the CF and one specifically for the NF. The IS contain 8% w/v HSA and 6.8% w/v Dextran 40 in 0.9% sodium chloride.

Manufacturing Summary
The manufacturing of OMISIRGE starts when patient matched allogeneic CBUs from eligible donors are selected from US cord blood banks and shipped to the Gamida Cell Ltd. manufacturing facility. OMISIRGE is manufactured from a single cryopreserved CBU. The thawed CBU cells undergo (b) (4) reagent and the (b) (4) instrument. The (b) (4) selected cells are then cultured at approximately (b) (4) containing culture medium with

(b) (4)
After (b) (4) the cells are harvested and washed by a (b) (4) processing system. The CF is resuspended in approximately 20 mL of cryopreservation solution containing 10% dimethyl sulfoxide, filtered across a (b) (4) filter directly into the attached cryopreservation bag. The final CF contains at least 8 x 10^8 TNVC and at least 9.2 x 10^7 CD34+ cells and a minimum of 8.7% CD34+ cells. The CF is stored at ≤ -150°C.

The NF is manufactured from cells eluted during the CF (b) (4) selection process. The NF is washed and formulated in approximately 10 mL of cryopreservation solution containing 10% dimethyl sulfoxide, filtered across a (b) (4) filter directly into the attached cryopreservation bag. The final NF contains at least 4 x 10^8 TNVC and at least 2.4 x 10^7 CD3+ cells. The NF is stored at ≤ -150°C.

Manufacturing Controls
The manufacturing control strategy includes: 1) specifying chain of identity and chain of custody (COI/COC), 2) raw material and reagent qualification programs, 3) in-process monitoring and control testing, 4) validation of manufacturing process, and 5) release testing. The source material is a patient matched CBU and the manufacturer maintains control and traceability from the receipt of the CBU through shipment of the product to the transplant center. The manufacture maintains a raw material and reagent qualification program consisting of vendor qualification, and confirmation of certificate of analysis and material testing. In-process monitoring and controls are implemented throughout the process to support process consistency, and testing includes multiple timepoints (b) (4) Lot release testing is performed on material collected at appropriate stages of the manufacturing process to evaluate product safety and function. Product testing on the formulated drug product include sterility, endotoxin, purity, identity, appearance, and mycoplasma (CF only). The CF is available for infusion based on a rapid contamination test and (b) (4) (b) (4) results, while the final (b) (4) sterility and (b) (4) (b) (4) forming unit results are still pending.

Process Validation
The Applicant validated the processes at the commercial manufacturing site, Gamida Cell Kiryat Gat Israel, using (b) (4) full scale batches manufactured from research grade CBUs and supplemented with an additional (b) (4) full scale batches following a revised (b) (4) procedure. The process validation was assessed against established process parameters and predefined release criteria. The process validation did not demonstrate the removal of all cell culture related impurities, specifically (b) (4) and (b) (4) The Applicant addressed this by revising the (b) (4) procedure to (b) (4) and provided batch data from additional (b) (4) full scale manufacturing runs using the revised methodology. Shipping and stability of the final products were established using full scale batches in a real time study.

Manufacturing Risks, Potential Safety Concerns, and Management
Transmission of infectious diseases is controlled by reagents, and control of the manufacturing process. The CBU starting donor material is controlled by donor

screening and testing, qualification of public cord blood collection sites, and CBU acceptance requirements. The risk mitigation measures include segregation activities during the manufacturing process, use of closed manufacturing processes (when possible), all aseptic operations performed in a positive pressure laminar flow cabinet in a Class (b) (4) Clean room, operator training and use of personal protective equipment, use of sterile single use materials, validated cleaning procedures, and environmental monitoring.

Drug Product Stability and Shelf life
Real-time long-term stability studies determined the CF is stable for 12 weeks and the NF is stable for 15 weeks when each is stored at ≤ -150°C in the final container closure. Real-time long-term stability studies determined that the IS is stable for five months when stored at 2 to 8°C in the final container closure. After thawing and dilution with the IS, the CF and NF in the final container closure are stable for up to (b) (4) hours at room temperature.

