U.S. FOOD & DRUG ADMINISTRATION

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Pharmacovigilance
Division of Pharmacovigilance

Pharmacovigilance Review Memorandum

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Through:	Kerry Welsh, MD, PhD Branch Chief, PB3, DPV, OBPV Meghna Alimchandani, MD Deputy Director, DPV, OBPV
Subject:	Pharmacovigilance Plan Review
Sponsor:	Gamida Cell Ltd.
Product:	OMISIRGE™ (omidubicel)
Proposed Indication:	(b) (4)
Submission Type/Number:	BLA 125738/0
Submission Date:	June 1, 2022
Action Due Date:	May 1, 2023

1. OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA 125738/0 based on the safety profile of omidubicel. Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for omidubicel, should the indication for this product be approved.

2. BACKGROUND

Hematopoietic stem cell transplant (HSCT) is a well-established, potentially curative therapy for patients with life-threatening hematologic diseases. HSCT allows for high dose chemotherapy administration to eradicate the underlying malignancy or otherwise malfunctioning cells, followed by a rescue dose of hematopoietic stem cells from a related or unrelated donor. In addition, allogeneic immune cells can elicit an alloimmune response that enables a graft-versus-tumor effect to scavenge remaining disease cells and prevent disease relapse. Regardless of the source of donor hematopoietic cells, HSCT is known to be associated with significant morbidity following transplantation.

3. PRODUCT INFORMATION

3.1 Product Description

Omidubicel is a cryopreserved cell-based product used in HSCT. It is comprised of 2 cell fractions, a Cultured Fraction (CF) and a Non-cultured Fraction (NF), which are both derived from the same patient-specific umbilical cord blood unit (CBU).

1) The CF consists of allogeneic, hematopoietic CD34+ progenitor cells. The cells are expanded and enhanced through a proprietary process in the presence of nicotinamide (NAM) (b) (4) of the hematopoietic progenitor cells (HPCs) CD34+ cells and to (b) (4) (b) (4) of the HPCs. In addition to the CD34+ HPCs, the CF consists of other cell populations, including more differentiated myelomonocytic cells, dendritic cells and granulocytes. The CF formulation contains a maximum of 35mg gentamicin. Following manipulation, the cells are washed, formulated into a suspension, and cryopreserved in a patient-specific bag.

2) The NF consists of allogeneic, hematopoietic mature myeloid and lymphoid cells that are washed, formulated into a suspension, and cryopreserved in a patient-specific bag.

Omidubicel is administered as a one-time treatment, and both fractions are infused on the day of transplant.

3.2 Proposed Indication

The sponsor's proposed indication statement as submitted to the original BLA 125738/0/2 is: (b) (4)

OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

4. PERTINENT REGULATORY HISTORY

Omidubicel was granted orphan drug designation for enhancement of cell engraftment and immune reconstitution in patients receiving hematopoietic stem cell transplant on 23 May 2018. The current submission represents the third and final installment of the Biologics License Application (BLA) submission.

5. MATERIALS REVIEWED

Materials reviewed in support of this assessment include the following:

5.1 Pertinent Sections of the Licensing Application

- Section 1.14 Proposed Labeling, BLA 125738/0/2
- Section 1.16 Risk Management Plan (RMP), BLA 125738/0/15
- Section 2.7.4 Summary of Clinical Safety, BLA 125738/0/2
- Section 5.3.5.3 Day 120 Safety Update, BLA 125738/0/26

5.2 Input from the Clinical Reviewer

The clinical review team raised no new safety concerns that require additional post-marking studies or a risk evaluation and mitigation strategy for omidubicel.

6. DESCRIPTION OF OMIDUBICEL CLINICAL TRIAL SAFETY DATABASE

6.1 Clinical Studies

The clinical study safety data reviewed are from the Summary of Clinical Safety submitted to BLA125738/0/2. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the U.S. Package Insert (USPI). Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125738/0 be approved. Please refer to the package insert for the final clinical safety data.

The safety data of omidubicel was based on seven prospective clinical studies (P0101, (b) (4), P0301, P0401, P0501, P0701, (b) (4) A summary of each study and the pertinent safety issues is presented in Table 1. The safety data for omidubicel were based primarily on results of Study P0501 and supplemented by Study P0301. The long-term safety data were from observational long-term follow-up (LTFU) of patients treated in Study P0501 and Study (b) (4)/P0301 (Study P0401).

