Najat Bouchkouj, MD

Emily Jen, MD, PhD

STN: 125738/0

BLA Clinical Review Memorandum

Application Type	BLA
STN	125738/0
CBER Received Date	1 June 2022
PDUFA Goal Date	1 May 2023 Revised due to Major Amendment
Division / Office	Division of Clinical Evaluation Hematology / Office of Clinical Evaluation / Office of Therapeutic Products
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Najat Bouchkouj, MD Emily Jen, MD, PhD
Review Completion Date / Stamped Date	14 April 2023
Supervisory Concurrence	Marc Theoret, MD Tejashri Purohit-Sheth, MD
Applicant	Gamida Cell Ltd.
Established Name	Omidubicel
(Proposed) Trade Name	OMISIRGE (formerly NiCord)
Pharmacologic Class	Nicotinamide modified allogeneic hematopoietic progenitor cell therapy derived from cord blood
Formulation(s), including Adjuvants, etc.	A single dose consists of a Cultured Fraction (CF) and a Non-cultured Fraction (NF) supplied separately in two cryopreserved bags and each suspended in approximately 10% dimethyl sulfoxide
Dosage Form(s) and Route(s) of Administration	Cell suspension for intravenous infusion
Dosing Regimen	A single dose consists of a CF (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) and an NF (a minimum of 4.0×10^8 total viable cells with a minimum of 2.4×10^7 CD3+ cells).
Indication(s) and Intended Population(s)	Applicant's proposed indication: (b) (4) <u>Review team's recommended indication:</u> 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.
Orphan Designated (Yes/No)	Yes

TABLE OF CONTENTS

GLOSSARY

ADAE	adverse event analysis
ADCE	clinical events analysis and clinical classification analysis
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
AR	adverse reaction
ARDS	acute respiratory distress syndrome
AT	as-treated
BIMO	FDA's Bioresearch Monitoring program
BLA	biologics license application
BM	bone marrow
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
CBC	complete blood count
CBT	cord blood transplantation
CBU	cord blood unit
CDRH	Center for Devices and Radiological Health
CF	cultured fraction
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CMC	chemistry, manufacturing and controls
CML	chronic myelogenous leukemia
COVID-19	coronavirus disease 2019
CR	complete remission
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMSO	dimethyl sulfoxide
DP	drug product
EBV	Epstein-Barr virus
EPC	Established Pharmacologic Class
ES	engraftment syndrome
FACT-BMT	Functional Assessment of Cancer Therapy – Bone Marrow Transplantation
FDA	U.S. Food and Drug Administration
GCSF	granulocyte colony-stimulating factor
GvHD	graft-versus-host disease
HCP	health care provider
HLA	human leukocyte antigen
HPC	hematopoietic progenitor cell
HQL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
(b) (4)	(b) (4)
iPSP	initial pediatric study plan

IR	information request
IRB	Institutional Review Board
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	intent-to-treat
IV	intravenous
KGI	Kiryat Gat manufacturing facility
LN_2	liquid nitrogen
LOQ	limit of quantification
LTFU	long-term follow-up
MAC	myeloablative conditioning
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MOP	manual of procedures
MPDs	major protocol deviation
mpds	minor protocol deviations
N/A	not applicable
NAM	nicotinamide
NF	non-cultured fraction
NIH	National Institutes of Health
NK	natural killer
NRM	non-relapse mortality
ODD	orphan drug designation
OOH	out of hospital
OOS	out-of-specification
PCR	polymerase chain reaction
PMC	post-marketing commitment
PMR	post-marketing requirement
PREA	Pediatric Research Equity Act
PT	preferred term
PTLD	post-transplant lymphoproliferative disorders
SAA	severe aplastic anemia
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
SOC	system organ class
SOS	sinusoidal obstruction syndrome
SP	safety population
STR	short tandem repeats
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitors
TNC	total nucleated cell
TP	transplanted population
UCBU	unmanipulated cord blood unit
UCBT	umbilical cord blood transplantation

USAN	United States Adopted Name
USPI	United States Prescribing Information
VOD	veno-occlusive disease
WBC	white blood cell
W&P	Warnings and Precautions

1. EXECUTIVE SUMMARY

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

Omidubicel is a nicotinamide modified allogeneic hematopoietic progenitor cell (HPC) therapy derived from cord blood that is developed to address the limitations of UCBT, including delayed neutrophil recovery and increased rates of serious and life-threatening infection compared to transplantation with other donor sources. The recommended regimen is a single dose administration of cultured fraction (CF) (a minimum of 8.0×10^8 total viable cells of which 8.7% are CD34+ cells and a minimum of 9.2×10^7 CD34+ cells) and a non-cultured fraction (NF) (a minimum of 4.0×10^8 total viable cells with a minimum of 2.4×10^7 CD3+ cells), administered sequentially, preceded by a myeloablative preparative conditioning regimen.

The Applicant is seeking approval of omidubicel for the indication:(b) (4)

The efficacy of omidubicel is based on Study GC P#05.01.020 (referred to as Study P0501 henceforth), a randomized, open-label, multicenter, Phase 3 study comparing transplantation of omidubicel to transplantation of one or two unmanipulated unrelated cord blood units (CBUs) 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 G/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. The study was designed with a two-sided significance level of 5% to assess the probability P =0.78 that a subject in the omidubicel arm has a shorter engraftment time than a subject in the UCBU group. A sample size of 120 corresponded to 99% power for the primary endpoint. One-hundred twenty-five subjects were enrolled; 62 subjects were randomized to receive omidubicel and 63 subjects were randomized to the unmanipulated cord blood unit (UCBU). The median time to neutrophil engraftment (with subsequent donor chimerism) was 12 days (95% confidence interval [CI]: 10, 16) in the omidubicel 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.

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 (b) (4)
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 BMT CTN Grade 2/3 bacterial or Grade 3 fungal infection through Day 100 following transplantation in subjects who received omidubicel 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 omidubicel 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. The study, as designed, demonstrates a clinically meaningful benefit with omidubicel 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 receiving myeloablative conditioning (MAC) followed by UCBT. Therefore, the Applicant's requested indication statement was revised to reflect this assessment.

The safety of omidubicel was based primarily on Study P0501 and included a total of 108 subjects in the safety population (SP): 52 subjects treated with omidubicel and 56 subjects treated with UCBU. These data were supported by safety data from subjects with hematologic malignancies and hemoglobinopathies who were treated with omidubicel in single-arm trials, with a total of 117 subjects treated with omidubicel. Assessment of graft function was essential to ensure there was no detriment introduced by manipulation of the graft source. The incidence of graft failure was lower and immune reconstitution occurred earlier in subjects who received omidubicel compared to those who received UCBU. Rates of relapse of hematologic malignancy were overall similar between arms. Rates of high grade infections (bacterial, fungal, and viral) and Grade III to IV acute GVHD were numerically lower in subjects who received omidubicel. The safety profile of omidubicel was consistent with the known toxicities and complications of myeloablative conditioning therapy followed by allogeneic HSCT.

Based on the results of Study P0501, the unmet medical need, and the favorable safety profile, the review team concludes that the Applicant provided substantial evidence of effectiveness and safety from an adequate and well controlled trial, and the clinical review team recommends approval.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

In Study P0501, of the 155 subjects who provided consent, 125 were enrolled and randomized: 62 subjects to the omidubicel treatment arm and 63 subjects to the UCBU arm. The median age of subjects was 40 years for the omidubicel arm and 43 years for the UCBU arm. Subject ages ranged from 13 to 65 years. The study population was ethnically diverse, with over 40% identified as non-Caucasian. Acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML) were the most common indications for transplant, and most subjects had moderate to high-risk disease. All CBUs were required to be human leukocyte antigen (HLA)-

matched at 4-6/6 HLA class I (HLA-A & HLA-B, low resolution) and class II (HLA-DRB1, high-resolution) loci. Most subjects (~73%) received CBUs that were HLA-mismatched at two loci.

Reviewer comment: *The study population was representative of the general population eligible for transplant. Demographics and baseline disease characteristics were well balanced in the two arms. None of the analyses revealed any impact of demographic or disease characteristics on outcome measures.*

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	6.1.11.5
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Allogeneic HSCT is a well-established treatment for hematologic diseases that cannot be cured with conventional treatments. Over 9,000 allogeneic transplants were performed in the United States in 2020, as reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).

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 (BM) 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 UCBT, are partially HLA-mismatched.

UCBT has been used clinically for over 30 years and is available at public cord blood banks contracted by the National Cord Blood Inventory program. Matching requirements for UCBT 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 hematopoietic cells 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 (Ruggeri et al. 2014) .

Stem and progenitor cells required for engraftment and recovery of hematopoiesis following HSCT express the CD34 cell surface antigen. Thus, an adequate dose of total nucleated cell (TNC) expressing CD34+ cells is necessary to ensure early and sustained hematopoietic recovery. The TNC and CD34+ cell dose can be considered the limiting factor for the use of UCBT, especially for hematopoietic transplant for adults. Several approaches (e.g., ex vivo expansion, homing, combined grafts) have been investigated to increase the TNC and CD34+ cell dose (Shpall et al. 1998; Kindwall-Keller and Ballen 2020).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

The Applicant's proposed indication is for the (b) (4) However, the clinical development program was not designed to support this indication. Omidubicel was developed to address the limitations of UCB as a graft source including delayed hematopoietic recovery and increased infections, and to provide additional graft options for patients with hematologic malignancies who need HSCT.

There are currently no marketed products that are designed to be used as HSCT grafts that are indicated to reduce the time to neutrophil recovery or reduce the incidence of bacterial and

fungal infections in patients with hematologic malignancies undergoing myeloablative regimen followed by UCBT.

2.3 Safety and Efficacy of Pharmacologically Related Products

Pharmacologic Class

Omidubicel is a nicotinamide modified allogeneic cord blood HPC therapy composed of:

- CF: Allogeneic, ex vivo expanded, hematopoietic CD34+ progenitor cells
- NF: Allogeneic, non-expanded, hematopoietic mature myeloid and lymphoid cells

Both fractions are derived from the same CBU.

Standard human cord blood HPC is associated with the Established Pharmacologic Class (EPC) text phrase 'allogeneic cord blood HPC therapy'. Omidubicel, however, is not standard (minimally manipulated) 'cord blood' (CFR 1271.10(a)) and is not therapeutically or clinically equivalent to standard cord, as the HPCs in omidubicel are no longer standard HPCs. Omidubicel is manipulated, expanded, cultured, and manufactured; in addition to CD34+ cells, the product delivered is made of two essential cell fractions, the CF and the NF. Nevertheless, subjects transplanted with omidubicel are potentially at risk of developing toxicities which typically occur following HSCT with other graft sources. These toxicities include infusion reactions, infections, graft-versus-host disease (GvHD), graft failure, engraftment syndrome (ES), and malignancies of donor origin.

Reviewer comment: *The chemistry, manufacturing and controls (CMC) review team recommended to designate the following EPC to describe omidubicel: "a nicotinamide modified allogeneic HPC therapy derived from cord blood." The clinical review team did not have an objection to the EPC.*

2.4 Previous Human Experience With the Product (Including Foreign Experience)

Omidubicel has not been marketed in any foreign country.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Pre-Submission Major Milestones

Table 1 below outlines the different communications that occurred between the Applicant and the U.S. Food and Drug Administration (FDA), which are related to the clinical development plan for malignant hematology conditions. In addition, several meetings were held with the CMC review team to discuss manufacturing and product comparability issues.