Comparability
The current manufacturing process at KGI produces CF, NF and IS with critical quality attributes that are comparable to those of clinical lots used in Study P0501.

CMC PMCs
The CMC team recommends three PMCs. The rationale for the PMCs is described below and the PMC agreements are detailed in Section 11c of this document:

1. The Applicant quantified the residual (b) (4) in (b) (4) full-scale batches following the latest modification to the commercial manufacturing process and an additional (b) (4) full-scale batches as part of the investigation. The data and estimated residual amounts based on Study P0501 support the predicted low residual amount. However, the Applicant has provided quantitative data from a small number of batches due, in part, to limited clinical manufacturing experience at the commercial manufacturing facility. Therefore, the Applicant should conduct a PMC study to quantify the residual (b) (4) OMISIRGE over the course of a year to confirm that the amount of residual (b) (4) in OMISIRGE is within the demonstrated range.

2. The Applicant provided a risk assessment of elemental extractables from materials in direct contact with OMISIRGE but did not conduct a real process study to evaluate elemental extractables. Therefore, the Applicant should assess elemental leachables in a real process study, or relevant simulated study.

3. To support the manufacturing of the CF, the applicant cross-references the CBER MF (b) (4) for information regarding the (b) (4) reagent. The cross-referenced MF contains insufficient information to support the use of the (b) (4) reagent in manufacturing the CF. The MF Holder, (b) (4) has committed to resolve the issues and provided an acceptable plan to address the concerns. To support use of the (b) (4) reagent, the Applicant should communicate with (b) (4) on the timeline to address the identified concerns and request notification when the MF concerns are adequately resolved by the MF Holder with the FDA, and for the Applicant to commit to notify the FDA. This is to ensure the Applicant is aware

of outstanding commitments from the MF Holder without sharing the specific details.

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for OMISIRGE were found to be adequate for their intended purpose. The lot release specifications for the CF, NF, and IS are shown in Table 2, Table 3, and Table 4, respectively.

Table 2. Cultured Fraction Lot Release Specifications

Attribute	Acceptance criteria
Appearance	Yellowish suspension, essentially free of visible white clumps and foreign particulates
Total number viable cells	≥ 8.0 x 0^8
(b) (4)	(b) (4)
% CD34+ cells	≥ 8.7
(b) (4)	(b) (4)
Number of CD34+ cells	≥ 9.2 x 10^7
Number of (b) (4) cells	(b) (4)
Number of (b) (4)	(b) (4)
CD34+ fold increase (Potency)	(b) (4)
Total colony forming units (b) (4)	(b) (4)
Total colony forming units harvest day	(b) (4)
Rapid contamination test	Not detected
Sterility[1]	No growth
Mycoplasma content	Not detected
Endotoxin content	(b) (4) (Total includes IS, CF and NF)

[1] Results available after Infusion for Final Release.

Table 3. Non-Cultured Fraction Lot Release Specifications

Attribute	Acceptance criteria
Appearance	Reddish suspension, essentially free of visible clumps and foreign particulates
Total number viable cells	≥ 4.0 x 10^8
(b) (4)	(b) (4)
Number of CD3+ cells	≥ 2.4 x 10^7
Sterility	No growth
Endotoxin content	(b) (4) (Total includes IS, CF and NF)

Table 4. Infusion Solution Lot Release Specifications

Attribute	Acceptance criteria
(b) (4)	

The analytical methods and their validations and/or qualifications reviewed for the OMISIRGE drug product and infusion solution were found to be adequate for their intended use.

c. CBER Lot Release

CBER Lot release and testing, including the submission of product samples to CBER, is not required. The basis for this decision is that each lot is a single OMISIRGE unit that

will treat a single patient. Lot release testing would negatively impact the often-limited quantity of cells available to the patient, and failure of a single lot will have minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of omidubicel-onlv are listed in the table below. The activities performed and inspectional history are noted in Table 5.