Table 1: Overview of Clinical Studies Contributing to the Safety Assessment of Omidubicel

Study ID Study Phase	Study Design Type of Control	Objective(s) of the Study	Test Product(s)	Number of Patients	Indication	Study Status
P0101 Phase I/Pilot	Open label single arm study	Evaluate the safety of co-transplantation of omidubicel and unmanipulated CBU to patients with hematologic malignancies following myeloablative therapy	Single dose of omidubicel in combination with unmanipulated CBU Intravenous	11 patients	Hematologic malignancies	Completed
P0301 Phase I/II	Open label single arm study	Evaluate the safety and efficacy of omidubicel transplantation in patients with hematologic malignancies following myeloablative therapy	Single dose of omidubicel Intravenous	38 patients: 36 patients received single unit omidubicel, 2 patients received omidubicel + unmanipulated CBU	Hematologic malignancies	Completed
P0501 Phase III	Randomized study; open label, sponsor was blinded to treatment assignment	Compare the safety and efficacy of omidubicel transplantation to unmanipulated CBU transplantation in patients with hematologic malignancies following myeloablative therapy	Single dose of omidubicel Intravenous	108 patients: 52 patients received omidubicel, 56 patients received unmanipulated single or double CBU	Hematologic malignancies	Final analysis of the main efficacy and safety endpoints completed, Long term follow up on patients ongoing.

P0701 Phase IIIb	Open label single arm study	Provide access to omidubicel for transplantation in patients with hematologic malignancies and collect additional safety and efficacy data	Single dose of omidubicel Intravenous	13 patients	Hematologic malignancies	Ongoing, Interim study report
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
P0401 Long term follow-up	Long term follow-up	Observational study to follow outcomes of patients treated on omidubicel studies P0101, P0301 and (b) (4)	No additional product is given in this study	33 patients	Hematologic malignancies and hemoglobin-opathies	Ongoing

6.2 Adverse Events

Adverse events associated with HSCT have been well-described and are expected regardless of graft source. Identified risks of omidubicel are similar in severity and frequency to those observed with unmanipulated cord blood, including infusion reactions, graft failure, Graft vs Host Disease (GvHD), and malignancies of donor origin. Potential risks include transmission of infection or genetic diseases.

6.2.1 Study P0501

6.2.1.1 Study design

The Study P0501 was an open-label, randomized, controlled, multicenter, international, Phase III study comparing the safety and efficacy of transplantation with omidubicel to unmanipulated cord blood in patients aged 12-65 years with hematologic malignancies. A total of 125 patients were randomized, including 62 to the omidubicel arm and 63 to the unmanipulated cord arm. Of these, 52 patients were transplanted with omidubicel and 56 patients were transplanted with unmanipulated CBUs per protocol. The median duration of follow up for omidubicel safety population was 14 months (range, 1-17 months).

6.2.1.2 Study results

The safety measures included treatment-emergent adverse events (TEAEs), serious AEs (SAEs), death, and adverse events of special interest: infusion reaction, graft failure, infections, acute/ chronic GvHD, and malignancies of donor origin.

TEAEs and SAEs

At least one TEAE was reported in all patients and a Grade 3-5[1] adverse event was reported in nearly all patients (98% of omidubicel and 95% of unmanipulated CBU patients) (Table A in Appendix). Treatment emergent SAEs were reported in 90% of omidubicel patients and 91% of unmanipulated CBU patients. Overall, 46% and 52% of patients had a TEAE that was related to omidubicel and unmanipulated CBU respectively.

For omidubicel patients, the most common Grade 3-5 adverse events by Preferred Term (PT) were pain in 17 (33%) patients, mucosal inflammation in 16 (31%) patients, and acute GvHD in 14 (27%) patients following grouping of acute GvHD events reported under different preferred terms. For unmanipulated CBU patients the most common Grade 3-5 adverse events were hypertension (38%), gastrointestinal disorder/toxicity (36%) and mucosal inflammation (34%).

In the first 42 days after transplant, the most common SAEs for omidubicel and unmanipulated CBU patients were infections (in nine [17%] omidubicel vs 12 [21%] unmanipulated patients) and GvHD (in nine [17%] omidubicel vs seven [13%] unmanipulated CBU patient). Following Day 42, the most common SAEs were also infections (in 21 [41%] of omidubicel vs 21 [38%] unmanipulated CBU patients) and GvHD (in eight [16%] omidubicel vs seven [13%] unmanipulated CBU patients).