Table 1. Key Communications Between the Applicant and the FDA During Product Development

Meeting Type[a]/ Correspondence	Discussion Topics	Format	Date
Pre pre-IND meeting	To present and discuss the pre-clinical program	TC	7 July 2009
Pre IND meeting (ID# 7329)	To hear the Agency's comments on manufacturing procedures, pre-clinical and clinical programs.	TC	18 February 2010
Type C-Quality and clinical meeting (ID# 8589)	To discuss the introduction of a cryopreserved CF configuration instead of the fresh CF	TC	9 October 2012
Correspondence	Study P0301 may proceed	Email	21 March 2013
Type C-Clinical meeting (CRMTS# 9692)	Phase 3 design	Meeting cancelled by the Sponsor after having received preliminary minutes	20 March 2015
Type B- End of Phase 2 Clinical meeting (CRMTS# 10008)	Phase 3 and BLA (study population, CBU, conditioning regimens and GvHD prophylaxis, endpoints, safety monitoring, safety database, BLA submission, statistical questions)	Meeting cancelled by Sponsor	14 December 2015
Breakthrough designation request	Breakthrough designation grant letter sent to Sponsor		7 October 2016
Type B-Breakthrough multidisciplinary meeting (CRMTS# 10614)	Communication plan, pre-BLA Day 42, expedited path for BLA review, indication, Phase 3 design, statistical questions	Meeting cancelled by Sponsor	29 March 2017
Type B - Clinical/statistical meeting (CRMTS# 10704)	Phase 3 design and feedback on question 5 from the FDA meeting minutes on 29 March 2017	TC	12 June 2017
Correspondence	FDA agreement to Protocol GC P#05.01.020 amendment IV	Email	7 December 2017
Type B-Clinical/statistics meeting	SAP	TC (informal)	8 January 2018
Type B-Clinical meeting (CRMTS# 12650)	Path to BLA submission for the Phase 3 pivotal Study (P0501)	Meeting cancelled by Sponsor	20 July 2020
Correspondence	December 11, Pre-BLA meeting converted to Type B Clinical meeting (CRMTS# 12928)	Email	24 November 2020
Correspondence	Rolling submission discussion	Email	2 December 2020
Type B-Clinical meeting (CRMTS# 12928)	Phase 3 data and BLA submission	TC	11 December 2020

Meeting Type[a]/ Correspondence	Discussion Topics	Format	Date
Type B-Clinical meeting (CRMTS# 13021)	SAP for ISS and ISE	TC	12 January 2021
Correspondence	Clinical advice regarding sequence 169	Email	5 November 2021
Type B Pre-BLA meeting (CRMTS# 13637)	To reach an agreement on the content of the BLA.	TC	9 November 2021
Type B-CMC meeting (CRMTS# 13773)	KGI Analytical Comparability agreement and BLA rolling submission plan	Written responses	18 January 2022

a. All IND meetings listed in this table are under IND 14459
Abbreviations: BLA, biologics license application; CBU, cord blood unit; CMC, chemistry, manufacturing and controls; FDA, U.S. Food and Drug Administration; GvHD, graft-versus-host disease; IND, investigational new drug application; ISE, integrated summary of efficacy; ISS, integrated summary of safety; KGI, Kiryat Gat manufacturing facility; SAP, statistical analysis plan; TC, teleconference

Key Regulatory Advice

Since 2010, FDA has provided the Applicant with advice on the clinical development program for treatment of patients with hematologic malignancies in several meetings.

Key points emphasized by FDA include:

- The Phase 3 randomized control study design was adequate.
- The choice of the control arm, which included standard unmanipulated cord blood transplantation with one or two CBUs, was appropriate. FDA acknowledged that, although the benefit of double versus single UCBT was unproven in the pediatric population and was unclear in the adult population, double cord blood transplantation remains the standard of care in many transplant centers. Therefore, the protocol should have delineated specific criteria for determining whether subjects were to receive single versus double CBUs.
- The single primary endpoint of time to neutrophil engraftment could be adequate if the secondary endpoints provided supportive evidence of clinical benefit.
- In order to minimize bias and decrease imbalances in the treatment arms in regard to the secondary endpoint of incidence of Grade 2/3 bacterial or invasive fungal infections, the case report forms (CRFs) should adequately capture potential confounders, including concomitant medications (used for prophylaxis or treatment), and any implementation or changes to the selection of anti-microbial treatment due to fever neutropenia or occurrences of toxicities.
- FDA found the Applicant ’s plan to use the minimization method (rather than randomization) for subjects’ treatment assignment, followed by re-randomization method for hypothesis testing, to be acceptable. This is because subjects in the treatment arm for this study will experience a longer delay between randomization and transplant than subjects in the control arm.

- For any key secondary endpoint(s) that the Applicant intended to investigate for potential inclusion in the labeling, FDA recommended that a family-wise type I error rate be controlled to support the regulatory decision making.
- An integrated summary of efficacy (ISE) and an integrated summary of safety (ISS) should be included in the biologics license application (BLA) submission. The ISE may include justification for not pooling all studies, but the studies with subjects who had hematologic malignancies and received the investigational product should be included in a pooled analysis for FDA's review. An integrated safety analysis for all subjects in the omidubicel safety database should be included in the ISS.
- FDA agreed with the Applicant 's plan to only submit data from Study P0501, as this study was expected to be Clinical Data Interchange Standards Consortium (CDISC) compliant; since Studies P0101, (b) (4), and P0301 began prior to 17 December 2016, the data from these supporting studies were not able to be submitted in TM and ADaM format. Datasets for the ISE and ISS should be CDISC compliant.
- Product comparability (of the proposed commercial product to the product used in the IND studies) should be based primarily on CMC determination. When changes are introduced to a manufacturing process, a comparability study should be conducted to demonstrate that product quality and critical quality attributes have not been adversely affected. The comparability data are critical in determining whether the clinical data generated under Study P0501 can be used to support a BLA. Data generated from the expanded access protocol Study P0701, which was conducted as a clinical bridging study, may be used to support safety outcomes but not effectiveness of the investigational product due to the difference in study design from that of Study P0501.
- FDA advised the Applicant not to submit any BLA modules until product comparability had been established.

On 8 February 2022, the Applicant submitted the initial module for the rolling BLA 125738 submission for the indication of the treatment of patients with hematologic malignancies in need of a hematopoietic stem cell transplant, with the results of Study P0501 as the basis of efficacy. Key dates for major BLA milestones are listed in Table 2.

Table 2. BLA Major Milestones

Milestone	Date
Initial non-clinical module received	8 February 2022
Clinical module received	4 March 2022
CDISC meeting	21 April 2022
Final module CMC and labeling received	1 June 2022
Dataset walkthrough and AOM	8 June 2022
PNR request	9 June 2022
First committee meeting	22 June 2022
Filing meeting	13 July 2022
Proprietary name unacceptable	7 September 2022
PNR request-resubmission	22 September 2022
Mid-cycle meeting	4 October 2022
Reconsideration of non-proprietary name request	12 October 2022
Major amendment letter	18 November 2022
Late-cycle meeting	23 February 2023
Original PDUFA action date	30 January 2023
Revised PDUFA action date	1 May 2023

Abbreviations: AOM, application orientation meeting; BLA, biologics license application; CDISC, Clinical Data Interchange Standards Consortium; CMC, chemistry, manufacturing and controls; PNR, proprietary name review; PDUFA, Prescription Drug User Fee Act

The IRs to the Applicant from the clinical review team are found in Table 3 below.

Table 3. Clinical Information Requests

Clinical Information Request	Date of Request
Clinical IR #1	6 July 2022
Clinical IR #2	21 July 2022
Clinical IR #3	1 September 2022
Clinical IR #4	12 September 2022
Clinical IR #5	10 & 14 November 2022
Clinical IR #6	8 December 2022
Clinical IR #7	10 January 2023
Clinical IR #8	3 February 2023
Clinical IR #9	8 February 2023
Clinical IR #10	13 February 2023
Clinical IR #11	3 April 2023
Clinical IR #12	7 April 2023

Abbreviation: IR, information request

The BLA clinical review covered the original BLA submission and the following amendments:

Table 4. BLA Amendments – Clinical/Clinical Pharmacology/Statistical/Pharmacovigilance

Amendment Number	Sequence Number	Date of Submission	Amendment Description – Clinical Summary
0	0001	8 February 2022	Rolling submission: Part 1 Module 1. Meetings Summaries, PREA Exemption, BTD, ODD
1	0002	3 March 2022	Part 2 Module 1, 2, 5. Clinical and Risk Management Plan
2	0003	1 June 2022	Part 3 Module (Final) 1, 2, 3, 5. Labeling, ISS, ISE
6	0007	29 June 2022	Response to IR to resubmit the USPI to comply with the PL)
8	0009	30 June 2022	USPI Clean Version
9	0010	5 July 2022	aCRFs for Clinical Studies, Correction in STF in the previously submitted Sequence number 0002
10	0011	6 July 2022	Response to IR (Biostatistics #1): analysis programs for safety and efficacy analyses.
11	0012	12 July 2022	Response to IR (Clinical #1): Datasets walkthrough
13	0014	27 July 2022	Response to IR (Clinical #2): ANC, platelets, Engraftment, and hospitalization
15	0016	15 August 2022	Response to pharmacovigilance IR: updated risk management “non-REMS” plan
17	0018	31 August 2022	Response to clinical pharmacology IR: Dose-efficacy analyses
20	0021	7 September 2022	Response to IR (Clinical #3): Chimerism assays, infections, AEs, Laboratory data files, GvHD grading
22	0024	15 September 2022	Partial response to IR (Clinical #4): Timeline for submission of updated lab data files and chimerism assays, and febrile neutropenia
28	0029	30 September 2022	Partial response to IR (Clinical #4): Febrile neutropenia
26	0027	29 September 2022	Day 120 Safety update report
33	0034	8 November 2022	Response to IR (Clinical #4): ADLB datasets with incomplete ANCs, chimerism assays details
36	0038	15 November 2022	Response to IR (Clinical #5): Updated ADLB (ANC) and ADTTE datasets. Classified as a Major Amendment
41	0042	13 December 2022	Response to IR (Clinical #6): Updated ADLB (lab toxicity)
46	0047	17 January 2023	Response to IR (Clinical #7): Chimerism assays details on LOQ

Amendment Number	Sequence Number	Date of Submission	Amendment Description – Clinical Summary
50	0051	7 February 2023	Response to IR (Clinical #8): Clarification regarding intended CBUs, chimerism "window" visits, AEs vs. ARs
51	0052	10 February 2023	Response to IR (Clinical #9): Request for additional data on Subject ID (b) (6)
52	0053	16 February 2023	Response to IR (Clinical #10): Request for additional data on Subject ID (b) (6)
62	0063	4 April 2023	Response to IR (Clinical #11): Request for clarification regarding infections in Study P0301
64	0065	10 April 2023	Response to IR (Clinical #12): Request for subjects' IDs of all subjects who experienced relapse of underlying malignancy in study P0501

Abbreviations: aCRFs, annotated case report forms; AE, adverse event; ANC, absolute neutrophil count; AR, adverse reaction; BTD, breakthrough therapy designation; CBU, cord blood unit; GvHD, graft versus host disease; IR, information request; ISE, integrated summary of efficacy; ISS, integrated summary of safety; LOQ, limit of quantification; ODD, orphan drug designation; REMS, risk evaluation and mitigation strategy; PLR, physician labeling rule; PREA, Pediatric Research Equity Act; STF, study tagging files; USPI, U.S. Prescribing Information

Notably, the Applicant requested a proprietary name review for (b) (4) The Center for Biologics Evaluation and Research's Advertising and Promotional Labeling Branch (CBER/APLB) and CMC review teams concluded that (b) (4) was unacceptable because it is considered to be misleading by implying that the product is a pluripotent stem cell product. The product is classified as a progenitor hematopoietic stem cell product that is multipotent, rather than as a pluripotent stem cell product. The Applicant submitted a new proprietary name review for consideration (primary: OMISIRGE or alternate: (b) (4)). FDA found OMISIRGE to be acceptable.

In addition, FDA determined that omidubicel should be the United States Adopted Name (USAN) for the CF only and, therefore, a new USAN should be provided for the entire product which consists of the CF and NF. The USAN (b) (4) was assigned; however, the Applicant requested FDA reconsideration to retain the name omidubicel to reference the entire product. The Applicant stated that the clinical development program of the product consisted of trials in HSCT where both the CF and NF were used as the graft source for the transplant; the CF was never administered without the NF. The product (both CF and NF) was referred to by the name omidubicel. A new USAN for the product this late in the product's development and during the BLA review may cause confusion among health care providers (HCPs) with impact to patient safety and access to the product. Therefore, changing the name of the product at this time, and retaining the name of omidubicel to reference the CF only, may be perceived by the medical community as implying that the Phase 3 trial results, in addition to the results of the previous clinical studies, were based on the CF only. This potential outcome is of concern, as it does not accurately represent the clinical development program and could mislead HCPs to administer the CF only, compromising patient outcomes. Furthermore, retaining the name omidubicel to reflect the CF only would also present a major concern as no clinical data exist to support the use of the CF only. Based on the Applicant's justification, FDA decided to retain the name omidubicel to reference the entire product.

2.6 Other Relevant Background Information

Not applicable (N/A).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The application was adequately organized and integrated to accommodate the conduct of a complete clinical review. On 5 July 2022, the Applicant submitted annotated CRFs for the clinical studies and corrected the study tagging files which were missing/incorrect from the original submission (Seq 0002).

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant stated that the studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki, current Good Clinical Practice, and in compliance with Federal and local regulatory requirements. Institutional Review Board (IRB)/Ethics Committee approval of the protocol, informed consent forms, and patient information and/or advertising (as relevant) was obtained prior to the authorization of omidubicel shipment to a study site and prior to any study procedure being conducted. All amendments to the protocol received IRB/Ethics Committee approval prior to implementation of any changes.