Table 5. Manufacturing Facilities Table for OMISIRGE (omidubicel)

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
Gamida Cell Ltd. Leshem 12 (b) (4) *Drug substance and drug product manufacturing, and drug product release testing*	3017482905	532501574	PLI	CBER/DMPQ October 2022 NAI
(b) (4)			Waiver	ORA (b) (4) VAI (b) (3) (A)
			Waiver	ORA (b) (4) NAI
			Waiver	ORA (b) (4) NAI
			Waiver	ORA (b) (4) VAI (b) (3) (A)

Acronym key: (b) (3) (A); DMPQ: Division of Manufacturing and Product Quality; HSA: human serum albumin; (b) (3) (A) ORA: Office of Regulatory Affairs; PLI: pre-license inspection; NAI: No Action Indicated; VAI: Voluntary Action Indicated

CBER conducted a PLI of Gamida Cell Ltd. in October 2022 for omidubicel-onlv drug substance and drug product manufacturing. A Form FDA 483 list of observations was not issued, and the inspection was classified as NAI.

(b) (3) (A)

ORA performed a pre-approval inspection (PAI) of (b) (4) in (b) (4) in (b) (4) A Form FDA 483 list of observations was not issued, and the inspection was classified as NAI.

ORA performed a PAI of (b) (4) in (b) (4) in (b) (4) (b) (4) A Form FDA 483 list of observations was not issued, and the inspection was classified as NAI.

(b) (3) (A)

e. Container/Closure System

Omidubicel-onlv drug product consists of cultured cell fraction (CF) and non-cultured cell fraction (NF) components, and each component is independently filled and cryopreserved in a sterile, single-use, (b) (4) freezing bag. One 50 mL bag is used for NF and one 250 mL bag is used for CF. The bags containing cryopreserved cells are thawed and diluted with infusion solution (IS). The IS is filled in 50 mL and 250 mL (b) (4) bags. The (b) (4) bags are made of (b) (4) and supplied by (b) (4)

(b) (4) performed the container closure integrity testing at the (b) (4) (b) (4) employing the (b) (4) test method; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

In vitro pharmacology studies evaluating the effects of nicotinamide (NAM) on the phenotype of (b) (4) cells indicated an increase in non-differentiated early progenitor cells following in vitro culture and increased migratory potential of CD34+ cells towards (b) (4) in a (b) (4) assay.

In vivo pharmacology, pharmacokinetic, and toxicology studies were conducted to evaluate the activity, distribution, and safety of the product in immunocompromised, irradiated mice. Studies evaluating (b) (4) cells cultured with NAM and cytokines (b) (4) (b) (4) in nonobese diabetic/severe combined immunodeficiency (NOD/SCID) mice at 1.2 x 10^6 to 1 x 10^7 cells/mouse (approximately 4.8 x 10^7 to 4 x 10^8 cells/kg) showed an increased overall engraftment (as measured by (b) (4) cells in the bone marrow) compared to (b) (4) cells cultured with cytokines only or unmanipulated cells. Cell distribution data showed the expected widespread distribution of cells following intravenous administration, and engraftment was observed through 6 weeks post-infusion, which was the longest time point evaluated. In the toxicology study, there were no adverse findings related to the test article.

The genomic integrity was evaluated using cytogenic and karyotype analysis. Results showed no difference in the occurrence of chromosomal abnormalities between the CF, NF, and control cells and no evidence of clonal aneuploidy.

No carcinogenicity or reproductive and developmental toxicity studies were conducted with OMISIRGE. These studies are not warranted based on the product characteristics and safety profile.

5. Clinical Pharmacology

The data supporting the clinical pharmacology of OMISIRGE is based on two clinical studies that included pharmacodynamic (i.e., immune reconstitution) and dose-response assessments. The precise mechanism of action of action of OMISIRGE is unknown. Like transplantation with UCBU, following single dose administration of OMISIRGE the hematopoietic progenitor cells migrate to the bone marrow where they divide and mature. The mature cells are released into the blood, where some circulate and others migrate to tissue sites, partially or fully restoring blood counts and function including immune function.

Immune cell reconstitution (IR) after a HSCT is a dynamic process which includes the recovery of the lymphoid cell subsets and maturation of T-cells in the thymus including the induction and generation of a diverse, de-novo lymphocyte repertoire. Thus, the IR

analysis serves as a pharmacodynamic (PD) endpoint and provides supportive clinical evidence for OMISIRGE effectiveness.