1 Events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v 4.03 (NCI CTCAE)

Death
In the safety population, deaths were reported for 12 (23%) patients treated with omidubicel, and 20 (36%) patients treated with unmanipulated CBU. Among patients treated with omidubicel, the common causes of death were infections, acute GvHD, and relapse (n=3 for each). One patient each died of pulmonary hemorrhage, thrombotic microangiopathy, and veno-occlusive disease/sinusoidal obstruction syndrome. In patients treated with unmanipulated CBU, the most common causes of death were respiratory disorders (n=6; including hypoxic respiratory failure, acute respiratory distress syndrome (ARDS), idiopathic pneumonia, and pulmonary organ failure), infection or septic shock (n=6), disease relapse (n=4), and GvHD (n=3). One patient died of veno-occlusive disease/sinusoidal obstruction syndrome.

Adverse events of special interest
Infusion reaction
Twenty-nine (56%) patients transplanted with omidubicel and 40 (71%) patients transplanted with unmanipulated CBU had at least one infusion reaction. Of these, nine (17%) patients transplanted with omidubicel and 12 (21%) patients transplanted with unmanipulated CBU had a severe (CTCAE Grade 3-4) adverse event within 24 hours of infusion. The most common Grade 3 or 4 event was hypertension, reported in three (6%) patients treated with omidubicel, and nine (16%) patients treated with unmanipulated CBU.

Engraftment failure
In the safety population, engraftment occurred in 96% of patients treated with omidubicel, compared to 89% of patients treated with standard cord blood. Among the patients exposed to omidubicel on the study, three patients failed to engraft and one patient had a secondary graft failure (SGF) approximately six months following transplantation.

Infections
Sixty-five percent of patients receiving omidubicel had at least one bacterial infection of any grade compared to 80% of patients receiving UCB. Twenty-one percent of patients receiving omidubicel had at least one fungal infection of any grade compared to 27% of patients receiving UCB. Seventy-five percent of patients receiving omidubicel had at least one viral infection of any grade compared to 80% in the patients receiving UCB.

Acute GvHD
Acute GvHD was analyzed at 100 days following transplantation on the transplanted (TP) population, comprising all patients transplanted with either omidubicel or unmanipulated CBU, analyzed according to their original treatment allocation (59 patients on the omidubicel arm and 58 patients on the unmanipulated CBU arm). In the omidubicel group, 24 (41%) patients had Grade II, seven (12%) patients had Grade III, and one (2%) patient had Grade IV acute GvHD as the maximum severity of acute GvHD experienced in the first 100 days. In the unmanipulated CBU group, 13 (22%) patients had Grade II, 12 (21%) patients had Grade III, and zero patients had Grade IV acute GvHD as the maximum severity of acute GvHD experienced in the first 100 days.

While the rate of Grade II-IV acute GvHD was slightly higher in the omidubicel group than in the standard group, the rates of Grade III-IV GvHD were similar. The cumulative incidence of grade II-IV acute GvHD was 56% in the omidubicel group and 43% in the unmanipulated CBU group. The Cox regression analysis of Grade II-IV GvHD demonstrated a cause-specific hazard ratio of Grade II-IV GvHD with omidubicel of 1.48 (95% CI: 0.87 - 2.49, p=0.14). Conversely, the cumulative incidence of more serious Grade III-IV acute GvHD was 14% in the omidubicel group and 21% in the unmanipulated CBU group, and the hazard ratio for Grade III-IV GvHD with omidubicel was 0.65 (95% CI: 0.23 - 1.60, p=0.35).

Chronic GvHD
Chronic GvHD was analyzed at 180 days and 1 year following transplantation. In the omidubicel group, four (7%) patients had mild, ten (17%) patients had moderate, and two (3%) patients had severe chronic GvHD as the maximum severity of chronic GvHD through one-year post-transplant. In the unmanipulated CBU group, six (10%) patients had mild, ten (17%) patients had moderate, and two (3%) patients had severe chronic GvHD as the maximum severity of chronic GvHD through one-year post-transplant. At one year, the cumulative incidence was 34% in the omidubicel arm and 29% in the unmanipulated CBU arm, and the hazard ratio was 1.06 (95% CI: 0.52 – 2.21, p=0.87).

Malignancies of donor origin
No cases of new malignancies were reported during the one-year follow-up of this Study. One patient treated with omidubicel had a Grade 3 increase in T-lymphocyte counts (clonal T-cell lymphocytosis) which was found to be monoclonal. The lymphocytosis persisted over time, without clinical sequelae, and with no evidence of malignancy.