After consideration of factors including subject enrollment and outcomes, protocol deviations, financial disclosures, geographic location, and inspection history, the FDA's Bioresearch Monitoring program (BIMO) conducted inspections for four clinical sites:

- Claudio Brunstein, MD — University of Minnesota
- Andrew Rezvani, MD — Stanford University Cancer Institute
- Mitchell Horwitz, MD — Duke University Medical Center
- Patrick Stiff, MD — Loyola University Medical Center

Overall, the inspections verified the data reported in the BLA, including but not limited to subject eligibility, protocol deviations, study drug administration, primary efficacy endpoint, and adverse events (AEs) for all subjects enrolled at the inspected clinical sites. Form FDA 483s, Inspectional Observations, were issued to Drs. Rezvani, Horowitz, and Stiff. BIMO determined the site's responses and corrective actions to be adequate if successfully implemented. The clinical review team did not consider the findings to have impacted data integrity or affected interpretation of the study results (see discussion below).

<u>Protocol Violations/Deviations:</u>

Protocol deviations were classified as minor, major, or critical, as defined in the protocol.

Major protocol deviations (MPDs) included issues that could potentially impact the integrity of the study or treatments such as consenting, eligibility, or administration of the study treatments. These included violations in the administration of the allocated graft or the dosing of the conditioning regimen, as well as the administration of granulocyte colony-stimulating factor (GCSF) or dosing of the mandatory prophylaxis regimen. Other protocol deviations were

classified as minor protocol deviations (mpds). Overall, a total of 61 MPDs and 740 mpds were reported for a total of 115/125 (94%) randomized subjects. No critical deviations were reported. Table 5 and Table 6 below provide a summary of deviation type by category in the intent-to-treat (ITT) population. The majority of deviations were reported as "Other protocol procedure or assessment", encompassing 11 MPDs and 476 mpds. These included primarily assessments that were missed or performed outside of the protocol allowed time window. A total of 9 MPDs and 51 mpds were reported as infusion day deviations in subjects treated with either omidubicel or UCBU. Most frequently, infusion day deviations were related to the dosing of pre-medications administered as infusion support. Among the subjects treated with omidubicel, there were more deviations reported related to product storage, or infusion not performed per protocol, as compared to the control arm. This difference was expected, since omidubicel was an experimental treatment that the centers had less experience with compared to the standard of care for those who received UCBU. Omidubicel infusions required closer monitoring to ensure correct utilization and subjects' safety and was therefore also associated with more deviations.

Table 5. Study P0501 Protocol Deviations by Type

Protocol Deviation Type	Omidubicel N=62 Deviations (n)	Omidubicel N=62 Subjects n (%)	UCBU N=63 Deviations (n)	UCBU N=63 Subjects n (%)
Minor protocol deviations [a]	370	59 (95)	370	56 (89)
Major protocol deviations [a]	34	25 (40)	27	23 (37)
Covid-19-related deviations	33	14 (23)	50	12 (19)

Source: FDA analysis ADDV dataset

a. Not including Covid-19-related deviations

Abbreviations: N, total number of subjects per treatment arm from the ITT population; n, number of deviations or subjects per deviation category for each treatment arm; ITT, intent-to-treat; UCBU, unmanipulated cord blood unit

Table 6. Study P0501 Protocol Deviations by Category

Protocol Deviation Category	Omidubicel N=62 Deviations (n)	Omidubicel N=62 Subjects n (%)	UCBU N=63 Deviations (n)	UCBU N=63 Subjects n (%)
All categories [a]	404	59 (95)	397	56 (89)
Eligibility criteria violation	2	2 (3.2)	2	2 (3.2)
Informed consent	5	5 (8)	5	4 (6)
Infusion day [b]	40	27 (44)	20	16 (25)
Other	5	5 (8)	1	1 (1.6)
Other protocol and procedure assessment	228	53 (86)	259	51 (81)
Received excluded concomitant medication	0	NA	1	1 (1.6)
Received non-randomized/OOS product	0	NA	1	1 (1.6)
Reporting timelines	25	17 (27)	24	17 (27)
Safety	2	2 (3.2)	0	NA
Screening assessment or procedure	79	35 (57)	66	32 (51)
Study medication and administration	16	14 (23)	20	15 (24)

Source: FDA analysis ADDV dataset

a. Not including Covid-19-related deviations

b. For Infusion day deviations, the data are provided according to the actual treatment received rather than the planned treatment – Omidubicel (N=52) and UCBU (N=56)

Abbreviations: N, total number of subjects per treatment arm from the ITT population; n, number of deviations or subjects per deviation category for each treatment arm; OOS, out-of-specification; ITT, Intent-to-treat; UCBU, unmanipulated cord blood unit

Protocol deviations that were pre-approved by IRB/FDA were categorized as “changes in research.” A total of eight changes in research were documented which included: infusing subjects with omidubicel that was out-of-specification (OOS), performing eligibility assessments out-of-window, changing the conditioning regimen dose, or using blood sample drawn for immune reconstitution to assess chimerism.

A total of 83 coronavirus disease 2019 (COVID-19)-related protocol deviations were reported in 26 subjects. All these deviations were mpds and were related to informed consent deviations, or to missed assessments or assessments performed out-of-window. The deviations were not considered to have a major impact on the outcomes of the study.

Reviewer comment: *In response to the clinical IR requesting updated laboratory datasets, the Applicant identified new protocol deviations: overall, 39 minor laboratory assessment protocol deviations related to ANC data were newly identified in 27 subjects, and seven MPDs were newly identified in seven subjects.*

The reviewer recommended that BIMO inspects the clinical sites with the most protocol violations.

In conclusion, the major protocol deviations appeared to be balanced between the study arms except for infusion day deviations, which were predictably more in the omidubicel arm. The deviations observed are not believed to have impacted subjects’ safety, the overall data quality of the study, or the interpretation of the study results.

3.3 Financial Disclosures

Covered clinical study: P0501
Was a list of clinical investigators provided? **X** Yes ☐ No (Request list from Applicant)
Total number of investigators identified: **485** principal investigators and sub-investigators
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0**
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____ Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from Applicant) Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☐ No (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): **0** Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from Applicant)

Reviewer comment: *The Applicant stated that they adequately disclosed the financial interests/arrangements with clinical investigators as recommended in the Guidance for Industry: "Financial Disclosure by Clinical Investigators." No financial conflicts of interest were identified.*

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Product name: Omidubicel (OMISIRGE, formerly NiCord)): Allogeneic Unrelated Umbilical Cord Blood Cells (b) (4) Selected with (b) (4))
Expanded Ex Vivo in the presence of Nicotinamide (NAM) along with (b) (4) Negative Fraction.

Omidubicel is an ex vivo expanded allogeneic human hematopoietic CD34+ progenitor cell therapy that contains two fractions from a single CBU: 1) ex vivo CF of CD34+ cells that will engraft and 2) a supportive 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

(DPs) are individually cryopreserved in 10% dimethyl sulfoxide (DMSO) until thawed for infusion. Each DP is diluted (b) (4) with infusion solution (IS), composed of human serum albumin and dextran, just prior to infusion by a closed port system. Each CF and NF DP has a corresponding IS DP bag for a total of two IS bags.

Omidubicel is manufactured from a cryopreserved CBU that is thawed and undergoes (b) (4) selection with the (b) (4) reagent using the (b) (4) instrument. The (b) (4) selected cells are then cultured in a medium containing (b) (4) NAM, (b) (4) (b) (4) The specific culture conditions allow the (b) (4) cells to proliferate while retaining a progenitor phenotype for engraftment. After the (b) (4) the remaining 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) cells. The final CF DP contains at least 8.0×10^8 total number viable cells 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 liquid nitrogen (LN_2) for storage at ≤-150°C.

The NF (b) (4) is manufactured from cells eluted during the CF (b) (4) selection and is cryopreserved. The final NF DP contains at least 4.0×10^8 total number viable cells and 2.4×10^7 CD3+ cells.

After manufacturing is complete, the cryopreserved omidubicel is released for shipping to the transplant center depending on if it passes the available in-process control testing. Because of the seriousness of the therapeutic condition, the CF DP is released for infusion before the final sterility results and harvest day colony-forming units results are available. The final CF DP release occurs after all release testing results are obtained and the acceptance criteria has been met. Release test methodology has been validated and release specifications have been reviewed and are 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 NF DP is thawed, diluted (b) (4) with IS DP, and administered within an hour of administration of the NF DP.

The commercial omidubicel product is to be manufactured at Gamida Cell Ltd. (GC) Kiryat Gat manufacturing facility (KGI). Notably, KGI is a (b) (4) facility and started manufacturing clinical batches of omidubicel in (b) (4) For the Phase 1 to Phase 3 clinical studies, omidubicel was manufactured at (b) (4) and (b) (4)

The CMC reviewer considers the manufacturing process to have been adequately validated. The chain of identity/chain of custody is appropriate for a patient-specific product and starts with the identification of the CBU, being maintained through the manufacturing and shipping process until administration at the transplant center using product specific identifiers.

The following major CMC concerns were raised during review of this submission and were resolved through multiple information requests (IRs):

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) to reduce residual cell culture impurities in the CF DP.
4) Higher than anticipated (b) (4) impurities in the KGI PPQ batches.
5) Lack of the 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 include both the CF and NF DPs.

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

7) A post-marketing confirmatory study to determine the concentration of residual (b) (4) in Misfire to provide assurance that residual (b) (4) levels remain within the established manufacturing range.
8) A post-marketing confirmatory study to assess the elemental leachables in a real process study, or relevant simulated study.
9) Agreement from the Applicant to notify the FDA when the master file issues are adequately resolved.

The CMC review team recommends approval, with three PMCs.

4.2 Assay Validation

N/A

4.3 Nonclinical Pharmacology/Toxicology

Omidubicel is a human-specific DP. No animal studies have been performed to evaluate the effects of omidubicel on carcinogenesis, mutagenesis, or impairment of fertility.

4.4 Clinical Pharmacology

The Clinical Pharmacology (Clin Pharm) reviewer provided the review for this Section.

Conventional clinical pharmacology studies such as absorption, distribution, metabolism, and excretion, drug-drug interaction, or renal and hepatic impairment studies were not performed due to the cellular nature of omidubicel. The clinical pharmacology review focused on pharmacodynamics (i.e., immune reconstitution) and dose-response assessments.

4.4.1 Mechanism of Action

CD34+ cell number is an established predictor of HSCT clinical success. The CF DS manufacturing process is designed to expand the progenitor population and to preserve CD34+

cell stemness and engraftment potential. NAM is an allosteric small molecule inhibitor of NAD-enzymes. NAM, with additional cytokines, modulates several transcription factors involved in hematopoietic stem cells self-renewal, differentiation, apoptosis, and migration. NAM can also downregulate genes, controlling the production of reactive oxygen species, matrix metalloproteinases, and reactive nitrogen species, while upregulating genes controlling metabolism and senescence.

The precise mechanism of action of action of omidubicel is unknown. Like transplantation with UCB, following single dose administration of omidubicel, the HPCs 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.

The CF and NF DP are administered to the patient sequentially.

4.4.2 Human Pharmacodynamics

Immune Reconstitution

Immune reconstitution after 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 Immune reconstitution analysis serves as a pharmacodynamic endpoint and provides supportive clinical evidence of effectiveness for omidubicel. The Applicant evaluated immune reconstitution in Studies P0301 and P0501:

Immune reconstitution results for Study P0301:

- The results were highly variable, but a positive trend in number of CD3+, CD4+, and CD8+ T cells from Day 70 to Day 180 was observed.

Immune reconstitution results for Study P0501:

- A total of 125 subjects were randomized in Study P0501, of which 67 subjects consented to participating in the immune reconstitution sub-study. A total of 37 subjects from 14 global sites were included in this sub-study, of whom 17 were transplanted with omidubicel and 20 with UCBU. Most subjects who consented but were not included in the sub-study did not have a sufficient sample collected for the immune reconstitution analysis. Table 7 below provides details of CD3+, CD4+, and CD8+ T cells.
- The CD4+ and CD8+ T cells were higher in the omidubicel group on Days 7 and 14 than in the UCBU group, which suggest earlier immune reconstitution. The CD4+ and CD8+ cells were similar in the two arms from Day 21 to 1 year.
- The results of natural killer (NK) cells (CD56+) analysis demonstrated that the omidubicel group showed a more rapid recovery during the first 3 weeks after transplant. After 1 month, NK reconstitution was similar between the UCBU and omidubicel groups.
- B-cell (CD19+) results were comparable between the omidubicel and UCBU groups.
- Overall, a higher early immune reconstitution (CD4+ cells, CD8+ cells, and NK cells at Day 7 and 14) was observed for omidubicel versus the UCBU group. However, the Day

7 and 14 immune reconstitution results are generally a small fraction of the overall immune recovery observed over the 1-year period.