The initial study (Study P0301) demonstrated an increased trend in the reconstitution of CD4+ T cells, CD8+ T cells and CD19+ B cells. In the pivotal study (Study P0501) a total of 37 subjects were included in the IR sub-study of which 17 were transplanted with OMISIRGE and 20 with UCBU. The recovery of CD4+ and CD8+ T cells were significantly higher in the OMISIRGE treated group on Days 7 and 14 compared to UCBU, which suggests early immune recovery. The CD4+ and CD8+ cell counts were similar in the two groups from Day 21 to 1 year. The recovery of Natural Killer (NK) cells (CD56+) and B-cells (CD19+) were generally comparable between the OMISIRGE and UCBU treated groups. A positive correlation between the CD34+ cell dose, and the reconstitution of T-cells (CD3+, CD4+ and CD8+ cells) and NK cells was identified.

Dose-efficacy assessment was conducted using a linear model between cell characteristics and days to neutrophil engraftment or recovery (Study P0501 or combined Study P0301 and P0501). The linear regression models showed a significant association between each cell characteristic tested (total nucleated cells (TNC), TNC/kg, CD34+ cells, and CD34+ cells/kg) and the time to neutrophil engraftment/recovery. The model estimated that time to neutrophil engraftment/recovery decreased with an increase in the administered dose of total nucleated cell dose (TNC) and CD34+ cells. For the pivotal study, the median (min, max) time to neutrophil recovery for OMISIRGE treated groups was 13 days (7, 35 days) and 8 days (6, 20) for subjects who received lower and higher than the median CD34+ cells/kg, respectively.

Graft failure and disease relapse are an indication of failure of the transplant procedure and was therefore also analyzed as part of dose-efficacy assessment. Primary graft failure was defined as failure to achieve neutrophil engraftment by Day 42.

- Primary graft failure occurred in two subjects who received lower than the median dose of CD34 cells/kg.
- The median (Min, Max) CD34 cells/kg (x 10^6) in subjects with and without primary graft failure was 4.9 (4,5.8) and 10.3 x 10^6 (2.1, 47.6), respectively.
- There was no statistically significant relationship between dose and disease relapse.

Dose-safety assessment was evaluated based on cell characteristics and selected adverse event such as acute graft versus host disease(aGvHD) and chronic GvHD(cGvHD). The dose-safety relationship is essentially flat suggesting that an increase in dose did not result in an increase in adverse events of interest such as aGvHD and cGvHD.

Overall, the clinical pharmacology analysis supports the proposed single dose administration of OMISIRGE with minimum of 12 x 10^8 TNC (from both CF and NF), and minimum of 9.2 x 10^7 CD34+ cells (from CF).

6. Clinical/Statistical

a. Clinical Program

Study P0501 forms the basis for the clinical review teams' recommendation for regular approval of OMISIRGE for use in adults and pediatric patients 12 years and older with hematologic malignancies who are planned for umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection.

Study P0501 is a randomized, open-label, multicenter, Phase 3 study comparing transplantation of OMISIRGE to transplantation of one or two unmanipulated unrelated UCBUs in subjects 12 to 65 years old with hematologic malignancies who underwent myeloablative conditioning. The primary endpoint was time to neutrophil engraftment, defined as achieving an absolute neutrophil count (ANC) ≥0.5 Gi/L on three consecutive measurements on different days on or before Day 42 with subsequent donor chimerism (>90% donor cells) on or before Day 100 following transplantation. Secondary endpoints included the incidence of Grade 2/3 bacterial or Grade 3 fungal infections.

One-hundred twenty-five subjects were enrolled; 62 subjects were randomized to the OMISIRGE treatment arm and 63 subjects were randomized to the unmanipulated UCBU treatment arm.

The median time to neutrophil engraftment was 12 days (95% confidence interval [CI]: 10, 16) in the OMISIRGE arm compared to 22 days (95% CI: 19, 25) in the UCBU arm ($p<0.001$). Therefore, the primary objective was considered to have been met.

The Applicant is seeking approval of OMISIRGE for the indication: "For the treatment of patients with hematologic malignancies in need of a hematopoietic stem cell transplant."