6.2.2 Study P0301
6.2.2.1 Study design
The Study P0301 was an open-label, single arm, multicenter, international, Phase I/II study assessing safety and efficacy of omidubicel transplantation in patients aged 12-65 years with hematologic malignancies. Thirty-six (36) patients were transplanted with single unit omidubicel and 2 patients received omidubicel with an unmanipulated CBU. The 36 patients treated with the single unit of omidubicel were included in the safety population. The median duration of follow up for omidubicel safety population was 11.8 months (range, 0.3-14.7 months).

6.2.2.2 Study results
The safety measures included treatment-emergent adverse events (TEAEs), serious AEs (SAEs), death, and adverse events of special interest: graft failure, acute/chronic GvHD, malignancies of donor origin.

TEAEs and SAEs
All patients reported at least one TEAE. Beyond 24 hours post-transplant, the only common events reported as related to omidubicel were GvHD and primary graft failure events. Other suspected AEs included hypertension and hypoxia in one patient each.

Overall, 17 (47%) patients had a TEAE that was related to the omidubicel, and 16 (44%) patients had a fatal TEAE.

Ninety-five SAEs were reported in 34 (94%) patients. The majority (68%) of the events were associated with initial or prolonged hospitalization. The most common SAEs were infections reported in 17 (47%) patients, GvHD in 11 (31%) patients, and relapse in 8 (22%) patients.

The most frequently reported AE during this study within 24 hours of infusion were hypertension, pain, and mucositis in six (17%) patients each. Other frequent infusion reactions included nausea and change in cardiac rhythm (arrhythmia and atrial fibrillation) in five (14%) patients each. Four (11%) patients also developed hypotension.

Death
Sixteen deaths were reported in the 36 omidubicel recipients (44%). The most common primary causes of death were disease recurrence/persistence in eight (22%) patients, infection in four (11%) patients, GvHD in two (6%) patients, interstitial pneumonia in one (3%) patient, and cardiogenic shock in one (3%) patient.

Adverse events of special interest
Infusion reactions
There were no instances of Grade 5 infusion reactions. One patient had a Grade 4 infusion reaction (somnolence), and five patients had a Grade 3 infusion reaction, which included arrhythmia, atrial fibrillation, mucosal inflammation, dyspnea, hypoxia, hypertension, and hypotension. There were 21 patients with a Grade 1/2 infusion reaction.

Graft failure
Two patients did not achieve neutrophil engraftment: one patient had a primary graft failure and the other patient died of cardiogenic shock and organ failure on Day 10 post-transplant, prior to engraftment. An additional patient achieved neutrophil engraftment but had a donor whole blood chimerism <95%, and thus was considered as primary graft failure per protocol definition. Two patients had secondary graft failure (SGF) in the year following omidubicel transplant. The cumulative incidence of SGF in the 36 omidubicel recipients was 2.8% (95% CI: 0.2-12.6%) at 6 months and 5.6% (95% CI: 1.0-16.6%) at one-year post-transplant.

Acute/chronic GvHD
The incidence of acute GvHD Grade II-IV at 100 days post omidubicel transplant was 44.4% (95% CI: 27.7-59.9). Similarly, for Grade III-IV acute GvHD, the cumulative incidence at 100 days post-transplant was 11% (95% CI: 3-24) for the omidubicel population. Fifteen (42%) patients had chronic GvHD in the year following omidubicel transplant. Of 15 patients with chronic GvHD in the year following omidubicel transplant, five cases were extensive while the other ten were limited. The cumulative incidence of chronic GvHD at one-year post-transplant was 40% (95% CI: 24-57) for the omidubicel population.

6.2.3 Long term safety data

The long-term safety data were from observational long-term follow-up (LTFU) of patients treated on Study P0501 and Study P0401.

6.2.3.1 Study P0501-LTFU

As of 05 Aug 2022, 62 patients (32 patients transplanted with omidubicel and 30 patients transplanted with UCB) were ongoing in long term follow up in Study P0501-LTFU. The median follow-up for the 62 patients was three years (range 2-3 years) post-transplant. Disease relapse was reported in one patient in each treatment group (omidubicel: a 60-year-old man relapsed with acute myeloblastic leukemia (AML) at 969 days post-transplant; UCB: a 48-year-old female with hepatosplenic T-cell lymphoma relapsed at 575 days post-transplant, and relapsed for a second time at 1176 days post-transplant and the patient died on Day 1206 post-transplant). One new case of mild chronic GvHD was reported in the omidubicel group during Year 3 post-transplant and two new cases of chronic GvHD were reported in the UCB group (one mild chronic GvHD in Year 2 and one moderate GvHD in Year 4). No secondary graft failure was reported in either treatment group. A new malignancy, not of donor origin, was reported in a patient in the omidubicel group (a 58-year-old female patient with AML was diagnosed with non-small cell lung cancer at Year 3 post-transplant).