- A positive correlation between the CD34+ cell dose and the reconstitution of T-cells (CD3+, CD4+, and CD8+ cells) and NK cells was identified. These data provided supportive evidence that the CD34+ progenitor cell content in the omidubicel group facilitated rapid reconstitution of the lymphoid and myeloid lineages in transplanted subjects.
- For subjects treated with omidubicel, but not with UCBU, a correlation was identified between CD3+ and CD4+ T cells and faster neutrophil engraftment (Day 7). A similar relationship was also observed for CD3+ T cells, CD8+ T cells, and CD19+ B cells and faster platelet engraftment. For subjects transplanted with UCBU, such correlations were observed after 14 to 28 days.

Table 7. Study P0501: Summary of CD3+, CD4+ and CD8+ T cells

Visit Day Product	CD3+ (cells / µL)	CD4+ (cells / µL)	CD8+ (cells / µL)
Day 7	-	-	-
Omidubicel (n=13)	2.8±19.6	1.9±13.4	0.9±6.2
UCBU (n=17)	0.8±0.3	0. 5±0.1	0.2±0.3
Day 14	-	-	-
Omidubicel (n=15)	87.6±31.4	47.2±14.7	61.8±20.0
UCBU (n=17)	28.1±8.4	6.1±3.8	15. 6±5.3
Day 21	-	-	-
Omidubicel (n=16)	171.7±47.5	106.6±23.6	82.4±29.2
UCBU (n=16)	152.9±35.1	61.1±17.3	76.0±20.2
Day 70	-	-	-
Omidubicel (n=15)	208.0±117.0	96.6±40.1	87.9±101.6
UCBU (n=19)	299.8±41.4	199.4±25.7	64.9±26.9
Day 180	-	-	-
Omidubicel (n=14)	735.2±342.4	427.4±190.1	197.4±191.4
UCBU (n=12)	396.3±243.3	165.5±182.0	108.5±84.0
Day 365	-	-	-
Omidubicel (n=9)	598.7±423.7	405.8±219.6	195.2±206.7
UCBU (n=9)	796.7±123.7	341.7±85.5	168.2±95.3

Source: FDA clin pharm reviewer
Abbreviation: UCBU, unmanipulated cord blood unit

Dose Response for Study P0301

- The median TNC per kg was 4.9×10^7cells/kg (range 2-13 $\times 10^7$cells/kg).
- The median CD34+ cell dose was 6.3×10^6cells/kg (range 1.4-14.9 $\times 10^6$/kg).
- Thirty-four of 36 (94%) subjects treated with omidubicel achieved neutrophil engraftment, defined as ANC by Day 42 post-transplant.
- There was no clear dose-efficacy relationship, potentially due to the limited sample size and variability.

Dose-Response for Study P0501:

- The median TNC dose was 4.7 × 10^7cells/kg (range 1.7-12.4 × 10^7/kg) for the omidubicel group and 3.4 ×10^7/kg (range 1.3-8.0 × 10^7/kg) for the UCBU group.
- The median CD34+ cell dose was 9 × 10^6cells/kg (range 2-48 × 10^6/kg) for the omidubicel group and 0.2 (range 0-0.8 × 10^6cells/kg) for the UCBU group.
- The median time to neutrophil engraftment was 12 days for the omidubicel group and 22 days for the UCBU group.
- A dose-efficacy assessment was conducted on log transformed data using a linear model between cell dose (TNC per kg and CD34+ cells per kg) and days to neutrophil engraftment or recovery.
- The linear regression model showed association between cell dose tested (TNC/kg and CD34/kg) and the days to neutrophil recovery or neutrophil engraftment. The model suggests that days to neutrophil recovery decrease as cell dose increases.
- The inclusion of age as a covariate did not improve the dose-response model.

Dose-Response for Studies P0301 and P0501 combined:

- The linear regression models showed an association between cell dose (TNC/kg and CD34/kg) and days to neutrophil engraftment.
- The dose-response model estimates a shorter day to neutrophil engraftment with a higher dose of omidubicel (TNC/kg or CD34/kg).
- The median (min, max) CD34 dose was 7.25 × 10^6cells/kg (1.5 × 10^6, 47.6 ×10^6cells/kg). The median (min, max) neutrophil engraftment days was 13 (7, 35 days) and 8 (6, 20) for subjects who received lower and higher than the median CD34 dose, respectively.
- No relationship was identified between cell dose (TNC/kg and CD34/kg) and platelet engraftment.

Overall, the dose-response analysis supports the proposed single dose administration of a minimum of 12 × 10^8 TNC (from both CF and NF) and a minimum of 9.2 × 10^7 CD34+ cells (from CF).

4.4.3 Human Pharmacokinetics

N/A

4.5 Statistical

The statistical reviewer replicated the primary and secondary study endpoint analyses according to the Applicant's statistical analysis plan (SAP), which were supported by the data submitted from Study P0501. The statistical reviewer also performed post hoc analyses of time to neutrophil recovery and subgroup analyses as requested by the clinical review team. See discussion of these efficacy analyses in Section 6.1.11.

4.6 Pharmacovigilance

No safety concerns have been identified that would require a risk evaluation and mitigation strategy or post-marketing requirement (PMR). The Applicant's proposed intervention plan for

identified risks, such as infusion reactions, graft failure, GvHD, and malignancies of donor origin (e.g., post-transplant lymphoproliferative disorders [PTLD]), include routine pharmacovigilance interventions. In addition, routine pharmacovigilance will be employed to monitor potential risks of transmission of serious infections or rare genetic diseases and adverse effects from DMSO exposure.

The effects of omidubicel on fertility and outcome of pregnancy are not fully evaluated. There is no clinical trial experience in subjects 65 years and older, and minimal experience with use of the product in children. The pharmacokinetic and safety profiles of omidubicel in patients with renal and hepatic impairment are not known.

Toxicities are managed by administration of appropriate prophylactic and therapeutic agents, surveillance for hematologic abnormalities and infections, and close clinical monitoring of patients at dedicated transplant centers. The Applicant is proposing to implement Gamida Cell Assist, which is a web-based, customer-management system for ordering of omidubicel, maintaining chain of identity for individual patients, and assisting prescribing HCPs and patients who are treated with omidubicel. Post-marketing monitoring of known or potential risks of omidubicel and detection of currently unknown safety events will be collected on an ongoing basis through the CIBMTR.

Reviewer comment: *Clinical trials with omidubicel in subjects with hematologic malignancies have identified similar risks to those observed in allogeneic transplantation with other graft sources. The United States Prescribing Information (USPI) will include information on identified and potential adverse drug reactions associated with omidubicel.*

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

Study P0501 served as the primary basis for the clinical review. In addition, the Applicant submitted supportive data from other studies of omidubicel in subjects with hematologic malignancies and benign hematologic conditions, as listed in Section 5.3 below.

Safety and efficacy analyses were performed using JMP 16 (SAS Institute, Inc.) and the Medical Dictionary for Regulatory Activities (MedDRA) Adverse Events Diagnostic v3.6 (FDA, Silver Spring, MD), Data cutoff date was 29 April 2021.

Efficacy

The determination of efficacy was based primarily on the analysis of data submitted for the 125 subjects in the ITT population in Study P0501. The clinical review focused on confirmation of the prespecified primary endpoint of time to neutrophil engraftment, and the secondary endpoints including the incidence of Grade 2/3 bacterial of invasive (Grade 3) fungal infection by Day 100, days alive and out of hospital (OOH) in the first 100 days following transplantation, and platelet engraftment by 42 days following transplantation. To determine clinical benefit of the

investigational product, the clinical review focused on time to neutrophil recovery and incidence of Grade 2/3 bacterial and Grade 3 fungal infections, which are considered the clinically meaningful efficacy outcome measures for this product.

Safety

The main safety population (SP) included 108 subjects from Study P0501 (52 subjects transplanted with omidubicel and 56 subjects transplanted with UCBU) who had hematologic malignancies and were transplanted within 90 days following randomization with product that met specifications for release. In Section 5 of the USPI, the SP represented all 117 subjects who received at least one dose of omidubicel, with or without UCBU, and who had underlying hematologic malignancies or benign hematologic conditions.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The key material used in the review of the efficacy and safety includes:

- IND 14459 eCTD documents and FDA reviews
- Prior regulatory history
- BLA 125738/0 submission (eCTD documents, datasets and clinical amendments listed in Table 4 Section 2.5 of this review), which includes the Applicant's response to the review team's several IRs
- Proposed labeling
- Relevant published literature

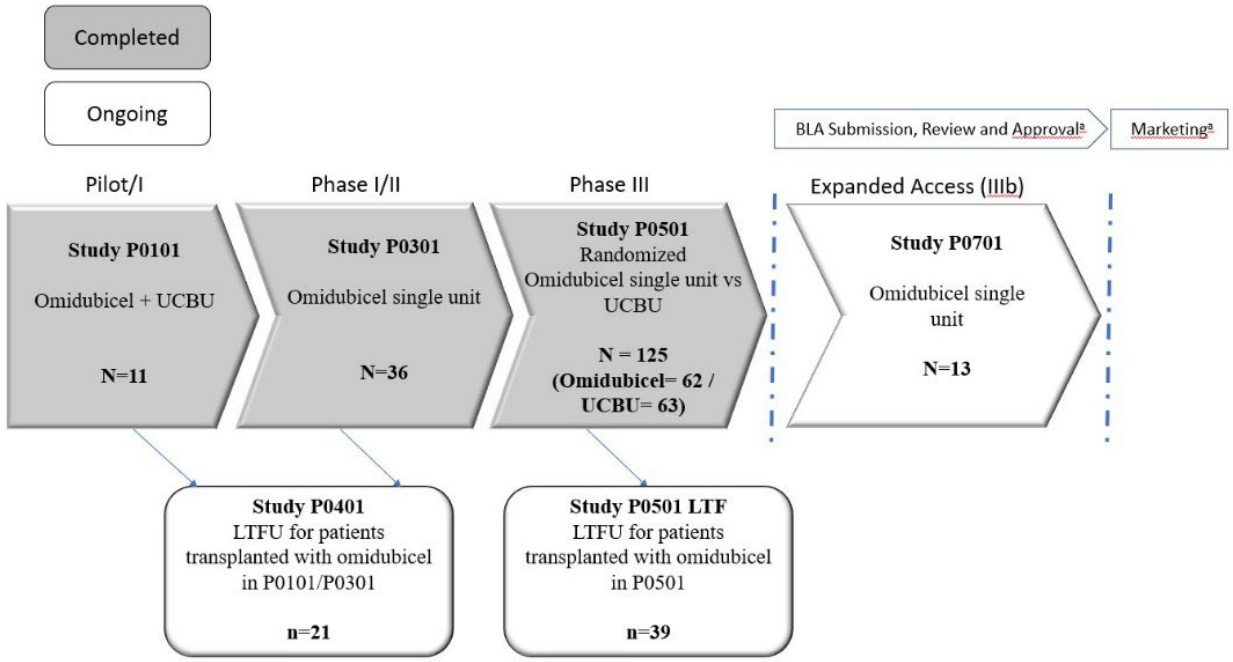
5.3 Table of Studies/Clinical Trials

The clinical development program consisted of trials with omidubicel in HSCT under IND 14459 and IND (b) (4) Omidubicel has also been studied in an investigator-sponsored study at the National Institutes of Health (NIH) under IND (b) (4)

The Applicant conducted nine clinical studies with omidubicel (six prospective treatment trials and two follow-up safety trials, in addition to one trial in the expanded access protocol). A total of 213 subjects have participated in these studies involving the use of omidubicel. Figure 1 describes the clinical development program of omidubicel in subjects with hematologic malignancies. These studies included three completed studies (P0101, P0301, and P0501), one ongoing expanded access study (P0701), and two ongoing long-term follow-up (LTFU) studies (P0401 and P0501 LTF).

Table 8 summarizes the Phase 1/2/3b clinical studies conducted with omidubicel in subjects with hematologic malignancies and with (b) (4)
(b) (4) Note that Table 8 doesn't include the Phase 3 Study P0501. Refer to Section 8.2.1 for details of these studies.