Although the trial was considered positive, the design of the trial did not support the proposed indication since it was not designed to demonstrate an effect on an endpoint relevant to the treatment of hematologic malignancies (e.g., complete remission or overall survival). Additionally, the prespecified primary endpoint was a composite of efficacy (time to neutrophil recovery) and safety (donor chimerism) assessed with different windows of follow-up (42- and 100-days following transplantation), and this combination of parameters did not clearly describe clinical benefit for the intended population. This presented a challenge in determining an appropriate indication statement supported by the data. Although UCBT offers a readily available graft source to patients who might not otherwise have an available matched donor source, a significant disadvantage of UCBT compared with transplantation from other donor sources is delayed hematopoietic recovery, including neutrophil recovery, and increased serious and life-threatening infections. Infection in the setting of severe neutropenia is one of the most common causes of non-relapse mortality (NRM) in the early post-transplantation period, and FDA considers a reduction in infection to be direct evidence of clinical benefit for interventions affecting myelopoiesis.

The Agency's determination of clinical benefit was therefore based on time to neutrophil recovery with 42 days of follow-up (without consideration of donor chimerism) and the

incidence of Blood and Marrow Transplant Clinical Trials etwork (BMT CTN) Grade 2/3 bacterial or Grade 3 fungal infection through Day 100 following transplantation in subjects who received OMISIRGE compared with those receiving UCBT, the latter of which was a prespecified key secondary endpoint. The median time to neutrophil recovery was 12 days versus 22 days, respectively, with an absolute difference of 10 [95% CI: 6, 14] fewer days to recovery in the OMISIRGE arm. The incidence of BMT CTN Grade 2/3 bacterial or Grade 3 fungal infection through Day 100 following transplantation was 39% versus 60%, respectively (absolute difference 22% [95% CI: 4, 39]). A treatment effect was observed across the subpopulation analyses as well.

The study, as designed, demonstrates a clinically meaningful benefit with OMISIRGE and addresses an unmet need for a graft option that addresses the limitations of standard UCBT by reducing the time to neutrophil recovery and the incidence of infection in subjects with hematologic malignancies who are planned for UCBT following myeloablative conditioning. Therefore, the Applicant's proposed indication statement was revised to reflect this assessment.

Efficacy was supported by Study P0301, a Phase 1/2 open-label, single-arm study of omidubicel in adolescent and adult subjects with hematologic malignancies undergoing allogeneic HSCT. The incidence of infections through Day 100 following transplantation was not a protocol-specified analysis for Study P0301. However, per protocol, data on infections were collected through at least Day 180 in the post-transplantation period, and the Applicant provided a data file with grading by BMT CTN criteria in the submission. Based on a post-hoc analysis of these data, the incidence of BMT CTN Grade 2/3 bacterial or Grade 3 fungal infections through Day 100 following transplantation in subjects who received single-unit omidubicel was 19% (7/36). These data were considered supportive of the incidence of infection seen in the omidubicel arm of Study P0501.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspection assignments were issued for four domestic Clinical Investigators (CI) who participated in the conduct of Study P0501. The inspections did not reveal substantive issues that impact the data submitted in this original BLA.

c. Pediatrics

The safety and efficacy of OMISIRGE have been established in adolescents (12 to < 17 years old). The results of Study P0501 suggest consistent efficacy across age groups studied. OMISIRGE is exempt from Pediatric Research Equity Act (PREA) requirements as it has orphan drug designation (ODD). OMISIRGE was granted ODD for "the treatment of myeloablation" and the indication was amended to "enhancement of cell engraftment and immune reconstitution in subjects receiving hematopoietic stem cell transplant." The review team and the Office of Orphan Products Development concluded that the indication under consideration for OMISIRGE is encompassed under the broader

ODD indication, as neutrophil recovery is considered to be a subset of immune reconstitution.

d. Other Special Populations

Clinical studies of OMISIRGE did not include subjects 65 years and older; therefore, we cannot determine whether subjects 65 years and older respond differently from younger subjects. However, given the mechanism of action of OMISIRGE, efficacy is expected to be similar across all adults and may be extrapolated to the full adult population.