6.2.3.2 Study P0401

Study P0401 is a LTFU of patients who were from Study P0301 and Study (b) (4)

As of 05 Aug 2022, four patients with hematologic malignancies from Study P0301 were ongoing in LTFU. There were no SGF, chronic GvHD, relapse, malignancies of donor origin, or death reported in five-year follow-up on these four patients.

As of 05 Aug 2022, eight patients with sickle cell disease from Study (b) (4) were ongoing in LTFU (through 4 years in three patients and 5 years in five patients). There were no SGF, GvHD, or malignancies of donor origin reported in these patients. One patient died unexpectedly during Year 4 of follow-up of a massive cerebrovascular accident, unrelated to omidubicel.

Reviewer comment: Data from these studies indicated that omidubicel had similar safety profile as unmanipulated cord blood and no new safety concerns were identified in the indicated patient population. All treatment-related AEs were well-known events following HSCT and are labeled in the proposed package insert. When interpreting these findings, it should be noted that the sample size was small (88 cases in omidubicel group in Study P0501 and Study P0301, 44 cases in P0501-LTFU and Study P0401) that is insufficient to detect the rare adverse events.

7. SUMMARY OF POSTMARKETING EXPERIENCE

The product has never been marketed, so there were no post-market adverse event analyses.

8. SPONSOR'S PHARMACOVIGILANCE PLAN

The sponsor Risk Management Plan (RMP, dated August 9, 2022) includes the Pharmacovigilance Plan (PVP). The summary of identified risks, potential risks, and the important missing information is presented in Table 2:

Table 2: Summary of Safety Concerns as Proposed by the Sponsor

Identified risk(s)	• Infusion Reactions • Graft Failure • GvHD • Malignancies of Donor Origin
Potential risk(s)	• Transmission of Serious Infections • Transmission of Rare Genetic Diseases
Missing information	• No information on safety in pregnant and lactating women and the breastfed infant • No information on safety in pediatric patients <12 years old and patients > 65 years old • No information on safety in patients with renal and hepatic impairment

8.1 Analysis of Sponsor's PVP

8.1.1 Identified risk

Infusion Reaction

Infusion reaction is defined as any adverse event that begins or worsens between the start of the omidubicel infusion and 24 hours from the end of the infusion, including hypertension, mucosal inflammation, dysphagia, dyspnea, vomiting and gastrointestinal toxicity. In Study P0501, 29 (56%) patients transplanted with omidubicel and 40 (71%) patients transplanted with UCB had at least one infusion reaction. Of these, 9 (17%) patients transplanted with omidubicel and 12 (21%) patients transplanted with UCB had a grade 3-4 adverse event within 24 hours of infusion. The most common grade 3 or 4 event was hypertension, reported in three (6%) patients treated with omidubicel, and nine (16%) patients treated with UCB. Analyses of infusion reactions by age, gender, race, disease, disease risk index, comorbidities, human leukocyte antigen (HLA) matching, conditioning regimen, and geography did not reveal increased risk associated with a particular subgroup. Patients received standardized premedication including antipyretics, histamine antagonists, and corticosteroids, as well as intravenous hydration, prior to the infusion of omidubicel. Patients were closely monitored for events over the first 24 hours of transplantation.

Graft Failure

Primary graft failure is defined as failure to achieve neutrophil engraftment by Day 42. Primary graft failure indicates a failure of the transplantation procedure, and may be due

to immunologic reactivity to donor stem cells. Secondary graft failure (SGF) is defined as persistent neutropenia and hypocellular marrow following initial neutrophil recovery. Secondary graft failure is an expected complication following HSCT, and may be related to immunologic graft rejection, viral infection, GvHD, medication-related toxicity, or persistent/recurrent disease (Rondon et al.2008[2]). In Study P0501, primary engraftment failure occurred in 2% of patients treated with omidubicel, compared to 9% of patients treated with UCB. SGF was reported in one patient treated with omidubicel, concurrent with a diagnosis of ALL relapses, and no patients in the UCB group. Long term follow-up of omidubicel recipients throughout the clinical trial experience (N=117) at a median follow-up of 12.4 months showed durable engraftment in 109 (93%) patients. Graft failure is a known and potentially fatal complication of allogeneic HSCT.