Figure 1. Clinical Development Program of Omidubicel in Subjects With Hematologic Malignancies



Source: BLA 125738/0 Module 2.5 Clinical Overview Figure 1
N=number of subjects analyzed (Studies P0101, P0301, P0501, P0701)
n=number of subjects enrolled, previously treated with omidubicel (P0401, P0501 LTF)
a. Subject to FDA approval
Abbreviations: BLA, biologics license application; LTFU, long-term follow-up; UCBU, unmanipulated cord blood unit

Table 8. Summary of Clinical Studies Conducted With Omidubicel

Study Number	ClinicalTrials.gov ID	Title	Countries	Patient Population	Phase	Patients Treated with Omidubicel	Treatment Description	Status
GC P#01.01.020 P0101	NCT01221857	Allogeneic Stem Cell Transplantation of omidubicel, in Combination with a Second, UCBU in Patients with Hematologic Malignancies	U.S.	Hematologic malignancies	I/Pilot	11	Omidubicel in combination with UCBU	Completed
GC P#03.01.020 P0301	NCT01816230	Allogeneic Stem Cell Transplantation of omidubicel in Patients with Hematological Malignancies	U.S., Spain, Italy, Netherlands, Singapore	Hematologic malignancies	I/II	36+2	Single unit omidubicel (36); 2 patients received omidubicel + UCBU	Completed
GC P#07.01.020 P0701	NCT04260698	An Open-Label Expanded Access Study of omidubicel, for Allogeneic Transplantation in Patients with Hematological Malignancies	U.S.	Hematologic malignancies	IIIb (Expanded access)	13	Single unit omidubicel	Ongoing
(b) (4)								

Abbreviations: CBT: Cord blood transplantation; MDS: Myelodysplastic Syndrome; UCBU: Unmanipulated cord blood unit

Source: Adapted from BLA 125738/0 Module 5.3.5.1, Clinical Study Report (CSR) Section 7 Table 2
Note that this table doesn't include the Phase 3 P0501 study.
Abbreviation: UCBU, unmanipulated cord blood unit

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

This application was not presented at an Advisory Committee meeting or to external consultants because it did not raise significant efficacy or safety issues for the proposed indication.

5.4.2 External Consults/Collaborations

None.

5.5 Literature Reviewed

Anasetti, C, BR Logan, SJ Lee, EK Waller, DJ Weisdorf, JR Wingard, CS Cutler, P Westervelt, A Woolfrey, S Couban, G Ehninger, L Johnston, RT Maziarz, MA Pulsipher, DL Porter, S Mineishi, JM McCarty, SP Khan, P Anderlini, WI Bensinger, SF Leitman, SD Rowley, C Bredeson, SL Carter, MM Horowitz, DL Confer, Blood, and N Marrow Transplant Clinical Trials, 2012, Peripheral-blood stem cells versus bone marrow from unrelated donors, N Engl J Med, 367(16):1487-1496.

Blouin, AG and M Askar, 2022, Chimerism analysis for clinicians: a review of the literature and worldwide practices, Bone Marrow Transplant, 57(3):347-359.

BMT CTN, 2013, Blood and Marrow Transplant Clinical Trials Network: Technical Manual of Procedures (version 3), Sponsored by the National Institute of Health.

Cordonnier, C, S Maury, P Ribaud, M Kuentz, F Bassompierre, E Gluckman, and S Chevret, 2006, A grading system based on severity of infection to predict mortality in allogeneic stem cell transplant recipients, Transplantation, 82(1):86-92.

Filipovich, AH, D Weisdorf, S Pavletic, G Socie, JR Wingard, SJ Lee, P Martin, J Chien, D Przepiorka, D Couriel, EW Cowen, P Dinndorf, A Farrell, R Hartzman, J Henslee-Downey, D Jacobsohn, G McDonald, B Mittleman, JD Rizzo, M Robinson, M Schubert, K Schultz, H Shulman, M Turner, G Vogelsang, and ME Flowers, 2005, National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report, Biol Blood Marrow Transplant, 11(12):945-956.

Glucksberg, H, R Storb, A Fefer, CD Buckner, PE Neiman, RA Clift, KG Lerner, and ED Thomas, 1974, Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors, Transplantation, 18(4):295-304.

Jagasia, MH, HT Greinix, M Arora, KM Williams, D Wolff, EW Cowen, J Palmer, D Weisdorf, NS Treister, GS Cheng, H Kerr, P Stratton, RF Duarte, GB McDonald, Y Inamoto, A Vigorito, S Arai, MB Datiles, D Jacobsohn, T Heller, CL Kitko, SA Mitchell, PJ Martin, H Shulman, RS Wu, CS Cutler, GB Vogelsang, SJ Lee, SZ Pavletic, and ME Flowers, 2015, National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report, Biol Blood Marrow Transplant, 21(3):389-401 e381.

Kindwall-Keller, TL and KK Ballen, 2020, Umbilical cord blood: The promise and the uncertainty, Stem Cells Transl Med, 9(10):1153-1162.

Parikh, S, JA Brochstein, E Galamidi, A Schwarzbach, and J Kurtzberg, 2021, Allogeneic stem cell transplantation with omidubicel in sickle cell disease, Blood Adv, 5(3):843-852.

Przepiorka, D, D Weisdorf, P Martin, HG Klingemann, P Beatty, J Hows, and ED Thomas, 1995, 1994 Consensus Conference on Acute GVHD Grading, Bone Marrow Transplant, 15(6):825-828.

Ruggeri, A, M Labopin, MP Sormani, G Sanz, J Sanz, F Volt, G Michel, F Locatelli, C Diaz De Heredia, T O'Brien, W Arcese, AP Iori, S Querol, G Kogler, L Lecchi, F Pouthier, F Garnier, C Navarrete, E Baudoux, J Fernandes, C Kenzey, M Eapen, E Gluckman, V Rocha, R Saccardi, Eurocord, E Cord Blood Committee, and Netcord, 2014, Engraftment kinetics and graft failure after single umbilical cord blood transplantation using a myeloablative conditioning regimen, Haematologica, 99(9):1509-1515.

Shpall, EJ, R Champlin, and JA Glaspy, 1998, Effect of CD34+ peripheral blood progenitor cell dose on hematopoietic recovery, Biol Blood Marrow Transplant, 4(2):84-92.

Shulman, HM, KM Sullivan, PL Weiden, GB McDonald, GE Striker, GE Sale, R Hackman, MS Tsoi, R Storb, and ED Thomas, 1980, Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients, Am J Med, 69(2):204-217.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study P0501

Study P0501, "A Multicenter, Randomized, Open-Label, Phase 3 Trial of Transplantation of omidubicel, Ex Vivo Expanded, Umbilical Cord Blood-derived, Stem and Progenitor Cells, versus Unmanipulated Umbilical Cord Blood for Patients with Hematological Malignancies."

- ClinicalTrials.gov Identifier: NCT02730299
- First enrollment (first subject first visit): 20 December 2016
- Last assessment (last subject last visit): 15 April 2021 (15 months post-randomization)
- Data cutoff date: 29 April 2021, at which point all subjects reached 365 days post-transplant/15 months post-randomization

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Objective

- To assess the time to neutrophil engraftment following transplantation.

Secondary Objectives

To assess the following:

- Incidence of Grade 2/3 bacterial or invasive fungal infections by 100 days following transplantation
- Days alive and OOH in the first 100 days following transplantation
- Platelet engraftment by 42 days following transplantation

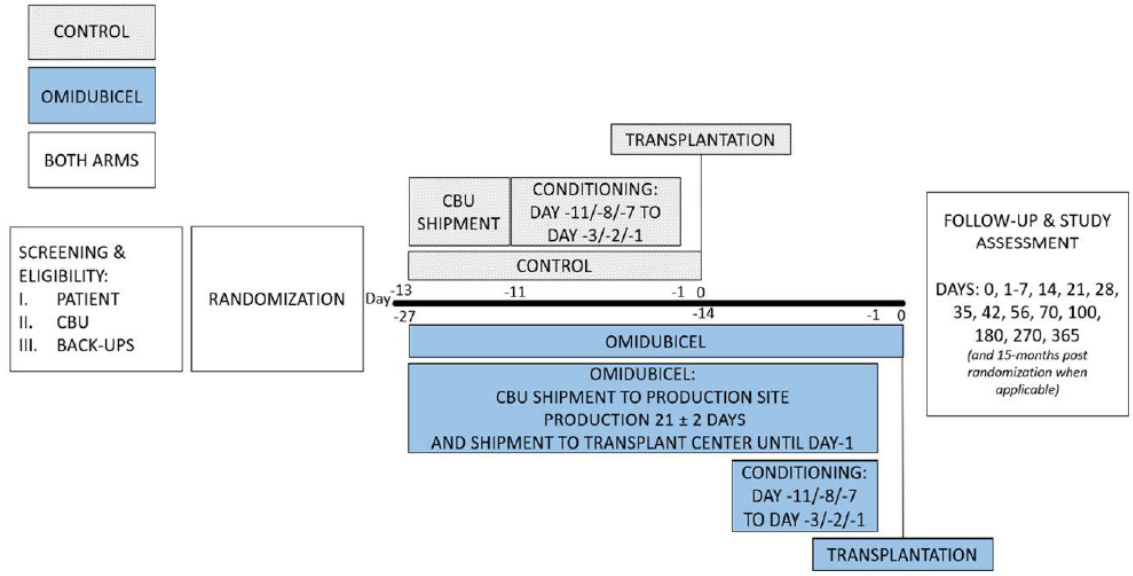
Tertiary Objective

- To assess NRM by 210 days following randomization

6.1.2 Design Overview

This study was designed as an open-label, controlled, multicenter, international, Phase 3, randomized study to compare transplantation of omidubicel to transplantation of one or two unrelated UCBU in subjects with hematologic malignancies for whom allogeneic HSCT is recommended. The study was planned to randomize 120 subjects to transplantation of omidubicel or UCBU in a 1:1 ratio. The study schema outlining the overall study design is presented in Figure 2.

Figure 2. Study P0501 Schema



Source: BLA 125738/0 CSR Section 9.2 Figure 1
Abbreviation: CBU, cord blood unit

6.1.3 Population

Key Inclusion Criteria

- Patients between 12 and 65 years old
- Patients with one of the following hematologic malignancies:

- ALL with high-risk first complete morphologic remission (CR1), or second or subsequent complete remission (CR).
- AML with CR1 that was not considered as favorable risk, CR1 with favorable risk but with additional high-risk features, or second or subsequent CR.
- Chronic myelogenous leukemia (CML) in chronic phase (who fail to respond or who are intolerant to tyrosine kinase inhibitors (TKI), accelerated phase (newly diagnosed who do not respond to TKI or patients treated with TKI who progress from chronic phase), or with prior blast crisis.
- Myelodysplastic syndrome (MDS) with International Prognostic Scoring System risk category of ≥ INT-1, or with Revised International Prognostic Scoring System risk category of intermediate or greater.
- Biphenotypic/undifferentiated/prolymphocytic/dendritic cell leukemias, NK cell malignancies, or adult T-cell leukemia/lymphoma in first or subsequent CR.
- Burkitt's lymphoma in second or subsequent CR, high-risk lymphoma in first CR, or chemosensitive lymphoma that have failed at least one prior therapy and are not candidates for autologous transplant.

- CBU criteria as described below:

- HLA-matched at 4 to 6/6 HLA class I (HLA-A and HLA-B, low resolution) and II (HLA-DRB1, high-resolution) loci with the patient. High-resolution matching was required for HLA class II. At least one allele match at DRB1 was required.
- The CBU intended for expansion was required to contain a pre-cryopreserved (postprocessing) total CD34+ cell count of at least 8×10^6, as well as a pre-cryopreserved (postprocessing) total nucleated cell (TNC) count of at least 1.8×10^9, and a TNC dose of at least 1.5×10^7 total number of viable cells (TNC)/kg of body weight.
- If the CBU was HLA-matched at 5 to 6/6 and contained a pre-cryopreserved (postprocessing) TNC dose of $<2.5 \times 10^7$ TNC/kg, OR a pre-cryopreserved (postprocessing) CD34+ cell dose of $<1.2 \times 10^5$ CD34+ cells/kg, a second CBU was required to be added for the control arm as a double cord blood transplantation.
- If the CBU was HLA-matched at 4/6 and contained a pre-cryopreserved (postprocessing) TNC dose of $<3.5 \times 10^7$ TNC/kg, OR a pre-cryopreserved (postprocessing) CD34+ cell dose of $<1.7 \times 10^5$ CD34+ cells/kg, a second CBU was required to be added for the control arm as a double cord blood transplantation (CBT).
- In case of double CBT in the control arm: The two CBUs were required to have a combined pre-cryopreserved (postprocessing) TNC dose of $\geq 3 \times 10^7$ TNC/kg.