7. Safety and Pharmacovigilance

The safety population in Study P0501 included 108 subjects: 52 subjects were treated with OMISIRGE and 56 subjects with UCBU. These data were supported by safety data from subjects with hematologic malignancies and hemoglobinopathies who were treated with OMISIRGE in single-arm trials, with a total of 117 subjects treated with OMISIRGE.

In Study P0501:

- Deaths were reported in 12 (23%) subjects who received OMISIRGE compared to 20 (36%) subjects who received UCBU.
    - Fatal adverse reactions (excluding death from disease relapse):
        - Among subjects treated with OMISIRGE, common causes of death were infections (6%), acute GvHD (6%), and relapse (6%). One subject each died of pulmonary hemorrhage, thrombotic microangiopathy, and veno-occlusive disease (VOD) / sinusoidal obstruction syndrome (SOS).
        - In subjects treated with UCBU, the most common causes of death were infection or septic shock (11%), respiratory disorders (11%), disease relapse (7%), and GvHD (5%). One subject died of VOD/SOS.
- Serious adverse events (SAEs) occurred in 90% (47/52) of subjects who received OMISIRGE compared to 91% (51/56) of subjects who received UCBU.
- Grade 3 or higher treatment emergent adverse events (TEAEs) occurred in 51 (98%) and 53 (95%) subjects treated with OMISIRGE and UCBU, respectively.
- The most common non-laboratory Grade 3 or higher TEAEs occurring in >10% of subjects treated in the:
    - OMISIRGE-treated arm included: pain (33%), mucosal inflammation (31%), hypertension (25%), gastrointestinal toxicity (19%), dysphagia (12%), hemorrhage (12%), respiratory failure (12%), and renal impairment (12%), and
    - in the UCBU arm included: hypertension (38%), mucosal inflammation (34%), gastrointestinal toxicity (34%), respiratory failure (30%), fatigue (21%), hemorrhage (18%), pain (18%), dyspnea (16%), dysphagia (12%), and pyrexia (11%).
- Most common adverse events of special interest (AESIs) that occurred in subjects treated with OMISIRGE included: infections (49 [94%]), acute GvHD (32 [62%]), infusion reaction (29 [56%]), and chronic GvHD (18 [35%]); and in subjects

treated with UCBU included: infections (56 [100%]); infusion reaction (40 [71%]); acute GvHD (24 [43%]); and chronic GvHD (14 [25%]).

- Infections:
  - Over the study follow-up period, 94% of subjects in the omidubicel arm and 100% of subjects in the UCBU arm experienced an infection of any kind. A comparison of infections in the omidubicel versus UCBU arms, respectively, is summarized below:
    - Bacterial: Any grade: 65% versus 80%; Grade 2: 27% versus 46%; Grade 3: 8% versus 23%
    - Fungal: Any grade: 21% versus 27%, Grade 2: 4% versus none, Grade 3: 6% versus 18%
    - Viral: Any grade: 75% versus 80%, Grade 2: 48% versus 32%, Grade 3: 8% versus 27%
- GVHD:
  - Acute GvHD Grade II to IV occurred in 62% of subjects treated with OMISIRGE versus 43% of subjects treated with UCBU. Acute GvHD Grade III to IV occurred in 15% versus 21% of subjects in the OMISIRGE and UCBU arms, respectively.
  - Chronic GvHD was reported in 35% of subjects treated with OMISIRGE and 25% of subjects treated with UCBU. Mild, moderate, and severe cGVHD were reported in 12%, 19%, and 4% of subjects who received OMISIRGE , and 5%, 16%, and 4% of subjects who received UCBU.
- Infusion reactions:
  - The most common infusion reactions included hypertension, mucosal inflammation, arrhythmia, and fatigue.
  - Grade 3 to 4 infusion reaction occurred in 9 (17%) subjects in the OMISIRGE arm and in 12 (21%) subjects in the control arm.

Assessment of graft function was essential to ensure there was no detriment introduced by manipulation of the graft source.