GvHD

Acute and chronic GvHD are multisystem disorders that are common and expected in patients undergoing allogeneic HSCT. Acute GvHD generally occurs within 100 days of transplant, and manifests as maculopapular rash, gastrointestinal symptoms, and elevated bilirubin. Chronic GvHD is usually diagnosed after 100 days post-transplant, and manifestations include scleroderma-like or lichen planus-like skin involvement, gastrointestinal ulcerations and sclerosis, and increased bilirubin. The etiology of GvHD includes the recognition of host cell antigens as foreign by donor immune cells, tissue damage due to the conditioning regimen, and altered mechanisms of tissue repair, including changes in the microbiome (Zeiser and Blazar 2017[3]). In Study P0501 (N=117), Grade II acute GvHD was reported in 24 (41%) patients in the omidubicel group and 13 (22%) in the UCB group, mostly driven by skin manifestations. The rates of Grade III to IV GvHD were similar 14% and 22%, respectively, in the omidubicel and UCB groups. The incidence of chronic GvHD of all grades was 9% in the omidubicel group and 11% in the UCB group. There were three patient deaths in each treatment group attributed to GvHD. While GvHD is an expected and potentially fatal complication of transplant, transplantation with omidubicel was not associated with an increase in the rate or severity of infusion reactions compared to UCB. Analyses of acute and chronic GvHD by age, gender, race, disease, disease risk index, comorbidities, and geography did not reveal increased risk associated with a particular subgroup, although interpretation was limited by the small size of some subgroups. Patients received standardized GvHD prophylaxis including mycophenolate mofetil and a calcineurin inhibitor for at least 100 days following transplant. Treatment of GvHD was determined by individual health care providers according to institutional guidelines.

Malignancies of Donor Origin

Malignancies of Donor Origin is defined as hematologic malignancies including myelodysplastic syndrome (MDS) and acute leukemia which may be related to abnormalities in donor cells, immunosuppression, and toxicity of chemotherapy.

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2 Rondon, G., R. M. et al. Long-term follow-up of patients who experienced graft failure post-allogeneic progenitor cell transplantation. Results of a single institution analysis. Biol Blood Marrow Transplant, 2008, 14: 859-66.

3 Zeiser, Robert, and Bruce R. Blazar. Acute Graft-versus-Host Disease — Biologic Process, Prevention, and Therapy. New England Journal of Medicine, 2017, 377: 2167-79.

Additionally, patients will be required to be monitored life-long for secondary malignancies. Post-transplant lymphoproliferative disorders (PTLD) represent a heterogeneous group of lymphoid disorders ranging from indolent polyclonal proliferation to aggressive lymphomas. PTLD is a known severe complication of HSCT, with an incidence of up to 11% reported in recipients of matched unrelated donor grafts (Compagno et al. 2020[4]). The etiology is thought to be related to reactivation of Epstein-Barr virus (EBV) infection in the setting of immunosuppression. Risk factors include EBV infection, prolonged immunosuppressive therapy, T cell-depleted grafts, age (<10 and >60 years), and race (White) (Al-Mansour, Nelson, and Evens 2013). Cord blood transplantation may be associated with a greater risk of PTLD, due to low numbers and naiveté of infused T-cells. In Study P0501, quantitative EBV viral load was tested by (b) (4) at standard intervals throughout the post-transplant period. Three patients in Study P0501 developed PTLD; all were treated with rituximab-based regimens, and one patient died. An additional patient in the omidubicel arm had clonal T-cell lymphocytosis, possibly related to cytomegalovirus (CMV), without clinical manifestations. There were no patients on the UCB arm of Study P0501 with PTLD.

Donor cell derived leukemias are a known and serious complication of allogeneic HSCT, with an estimated incidence of 124 per 100,000 transplants (Wiseman 2011[5]). Donor cell derived MDS has also been described (Wang et al. 2011[6]). The etiology of donor cell leukemia may be related to impaired immune surveillance, toxic effects of post-transplant care, or as a result of occult leukemia or a genetic predisposition in the donor (Wiseman 2011). One patient treated with omidubicel in Phase I/II Study P0301 developed donor-derived MDS, and one patient treated with UCB in Phase III Study P0501 developed fatal donor-derived AML. Overall, donor-derived malignancies are a rare and potentially fatal toxicity observed in patients undergoing HSCT. There is no evidence that the incidence is greater in patients treated with omidubicel than with other graft sources. The therapeutic approach includes reduction of immunosuppression, rituximab, and chemotherapy.