- Subjects who were to start conditioning prior to omidubicel release for infusion (i.e., omidubicel arrival on site in adequate condition) had to have an additional partially HLA-matched CBU, reserved as a backup to the omidubicel arm in case of production failure.
- Performance score ≥70% by Karnofsky or Lansky.
- Adequate organ function:

- Cardiac: Left ventricular ejection fraction of ≥40% or left ventricular shortening fraction ≥29%
- Pulmonary function tests demonstrating FVC and FEV1 of >50% predicted for age and carbon monoxide diffusing capacity (cDLCO) >50% of predicted
- Renal: Creatinine clearance test (by Cockcroft-Gault equation) ≥60 mL/min
- Hepatic: Serum bilirubin <2.0 mg/dl; hepatic transaminases alanine transaminase and aspartate transaminase <3× upper limit of normal range

<u>Key Exclusion Criteria</u>

- MDS or CML with “marked” or “3+” fibrosis
- Chronic lymphocytic leukemia
- Fewer than 21 days had elapsed since initiation of the subject’s last chemotherapy cycle and the initiation of the HSCT preparative regimen
- Persistent clinically significant toxicities that, in the investigator’s opinion, made the subject unsuitable for transplant
- Evidence of donor-specific anti-HLA antibodies to the selected treatment CBU #1 (mean fluorescence index >3,000 to HLA-A, B, C, or DRB1)
- Evidence of HIV infection or HIV-positive serology

- Evidence of active Hepatitis B or Hepatitis C as determined by serology or polymerase chain reaction (PCR)
- Pregnancy or lactation
- Active malignancy other than that for which the UCBU transplant was being performed within 12 months of enrollment
- Evidence of uncontrolled bacterial, fungal, or viral infections or severe concomitant diseases
- Subjects with presence of leukemic blasts in the central nervous system
- Subjects with an 8/8 allele level HLA-matched and readily available related or unrelated donor. (Subjects who had haploidentical related donors or syngeneic donors were not excluded.)
- Prior allogeneic HSCT
- Allergy to bovine products, gentamicin, or to any other product that may interfere with the treatment

6.1.4 Study Treatments or Agents Mandated by the Protocol

Enrolled subjects (N=125) were randomized in a 1:1 ratio and received either omidubicel or UCBU transplantation. Subjects were randomized to one of two treatment arms:

- Omidubicel
- UCBU (single or double units)

Conditioning Regimen

All subjects received one of three conditioning regimens as outlined in Table 9, Table 10, and Table 11. Each transplant center was required to commit to using the same conditioning regimen for all subjects transplanted at their center or according to primary diagnosis/age group. Prior to randomization, the investigator determined the conditioning regimen intended for use in the transplantation.

Table 9. Study P0501: Conditioning Regimen A.1

Study Day / Treatment	-11	-10	-9	-8	-7	-6-	-5	-4	-3	-2	-1	0
TBI 1350 cGy in 8 or 9 fractions[a]			×2 or ×1 or ×0	×2	×2	×2	×0 or ×1 or ×2				REST	Infusion of omidubicel or unmanipulated CBU/s
Fludarabine[b] 40 mg/m^2 IV							×	×	×	×		
Thiotepa[a] 5 mg/kg IV	×	×										

Data Source: Protocol GC P#05.01.020 (Appendix 16.1.1)

[a] Or TBI 1200 cGy, administered as per institutional practice

[b] Adjusted body weight

Abbreviations: TBI: Total body irradiation; CBU: Cord blood unit

Table 10. Study P0501: Conditioning Regimen A.2

Study Day / Treatment	-8	-7	-6	-5	-4	-3	-2	-1	0
TBI 1320 cGy in eight fractions[a]				REST[b]	×2	×2	×2	×2	Infusion of omidubicel or UCBU/s
Fludarabine 25 mg/m^2 IV	×	×	×						
Cyclophosphamide[c] 60 mg/kg IV	×	×							

Data Source: Protocol GC P#05.01.020 (Appendix 16.1.1)

[a] Or TBI 1200 cGy, administered as per institutional practice

[b] A day of rest may be included between the last dose of fludarabine and the start of TBI (as shown above). Alternatively, the day of rest may be moved to Day -1 without any rest between fludarabine and TBI (TBI on Day -5, -4, -3, -2) or the day of rest may be omitted altogether (Cyclophosphamide on Day -7 and -6 and fludarabine on Day -7, -6 and -5)

[c] Adjusted body weight

Abbreviations: TBI: Total body irradiation; CBU: Cord blood unit; UCBU: Unmanipulated cord blood unit

Table 11. Study P0501: Conditioning Regimen B

Treatment \ Study Day	-7	-6	-5	-4	-3	-2	-1	0
Thiotepa[a] 5 mg/kg IV	×	×				REST		Infusion of omidubicel or UCBU/s
Busulfan[a] 3.2 mg/kg IV or weight-based dosing + TDM[b]		×[c]	×	×	×			
Fludarabine[a] 50 mg/m^2 IV			×	×	×			

Data Source: Protocol GC P#05.01.020 (Appendix 16.1.1)

[a] Adjusted body weight

[b] TDM= therapeutic drug monitoring: aiming for cumulative target AUC = 75 mg*h/L. Busulfan levels after 1st dose will be measured at 5 min, 1h, 2h and 4h after end of Bu infusion and AUC will be calculated based on previously described population PK model (2)

[c] Can be added as per institutional practice

Abbreviations: AUC: Area under the curve; IV: Intravenous PK: Pharmacokinetic; UCBU: Unmanipulated cord blood unit.

Reviewer comment*: Based on the literature review and clinical practice, the reviewer agrees that the conditioning regimens listed above are considered myeloablative.*

GvHD Prophylaxis

All subjects received GvHD prophylaxis with two drugs as follows:

- Calcineurin inhibitor (tacrolimus or cyclosporine): from Day -3 to at least Day +100, with the goal for discontinuation between Day 180 and 200. Each transplant center had to commit to using the same calcineurin inhibitor (tacrolimus or cyclosporine) for all subjects transplanted at their center. Prior to randomization, the investigator had to decide and document the GvHD prophylaxis intended to be used for transplantation.
- Mycophenolate mofetil: Day -3 to at least Day +60.

Supportive Care and Concomitant Medication

All subjects received the following medications 30 to 60 minutes prior to omidubicel or UCBU infusion:

- Diphenhydramine or dexchlorpheniramine
- Hydrocortisone 50 mg intravenous (IV) (or 0.5 mg/kg up to a maximum of 50 mg) (methylprednisolone was not used)
- Acetaminophen

GCSF (e.g., filgrastim, Neupogen, Granix) (5 µg/kg/day (rounded to nearest vial size) IV or subcutaneous) was started on Day 1 and continued through Day 2 of ANC >1,000/µL for two consecutive days. Platelet counts were to be maintained at >10,000/µL after transplantation by transfusion of platelets. Institutional guidelines were followed to provide prophylaxis for infections.

The following concomitant medications were prohibited to be administered post-transplant:

- Cytokines except GCSF
- Bactrim (sulfamethoxazole and trimethoprim) or methotrexate, as it could delay engraftment
- Maintenance therapies (e.g., TKIs, hypomethylating agents, antibodies) within the first 100 days post-transplant, unless the platelet count was >50 × 10^9/L with no platelet transfusions in the preceding 7 days.

Omidubicel

Omidubicel is a cryopreserved cell-based product of allogeneic, ex-vivo-expanded, UCBU-derived, hematopoietic CD34+ progenitor cells (omidubicel CF) and the nonexpanded cell fraction of the same CBU (omidubicel NF), consisting of mature myeloid and lymphoid cells.

Production of omidubicel involves ex vivo culture of purified (b) (4) cells derived from a single CBU for (b) (4) in the presence of the cytokines (b) (4) (b) (4) NAM, (b) (4) and culture medium. On (b) (4) the cells are washed (b) (4) and cryopreserved in (b) (4) On the day of transplantation, the cells are thawed and reconstituted by a (b) (4) dilution with the infusion solution. Harvest can be carried out from (b) (4) and up to (b) (4) if the subject's clinical condition or logistic considerations require an earlier transplantation date or a delay.

6.1.5 Directions for Use

Dosage Form

- CF: ≥8.0×10^8 TNC (and >5.6 × 10^7 CD34+ cells) in approximately 20 mL of cryopreservation solution frozen in LN_2 reconstituted to 100 mL thawed
- NF: ≥4.0×10^8 TNC (and >2.4 × 10^7 CD3+ cells) in approximately 10 mL of cryopreservation solution frozen in LN_2 reconstituted to 50 mL thawed

Omidubicel is administered as a single, one-time IV infusion of two separate fractions (CF and NF), via central venous catheter. The CF is infused first, followed immediately (up to 1 hour) by the infusion of the NF. Total duration of CF infusion targeted a maximum of 2 hours from end of thaw to end of infusion, to target a rate of (b) (cc/kg/hr with a maximal rate of 10 cc/kg/hr.

For the control arm, one or two UCBU(s) were given on a single day per institutional procedures.

Notably, all subjects who received omidubicel received the full dose. One subject who received UCBU (b) (6) did not receive the entire dose. This subject received a double UCBU infusion. Toward the end of the first CBU infusion, the subject developed abdominal pain, headache, and hypertension. Infusion was withheld and a decision was made to discard the remaining product. Infusion of the second CBU unit was postponed to the following day. The second CBU infusion was completed the following day with a temporary interruption due to headache.

6.1.6 Sites and Centers

Thirty-three clinical sites in seven countries enrolled subjects into this study. Among the 125 randomized subjects, 87 (70%) were enrolled in the United States, 15 (12%) in Spain, nine (7%) in Singapore, and six (5%) in the Netherlands. All other countries contributed less than 5% of subjects each.

6.1.7 Surveillance/Monitoring

Table 12 presents the schedule of events for all study visits.

Table 12. Study P0501: Schedule of Events

	Schedule of Assessments Summary																
	Baseline			Transplantation and Follow-Up													
	Screening	Prep		Days Post-transplant													
	Within three weeks prior to randomization	From randomization to conditioning[1]	Conditioning	0	1	2-6	7[18]	14 ±3	21 ±3	28 ±3	35 ±3	42 ±3	56 ±3	70 ±3	100 ±14	180 ±21	270 ±21	365 ±21
Identify qualifying CBUs [2]	X																
Written Informed Consent[3]	X																
Eligibility Criteria[4]	X																
Confirm transplant suitability within 24 hours prior to conditioning		X															
Omidubicel arm: CBU sent to the production site to arrive no later than two working days before the start of manufacturing		X															
Medical History	X																
Infectious disease markers [5]	X																
Anti-HLA antibodies[6]	X																
Cardiac: EKG, Echocardiography or MUGA scan with LVEF [7]	X																
Chest X-ray [7]	X																
Pulmonary Function Tests (prior to treatment with bronchodilators) with cDLCO, FEV1, FVC, and oxygen saturation[7]	X																
Serum or urine beta HCG (females)[29]	X[24]																
Confirmatory HLA typing[8]	X																
BASELINE DISEASE ASSESSEMENT[9] All patients: when clinically indicated, PB and BM morphology (aspiration, and biopsy if applicable) Leukemia/MDS: BM FACS analysis (flow cytometry), cytogenetics, and molecular markers Lymphoma: CT scan or PET-CT chest, abdomen, pelvis	X																

		Schedule of Assessments Summary																	
		Baseline			Transplantation and Follow-Up														
		Screening	Prep		Days Post-transplant														
		Within three weeks prior to randomization	From randomization to conditioning [1]	Conditioning	0	1	2-6	7[18]	14 ±3	21 ±3	28 ±3	35 ±3	42 ±3	56 ±3	70 ±3	100 ±14	180 ±21	270 ±21	365 ±21
Disease assessment follow-up																			
Leukemia MDS	Clinical evaluation for relapse per physician's judgment										X					X	X		X
	BM morphology															X			X
	CBC with differential										X						X		
	FACS analysis (flow cytometry)[26]															X	X		X
	Cytogenetics and molecular markers[27]															X			X
	Further tests as clinically indicated										X					X	X		X
CML	Clinical evaluation for relapse per physician's judgment										X				X	X	X		X
	Quantitative RT-PCR BCR/ABL in peripheral blood[28]														X	X	X		X
	Further tests as clinically indicated										X				X	X	X		X
Lymphoma	Clinical evaluation for relapse per physician's judgment										X					X	X		X
	BM morphology as clinically indicated																		X
	CT- Scan or PET-CT															X			X
	Further tests as clinically indicated										X					X	X		X
Vital Signs[10]		X[11]		X	×10	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory (CBC and Chemistry) [12]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Historical and Concomitant medications[13]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Karnofsky/Lansky performance score		X																	X
Physical Examination		X		X	X						X[14]				X[14]	X[14]	X[14]	X[14]	X[14]
Complete urinalysis with microscopic analysis		X																	
Immunophenotyping Lymphocyte subsets[15]											X				X	X	X		X
Peripheral blood sample for Chimerism[16]		X																	
Peripheral blood chimerism[17]										X			X			X	X		X
Conditioning regimen as per protocol				X															