- Primary graft failure occurred in one (2%) subject treated with OMISIRGE, compared to six (11%) subjects receiving UCBU.
- Chimerism data showed that the proportion of subjects who achieved >90% donor chimerism by Days 28, 42, and 100 in the OMISIRGE arm were numerically higher than or similar to the UCBU arm at all timepoints.

- Relapse of underlying hematologic malignancy was numerically higher in subjects treated with OMISIRGE: 21% (11/52) compared to 13% (7/56) in the UCBU arm in Study P0501. However, the difference between arms is <10% and the study population is heterogeneous with regard to hematologic malignancy diagnosis and disease-specific risk factors (including risk categorization and baseline disease status, which ranged from acute leukemia in CR1 to CR3, MDS with ≤10% blasts, CML of varying phase, and lymphoma in CR, partial response, or stable disease). Therefore, a firm conclusion cannot be drawn regarding the observed numerical difference in relapse rate.

- The most common Grade 3 to 4 laboratory abnormalities reported in subjects treated with OMISIRGE or UCBU were neutropenia, lymphopenia, thrombocytopenia, anemia, increased alanine aminotransferase, increased aspartate aminotransferase, and hyperbilirubinemia.
- A total of 37 subjects were included in an immune reconstitution sub-study of which 17 were transplanted with OMISIRGE and 20 with UCBU. The recovery of CD4+ and CD8+ T cells were significantly higher in the OMISIRGE group on Days 7 and 14 compared to the UCBU group, suggesting early immune recovery. The CD4+ and CD8+ cells were similar in the two arms from Day 21 to 1 year. The recovery of NK cells (CD56+) and B cells (CD19+) were generally comparable between the OMISIRGE and UCBU-treated groups.

These safety findings in Study P0501 were similar to the safety profile of OMISIRGE in the full safety population.

8. Labeling

The proposed proprietary name, (b) (4) was reviewed by the Advertising and Promotional Labeling Branch (APLB) on August 30, 2022, and was found unacceptable. CBER communicated the unacceptability of the proprietary name to the Applicant on September 7, 2022.

The proposed proprietary name, OMISIRGE, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on December 12, 2022, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on December 16, 2022.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed prescribing information and container and package labels on April 6, 2023, and found them acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

No advisory committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

This application received Priority Review, Breakthrough Therapy and Orphan designations.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness and safety based on a single adequate and well controlled trial with confirmatory evidence. Study P0501 represents an adequate and well-controlled study that provided substantial evidence of effectiveness in support of regular approval. Efficacy is based on a significant reduction in the time to neutrophil recovery as well as evidence of direct clinical benefit as measured by a decreased incidence of BMT CTN Grade 2/3 bacterial or Grade 3 fungal infection through Day 100 following transplantation compared to subjects receiving UCBU in the randomized pivotal trial. These findings represent a clinically meaningful effect on severe or irreversible treatment-related morbidity for the study population. The results of Study P0501 were supported by additional evidence from Study P0301 which showed a similarly low incidence of BMT CTN Grade 2/3 bacterial and Grade 3 fungal infections through Day 100 following transplantation in subjects who received omidubicel.

The review team recommends regular approval of OMISIRGE indicated for use in adults and pediatric patients 12 years and older with hematologic malignancies who are planned for umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection.

b. Benefit/Risk Assessment

The clinical benefit of OMISIRGE was based on reduction of time to neutrophil recovery and incidence of bacterial and fungal infection in subjects with hematologic malignancies undergoing myeloablative conditioning followed by UCBT compared to subjects receiving standard UCBT. Therefore, OMISIRGE addresses an unmet need for a graft option that addresses known limitations of standard UCBT.

No detriment to graft function was observed with OMISIRGE in comparison to UCBT. The risks of OMISIRGE relate to its mechanism of action as an UCBT product. These include infusion reaction, GvHD, graft failure, and malignancies of donor origin and can be managed by routine pharmacovigilance.

The review of the BLA clinical and safety data provides a favorable benefit/risk profile for OMISIRGE.

c. Recommendation for Postmarketing Activities

Three CMC postmarketing commitments were proposed by FDA and agreed upon by the Applicant during review of the BLA.

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 (b) (4) batches for each number

of (b) (4) used in manufacturing (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