8.1.2 Potential risks

Transmission of Serious Infections

Transmission of infectious disease by known or unknown infectious agents may occur because omidubicel is derived from human blood. Donor screening and testing for a cord blood unit (CBU) is performed on the birth mother/ maternal specimen for HIV-1/HIV-2 Ab Plus O, Hepatitis B Surface Antigen, Hepatitis B Core Antibody (IgG and IgM), hepatitis C virus (HCV) Ab, Treponema pallidum (syphilis), HTLV types 1 and 2 Ab, Hemoglobinopathy, CMV IgM, CMV IgG, Nucleic Acid Test (NAT) HIV, NAT hepatitis B virus (HBV), NAT HCV, NAT West Nile Virus (WNV), sterility, transmissible spongiform encephalopathies including Creutzfeldt-Jakob disease, sepsis,

4 Compagno, F., S. et al. Management of PTLD After Hematopoietic Stem Cell Transplantation: Immunological Perspectives. Front Immunol, 2020, 11: 567020.

5 Wiseman, Daniel H. Donor Cell Leukemia: A Review. Biology of Blood and Marrow Transplantation, 2011, 17: 771-89.

6 Wang, E., C. B. et al. Donor cell-derived leukemias/myelodysplastic neoplasms in allogeneic hematopoietic stem cell transplant recipients: a clinicopathologic study of 10 cases and a comprehensive review of the literature. Am J Clin Pathol, 2011, 135: 525-40.

Vaccinia and Zika. After manufacturing, omidubicel is tested for sterility. There were no cases of transmission of infection in the omidubicel clinical experience. The risk of transmission of infection through transplantation with omidubicel has not been determined.

Transmission of Rare Genetic Diseases
Omidubicel may transmit rare genetic diseases involving the hematopoietic system. No case of clinically significant transmission of genetic diseases was reported in the omidubicel clinical program. The risk of transmission of rare genetic diseases through transplantation with omidubicel has not been determined.

8.1.3 Important missing information

There are no available data with omidubicel use in pregnant women. There are no available data with omidubicel in lactating women or information on the effects on the breastfed infant.

Safety and efficacy of omidubicel in pediatric patients below the age of 12 and above the age of 65 has not been established.

Patients with chronic lymphocytic leukemia (CLL), myeloproliferative neoplasms (MPN), or with MDS or chronic lymphocytic leukemia (CML) with marked bone marrow fibrosis were excluded in omidubicel clinical studies. Safety in those populations has not been determined.

Patients with hematologic malignancies characterized as “low risk,” such as patients with favorable risk AML and no high risk features or low risk MDS were not studied, and safety of omidubicel has not been determined.

Omidubicel studies excluded patients with Karnofsky performance score (KPS) < 70%. Safety in patients with lower performance scores has not been determined.

Omidubicel studies excluded patients with clinical /laboratory characteristics consistent with impaired organ function, including left ventricular ejection fraction (LVEF) < 40%, certain pulmonary function tests < 50% of predicted, calculated creatinine clearance < 60 mL/mi, bilirubin > 2.0 mg/dl, or hepatic transaminases > 3 times the upper limit of normal.

Safety in patients with hepatic, renal, pulmonary, or cardiac disorders has not been determined.

Patients with human immunodeficiency virus (HIV) were excluded, and the safety of omidubicel in patients with HIV has not been determined.

8.2 Analysis of Sponsor’s PVP Activities

The sponsor proposed to use routine pharmacovigilance to monitor postmarketing safety of omidubicel. Routine pharmacovigilance activities include submission of Individual

Case Safety Reports (ICSR), signal detection, literature review, and submission of sponsor summary of aggregate safety data in Periodic Adverse Experience Report (PAER).