	Schedule of Assessments Summary																	
	Baseline			Transplantation and Follow-Up														
	Screening	Prep		Days Post-transplant														
	Within three weeks prior to randomization	From randomization to conditioning [1]	Conditioning	0	1	2-6	7[18]	14 ±3	21 ±3	28 ±3	35 ±3	42 ±3	56 ±3	70 ±3	100 ±14	180 ±21	270 ±21	365 ±21
Omidubicel arm: Omidubicel CF, NF, and infusion solutions shipped to clinical site before or during conditioning Control Arm: CBU sent to the clinical site before or during conditioning		X	X															
Stem cell (omidubicel CF/NF, UCBU(s), or other) thawing and infusion				X														
Toxicity assessment 24 hours post infusion				X	X													
Assess Acute GvHD							X	X	X	X	X	X	X	X	X	X		
Assess Chronic GvHD															X	X	X	X
CMV PCR			X[19]				X	X	X	X	X	X	X	X	X			
EBV PCR									X				X		X	X[20]	X[20]	X[20]
HHV6 PCR until ANC > 500							X	X	X	X	X	X						
HRQoL patient self-report questionnaires[25]	X											X			X	X		X
Optional supplemental immune reconstitution sub-analysis – blood sample collection [23]	X						X	X	X	X		X	X	X	X	X		X
Between Visit Monthly Check Up[21]															X[21]			
15-month post-randomization survival and relapse status[22]																	X	
Infections		From randomization until end of study																
AEs	From time of consent until end of study																	
Hospital Admission			From start of conditioning regimen until end of study															

Source: Protocol GC P#05.01.020 (Appendix 16.1.1)

[1] The time between randomization and conditioning varies by treatment and may be further delayed due to changes in the patient's health. In the event of a failure to transplant the patient by Day 90 post-randomization, an assessment of survival, relapse history, infection history, and HRQoL (optional, if possible) are required at days 90, 130, 210, and 365 post-randomization (or more frequently as clinically indicated) as well as an assessment of survival and relapse history at 15 Months post-randomization.

[2] Before signing informed consent and according to CBUs matching criteria as detailed in the protocol. After consent, the CBU documents for the CBU selected for expansion (treatment CBU #1) must be redacted and uploaded to Advantage eClinical ® prior to randomization.

[3] Signed consent is required prior to performing any protocol specific tests or procedures that are not part of the standard site practice. The ICF signature can be obtained earlier than 3 weeks prior to randomization.

[4] All eligibility criteria must be met prior to randomization. Unless otherwise indicated, screening and eligibility testing must be performed and resulted within three weeks prior to randomization.

[5] Infectious disease markers must include: HIV I/II Ab, HTLV I/II Ab, HBsAg, HBcAb, HCV Ab, VZV Ab, syphilis Ab (such as RPR), EBV Ab, and CMV screen (IgG or Total).

[6] Tests performed within 4 weeks prior to randomization are acceptable.

[7] Test results from within 9 weeks prior to randomization are acceptable. Chest X-ray is not mandatory if a chest CT or MRI was performed.

[8] Verification typing (confirmatory typing) must be performed and resulted prior to CBU shipment to the production site. Extended high-resolution typing at HLA -A, -B, -C, -DRB1 is also required for the patient and CBU#1 but (with the exception of -DRB1) can be performed after randomization unless anti-HLA antibody testing reveals a positive result (MFI>3000) at HLA-A, B, C, or DRB1. If assigned to the control arm and treatment CBU #2 is selected, then HLA -A, -B, -C, -DRB1 high-resolution typing is also required for treatment CBU #2; ABO and Rh typing is also required for the patient, CBU#1 and CBU#2 (if applicable).

[9] Baseline disease assessment should be as close as possible to randomization to minimize findings of relapse during CBU expansion. Specific requirements for the timing of this assessment are provided in Section 9.4.5 T scan (for lymphoma patients); tests from within 9 weeks prior to randomization are acceptable. For MDS and CML patients, biopsy should have been performed within one year prior to transplant and should be repeated prior to transplant if fibrosis was noted on a prior biopsy. For ALL, AML, and other leukemia (not including MDS and CML) patients an aspiration is sufficient. FACS analysis/flow cytometry is required prior to randomization for AML, ALL and other leukemia (not including MDS and CML) patients and required prior to conditioning for CML and MDS patients. For Leukemia/MDS patients, cytogenetics and molecular markers may be done after randomization prior to conditioning (it is not mandatory to repeat molecular markers tests that were negative at diagnosis).

[10] Temperature, blood pressure and pulse at all visits; Weight through Day 100 visit Respiratory rate through Day 1 post-transplant.

[11] Including height, weight, and BSA.

[12] CBC performed at screening, daily from Day 0 until neutrophil engraftment, and at all study visits post-transplant. Differentials required if WBC $\geq$ 0.5. Blood chemistries must include (at a minimum): serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT, and magnesium (at screening, Day -1 (creatinine only), Day 0 and then at least twice weekly until Day 28, and weekly after Day 28 until 10 weeks post-transplant; at 100 days, 6 months, 9 months, and 1 year post-transplant).

[13] All concomitant medications and blood products administered, including total number of RBC and platelet units transfused, from time of signature on the IC until the end of the study, will be recorded in the source documents and the reason for administration should be clearly stated. Concomitant medications will also be recorded in the eCRF as detailed in the Data Management Handbook.

[14] Including standard of care cardiac and pulmonary monitoring.

[15] On Days 28, 70, 100, 180, and 365, site will perform a basic lymphocyte subset analysis (CD3, CD4, CD8, CD19, CD56/16) locally. Additional assessments requested (but not required) are: CD123+ (dendritic lymphocytes), CD11c+ (dendritic myeloid cells), CD3+CD56+CD16+ (NKT cells), CD45RA+/CD62L+(RTE), CD25+/CD62L+(T-Reg), Total CD25+, CD57+/CD28+(CTL), HLA-DR+(Activated), and quantitative immunoglobulins (In case quantitative immunoglobulins are assessed, a record of the most recent IVIG administrations is required).

[16] Patient sample will be obtained anytime during the screening period or post-randomization prior to the initiation of the conditioning regimen; CBU sample will be shipped to the clinical site along with the UCBU or omidubicel product.

[17] Measured by molecular methods, in whole blood at Day 21 or Day 28 and at Days 42, 100, 180, and 365. BM chimerism is an acceptable alternative.

[18] Day 7 GvHD assessment must be done on Day 7 post-transplant. All the other Day 7 assessments can be done until Day 10 post-transplant included.

[19] All recipients must be tested for CMV (using the PCR method) at least once during the conditioning period.

[20] Not required if patient no longer on immunosuppression.

[21] Beginning after the Day 100 visit, the site will continue at least monthly contact with the subject until Day 365 visit. If there is no hospital or clinic visit scheduled at the transplant center for more than 30 days, then a member of the study team will contact the subject via phone or email within 35 days from the last contact to inquire about AEs, hospitalizations, infections, and medication changes (including transfusions). This contact will be documented in the subject's medical or research record.

[22] The patient survival and relapse status should be assessed at 15 Months or later post-randomization.

[23] Samples to be shipped to a central laboratory for analysis.

[24] Serum or urine beta HCG can be collected up to 4 weeks before randomization.

[25] HRQoL not required if a survey is not available in the patient's primary language. Refer to Protocol Section for details on HRQoL administration (Appendix 16.1.1).

[26] Flow cytometry on BM or PB sample if judged necessary by the treating physician.

[27] It is not mandatory to repeat molecular markers tests that were negative at diagnosis.

[28] If positive: BM aspirate with morphology, cytogenetics, and quantitative RT-PCR BCR/ABL.

[29] Serum or urine beta HCG can be collected up to 2 weeks before randomization.

Source: BLA 125738/0 Module 5.3.5.1 CSR Protocol GC P#05.01.020 (Appendix 16.1.1)
Abbreviations: Ab, antibody; AE, adverse event; ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; ANC, absolute neutrophil count; BM FACS, bone marrow fluorescence-activated cell sorting; BCR/ABL, mutation caused by the combination of the BCR and ABL genes; CBC, complete blood count; CBU, cord blood unit; cDLCO, diffusion capacity for carbon monoxide corrected for hemoglobin level; CF/NF, cultured fraction/non-cultured fraction; CMC, chemistry, manufacturing and controls; CMV, cytomegalovirus; CT, computerized tomography; EBV, Epstein-Barr virus; eCRF, electronic case report form; EKG, electrocardiogram; FEV1, forced expiratory volume; FVC, forced vital capacity; GvHD, graft-versus-host disease; HBcAb, hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HCG, human chorionic gonadotrophin; HHV6, human herpesvirus 6; HLA, human leukocyte antigen; HQL, health-related quality of life; HTLV I/II Ab, human T-lymphotropic virus I/II antibody; IC, informed consent; LVEF, left ventricular ejection fraction; MDS, myelodysplastic syndrome; MRI, magnetic resonance imaging; MUGA, multigated acquisition; PB, peripheral blood; PET, positron emission tomography; RBC, red blood cell; RPR, rapid plasma regain; RT-PCR, reverse transcription polymerase chain reaction; UBCU, unmanipulated cord blood unit; VZV ab, varicella zoster virus ant body; WBC, white blood cell

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint

- Time to neutrophil engraftment by 42 days following transplantation

Secondary Endpoints

- Incidence of Grade 2/3 bacterial or invasive fungal infections by 100 days following transplantation
- Days alive and OOH in the first 100 days following transplantation
- Platelet engraftment by 42 days following transplantation

Tertiary Endpoint

- NRM by 210 days following randomization

Exploratory Endpoints:

- Neutrophil engraftment by 16 days following transplantation
- Time from transplantation to platelet engraftment
- Duration of primary hospitalization
- NRM by 130 days and 15 months following randomization
- Overall survival at 210 days and 15 months following randomization
- Disease-free survival at 15 months following randomization
- Neutrophil engraftment by 42 days following transplantation
- Acute GvHD Grade II to IV and Grade III to IV by 100 days following transplantation
- Chronic GvHD (mild/moderate/severe) by 180 days and 1 year following transplantation
- Secondary graft failure by 1 year following transplantation
- Grade 3 viral infections by 180 days and 1 year following transplantation
- Safety and tolerability of omidubicel transplantation
- Relapse by 15 months following randomization
- Relapse mortality by 15 months following randomization
- Immune reconstitution at 28, 70, 100, 180, and 365 days following transplantation
- Supplemental immune reconstitution assessments at a central laboratory (optional)
- Health-related quality of life (HQL)
- Long-term clinical outcomes up to 5 years following transplantation (optional)

6.1.9 Statistical Considerations & Statistical Analysis Plan

The study randomized subjects using the enrollment module of the (b) (4) (b) (4) To provide a balanced allocation to the treatment groups, the study used the minimization method for randomization, which is designed to ensure that the treatment groups were well balanced with respect to selected factors of prognostic importance. The factors in the minimization algorithm included the following: treatment center, disease risk group, age group, and intent to perform single versus double cord transplant in the control arm. Although all patients treated with omidubicel were to receive a transplant from a single CBU, specification of intent to perform single versus double cord transplantation prior to randomization was included to address potential imbalances resulting from differences in CBU selection based on patient weight or HLA matching options.

Reviewer comment: *Although all subjects treated with omidubicel received a transplant from a single CBU source, the intent to perform single versus double cord transplant was included as a factor in the randomization algorithm to address potential imbalances resulting from differences in CBU selection based on the subject weight or HLA matching options.*

The prespecified primary endpoint was time from transplant to neutrophil engraftment by 42 days following transplantation. The study compared the distribution of time to neutrophil

engraftment in the omidubicel versus UCBU arms, based on the Mann-Whitney test statistic. This test was equivalent to using a Gehan-Wilcoxon alternative in a time-to-event analysis with competing risks, with the following events treated as competing risks:

- Failure to receive a transplant within 90 days following randomization
- Relapse prior to ANC recovery
- Death
- Second transplant

All competing risks were assigned as Day 43 in the primary endpoint analysis, the same value given to primary graft failures.

Follow-up was between Day 0 and Day 42 following transplantation. Those not achieving engraftment by Day 42 were censored on Day 43 (and were viewed as never achieving engraftment). The estimated cumulative distribution of the times, as well as the median times to engraftment, were presented for each treatment group. The statistical test was based on the rerandomization distribution in view of using the minimization method for treatment allocation.