In addition to the post-marketing activities described above, there are three open-label and long-term follow-up (2-5 years following transplantation) studies that aim to collect additional data on the safety of omidubicel:

1. P0701 An Open Label Expanded Access Study of Omidubicel, for Allogeneic Transplantation in Patients with Hematological Malignancies (Two years following transplantation).
2. P0501 A Multicenter, Randomized, Phase III Registration Trial of Transplantation of NiCord®, Ex Vivo Expanded, Umbilical Cord Blood-derived, Stem and Progenitor Cells, versus Unmanipulated Umbilical Cord Blood for Patients with Hematological Malignancies (Five years following transplantation).
3. P0401 Long Term Follow Up for Patients who have received Allogeneic Stem Cell Transplantation of NiCord®/CordIn™, Umbilical Cord Blood-derived Ex Vivo Expanded Stem and Progenitor Cells (Five years following transplantation).

The sponsor is planning to conduct the following activities in order to ensure that physicians who prescribe omidubicel for transplantation in patients with hematologic malignancies are well-informed of the benefit-risk profile of the product, and can ensure safe and appropriate use for patients:

- The Full Prescribing Information (PI) describes the adverse drug reactions associated with omidubicel treatment and provides guidance on the known risks.
- Assessment of individual transplant centers will be conducted prior to the provision of omidubicel, to ensure appropriate equipment and procedures are in place for receipt, handling, and storage of omidubicel.
- Limitation of use to qualified transplant centers with expertise in hematopoietic stem cell transfers and healthcare providers (HCPs) trained in the treatment of hematologic malignancies.
- Transplant center personnel training will be conducted to educate Healthcare Providers (HCPs) and other members of the transplant center team on the benefit-risk profile of omidubicel, the label-based recommendations for management of risks, the receipt, handling, storage, and administration of omidubicel (designated and matched appropriately for a specific patient), and the reporting of adverse events and product complaints.
- The administration of omidubicel is limited to the inpatient setting at transplant centers with appropriate expertise. Healthcare professionals at the transplant center provide counseling and education to patients prior to transplantation, including information on the potential risks and benefits of myeloablative conditioning and allogeneic transplantation with available graft sources.
- Gamida Cell Assist (GCA), a web based, customer-management system, will be implemented for ordering of omidubicel and maintaining chain of identity (COI) for individual patients.

Reviewer's assessment: The sponsor's proposed post-marketing pharmacovigilance plan is adequate for all safety concerns noted in Table 2. No new safety signals have been identified that would justify further postmarketing study or a Risk Evaluation and Mitigation Strategy (REMS).

9. DPV ASSESSMENT

Based on the review of the final results of two pivotal studies P0501 and P0301, the long-term follow up of Study P0501 and Study P0401, we conclude that omidubicel has a similar safety profile to unmanipulated cord blood and no new safety concerns were identified in the indicated patient population. DPV concurs with the sponsor's proposed pharmacovigilance activities in the proposed RMP.

10. DPV RECOMMDENDATIONS

Should omidubicel be approved, DPV agrees with routine pharmacovigilance for safety monitoring, as proposed by the sponsor in the RMP, with adverse event reporting as required under 21 CFR 600.80. The reviewed available safety data do not indicate a need for safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs), or a Risk Evaluation and Mitigation Strategy (REMS). The sponsor is also conducting ongoing studies for long-term follow up of clinical trial participants. Please see the final version of the Package Insert submitted by the sponsor for the final agreed-upon language describing omidubicel.

Appendix

Table A. Overview of TEAEs Reported in Patients with Hematologic Malignancies Treated with Single Unit Omidubicel (Focused Safety Population)

	P0301 Omidubicel (N=36)	P0501 Omidubicel (N=52)	P0501 UCBU (N=56)
	n (%)	n (%)	n (%)
Patients with any TEAE	36 (100%)	52 (100%)	56 (100%)
Patient with any TEAE possibly related to infused stem cell product	17 (47%)	24 (46%)	29 (52%)
Patients with any treatment emergent SAE	34 (94%)	47 (90%)	51 (91%)
Patients with any treatment emergent SAE possibly related to infused stem cell product	17 (47%)	21 (40%)	23 (41%)
Patients with any TEAE of Grade 3-4	33 (92%)	51 (98%)	52 (93%)
Patients any TEAE of Grade 3-5	34 (94%)	51 (98%)	53 (95%)
Treatment emergent death	16 (44%)	12 (23%)	20 (36%)

Source: Summary of Clinical Safety, BLA 125738/0/2, Table 13 in Page 57
N =Total number of patients in each treatment group; n= number of patients with respective safety events
SAE: Serious adverse event; TEAE: Treatment emergent adverse event; UCBU: Unmanipulated cord blood unit