For the secondary endpoint of platelet engraftment, subjects were counted as not having been engrafted if they either had not received a transplant within 90 days following randomization or if they died or relapsed prior to engraftment.

For the secondary endpoint of incidence of Grade 2/3 bacterial infection or invasive fungal infection, death was considered a competing risk.

For the secondary endpoint of days alive and OOH, subjects who did not receive a transplant within 90 days following randomization were assigned a value of 0 days alive and OOH.

Primary graft failure was defined as failure to achieve neutrophil engraftment by Day 42. Secondary graft failure was defined as documented neutrophil engraftment, followed by severe neutropenia ($<0.5 \times 10^9$/L for three or more consecutive laboratory values on separate days) with marrow cellularity <5%, without subsequent improvement occurring either spontaneously or after growth factor treatment. Infusion of an additional stem cell product after documented neutrophil engraftment was considered secondary graft failure.

Determination of Sample Size

The primary analysis for comparing time to engraftment between the two treatment groups was based on the Mann-Whitney test statistic. Noether's formula was used to calculate the sample size. Noether's formula requires specifying the probability P that an omidubicel subject has a shorter engraftment time than a control subject. The estimate of this probability was based on data from 16 subjects treated with a single cord omidubicel transplant and 152 subjects in the CIBMTR registry database treated with CBT from 2010 to 2013 with criteria that would make them eligible for Study P0501. Based on these datasets and factoring in adjustments, assuming (a) that 10% of subjects allocated to omidubicel would fail to receive a transplant compared to 4% of subjects allocated to UCBU and (b) that 5% of subjects allocated to omidubicel would receive not omidubicel but UCBU due to failure of the omidubicel expansion, the estimate of P was 0.78. A pessimistic estimate that is one standard error lower than the estimate of 0.78 was

0.72. Noether's formula for a trial using a two-sided significance level of 5% and having 90% statistical power gave a total sample size of 45 for P=0.78 and 72 for P=0.72.

Although formal sample size calculation for the primary endpoint showed that 45 to 72 subjects were needed to provide 90% statistical power, the study included a larger number of subjects to:

- Provide a larger safety database for omidubicel
- Ensure that statistical significance on the primary endpoint would be strong
- Reduce the chance of seeing higher mortality in the omidubicel group than in the control group

Therefore, a sample size of 120 subjects was planned, and the statistical power for the primary endpoint was estimated to be >0.99.

To minimize potential bias, the Applicant and the principal statistician did not have access to the aggregate clinical trial data and were blinded from all interim analyses provided to the data monitoring committee. The data monitoring committee was used to review the progress of the trial during the enrollment of subjects on a regularly scheduled basis and as requested on an ad hoc basis. Six meetings were held through the accrual period.

There were five versions of the statistical analysis plan (SAP). The Applicant provided a copy of the final SAP Version 5.0 dated 8 March 2020, in Appendix Section 16.1.9. Notably, the SAP was updated on 31 August 2020 in response to the COVID-19 public health emergency to assess the impact of COVID-19 infection on study data collection, analysis, and interpretation. All changes to the SAP were made prior to the first data analysis by the principal statistician, who remained blinded to the data throughout the study until data lock. The SAP COVID-19 amendment was incorporated following the analysis of neutrophil engraftment and prior to the analysis of all other endpoints.

Protocol Amendments

A total of seven protocol amendments were included in addition to four local amendments. The initial study protocol was dated 8 March 2016. Key changes from the original protocol included revision to the secondary and exploratory endpoints based on FDA's recommendation, details of when chimerism testing must show donor cells to be considered neutrophil engraftment, expansion of the eligibility criteria to enroll pediatric subjects and subjects with other underlying hematologic malignancies, and updates to the conditioning regimen, supportive care measures, and GvHD prophylaxis administered during the study.

Most of the amendment changes were implemented based on investigator and site feedback to better align the protocol with standard criteria and/or assessment schedules at clinical sites. The last amendment was implemented on 22 January 2019, when 44% of subjects had been enrolled. Country-specific versions were issued as required by the country to meet specific regulations.

Analysis Timepoints and Data Locks

Study data were analyzed per protocol based on three prespecified data locks:

- 7 May 2020: Analysis of the primary endpoint.
- 8 September 2020: Analysis of all other endpoints when all subjects had completed 210 days of follow-up following randomization.
- 29 April 2021: All subjects' follow-up data through completion of the study. This data lock was originally intended to provide re-analysis of the exploratory endpoints at 1-year post-transplant and 15 months post-randomization. However, given the unplanned delay in the BLA submission, the Applicant decided to use this final data lock as the basis for the results presented in the clinical study report (CSR).

Data Quality

Several major data quality issues were identified during the review of this BLA. Using the available raw data in the initial BLA submission, FDA was not able to confirm the results of the primary endpoint or the overall safety analyses.

Importantly, the lb.xpt and adlb.xpt data files that the Applicant submitted with the initial BLA submission were incomplete and included only laboratory values on selected study visits. In order to independently confirm the efficacy analyses, FDA requested that the Applicant submit complete granular data for confirmation of all components of the prespecified endpoint of neutrophil engraftment (including chimerism assay and all labs required per protocol). FDA requested that lb.xpt, adlb.cpt, and supplb.xpt data files be updated to include all laboratory values (specifically complete blood counts [CBCs], white blood cell [WBC] differential, and ANC automated and manual when applicable) that were collected per protocol. These labs were required to be collected daily from Day 0 until neutrophil engraftment and at all study visits post-transplant. Per protocol, starting on transplant day, WBC differential was required if WBC was ≥0.5. In addition, the reviewer requested that the Applicant provide details on GCSF use (dose and dates of administration) and platelet transfusion during the study.

Notably, the following laboratory data were required to be documented on the Laboratory Assessment Form CRF in Study P0501: CBCs, WBC differential, and blood chemistries at Days -1, 0, 7, 14, 21, 28, 35, 42, 56, 70, 100, 180, 270, and 365 post-transplant. Per protocol "Schedule of Assessments Summary", CBCs were to be performed at screening, daily from Day 0 until neutrophil engraftment, and at all study visits post-transplant.

On 15 November 2022 (STN 125738/0.36), the Applicant provided substantial amount of new clinical study data required to independently adjudicate the primary endpoint, evaluate key secondary endpoints, and conduct a comprehensive review of safety of the clinical data. These data were determined to constitute a major amendment. Analyses based on these updated data are described below.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

- Screened population consist of all subjects who signed informed consent document.
- ITT population includes all subjects randomized to the treatment groups to which they were allocated. Analysis of the ITT population provides the primary analysis of the primary endpoint, secondary endpoints, tertiary endpoint, and the analyses of exploratory endpoints unless otherwise stated.
- Transplanted population (TP) includes all subjects randomized who received a CBT on or before 90 days post randomization. Subjects who received a CBT that was out of specifications are included in the TP. Subjects are assigned to the treatment groups to which they were allocated. Analysis of the TP provides the analyses for the exploratory endpoints that depend on transplant, GvHD.
- As-treated (AT) population (or per protocol population) includes all subjects randomized who received a CBT on or before 90 days post randomization, grouped by treatment actually received. Subjects who received a CBT that was out of specifications are not included in the AT population. Analysis of the AT population is for supportive purposes.
- SP is equivalent to the AT population.

Reviewer comment: *The Applicant described two additional populations; however, the Reviewer did not use these patient populations in the analyses:*

- *ANC engrafted population (AEP) which included all subjects who received a CBT on or before 90 days post randomization and achieved neutrophil engraftment by Day 42 with subsequent chimerism. The Applicant's analysis was focused on the treatment actually performed. Subjects who received a CBT that was out of specifications were not included in the AEP. Analysis of the AEP was for supportive purposes.*

- *Platelets engrafted population (PEP) which included all subjects who received a CBT on or before 90 days post randomization and achieved platelet engraftment. The Applicant's analysis was focused on the treatment actually performed. Subjects who received a CBT that was out of specifications were not included in the PEP. Analysis of the PEP was for supportive purposes.*

6.1.10.1.1 Demographics

Demographics of the ITT population are presented in Table 13 below. The median age of study subjects was 40 years for the omidubicel arm and 43 years for the UCBU arm (range 13 to 65 years). The study population was ethnically diverse, with over 40% identified as non-Caucasian. Over 2/3 of subjects were enrolled in U.S. sites. Across all study sites, 9 clinical sites randomized at least 6 subjects each (range 6 to 14); 12 clinical sites randomized 2 to 4 subjects each; 12 clinical sites randomized 1 subject each.

Table 13. Study P0501 Demographic Characteristics in the ITT Population

Demographic Group	Omidubicel N=62 n (%)	UCBU N=63 n (%)
Age	-	-
12-39	31 (50)	29 (46)
40-59	27 (44)	31 (49)
60-65	4 (6)	3 (4.8)
≥65	0	1 (1.6)
Mean (SD)	38.6 (15.7)	38 (15.4)
Median (Range)	40 (13-62)	43 (13-65)
Sex	-	-
Male	32 (52)	40 (63)
Female	30 (48)	23 (37)
Race	-	-
White	35 (56)	37 (59)
Black or African American	11 (18)	9 (14)
Asian	7 (11)	10 (16)
Multiple	3 (4.8)	1 (1.6)
Not reported	3 (4.8)	1 (1.6)
Unknown	2 (3.2)	1 (1.6)
Other	1 (1.6)	3 (4.8)
Native Hawaiian or other Pacific Islander	0	1 (1.6)
Ethnicity	-	-
Not Hispanic or Latino	46 (74)	52 (83)
Hispanic or Latino	10 (16)	6 (10)
Unknown	4 (6)	2 (3.2)
Not reported	2 (3.2)	3 (4.8)
Country	-	-
USA	42 (68)	45 (71)
ESP	8 (13)	7 (11)
SGP	4 (6)	5 (8)
NLD	3 (4.8)	3 (4.8)
BRA	3 (4.8)	1 (1.6)
GBR	1 (1.6)	1 (1.6)
ISR	1 (1.6)	1 (1.6)
Geographic region	-	-
U.S.	42 (68)	45 (71)
Europe (ESP, NLD, UK)	12 (19)	11 (17)
Other (BRA, SGP, ISR)	8 (13)	7 (11)

Source: FDA analysis ADSL dataset
Abbreviations: BRA, Brazil; ESP, Spain; GBR, Great Britain; ISR, Israel; ITT, intent-to-treat; NLD, Netherlands; SGP, Singapore; SD, standard deviation; UCBU, unmanipulated cord blood unit; UK, United Kingdom

Reviewer comment: *Randomization assignments were well-balanced across patient characteristics and geographical regions. Eight (13%) subjects in the omidubicel arm and 6 (10%) in the UCBU arm were pediatric subjects between 12 and 17 years old.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline and disease characteristics of the ITT population are presented in Table 14 below. AML and ALL were the most common indications for HSCT, and most subjects had moderate to high-risk disease. Subjects with weights up to 135 kg were enrolled in both arms. Eligible CBUs for the study were required to meet HLA-match and cellular requirements. All CBUs were required to be HLA matched at 4-6/6 HLA class I (HLA-A & HLA-B, low resolution) and II (HLA-DRB1, high-resolution) loci with the subject.

Table 14. Study P0501: Baseline Characteristics

Characteristic	Omidubicel N=62 n (%)	UCBU N=63 n (%)
HCT-specific comorbidity index	-	-
0	12 (19)	14 (22)
1-2	19 (31)	16 (25)
3+	31 (50)	33 (52)
Primary diagnosis	-	-
AML	27 (44)	33 (52)
ALL	20 (32)	21 (33)
MDS	6 (10)	3 (4.8)
CML	4 (6)	2 (3.2)
Lymphoma	3 (4.8)	2 (3.2)
Other rare disease [a]	2 (3.2)	2 (3.2)
Disease risk group	-	-
Low	15 (24)	15 (24)
Moderate/intermediate	27 (44)	25 (40)
High/very high	20 (32)	23 (37)
Intended cord blood transplant	-	-
Single	20 (32)	21 (33)
Double	42 (68)	42 (67)
Antigen-level HLA match score (intended treatment CBU #1)	-	-
4/6	46 (74)	46 (73)
5/6	15 (24)	16 (25)
6/6	1 (1.6)	1 (1.6)

Source: FDA analysis ADSL dataset

a. Rare diseases included: dendritic cell leukemia, biphenotypic leukemia, and adult T cell leukemia/lymphoma

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CBU, cord blood unit; CML, chronic myelogenous leukemia; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; ITT, intent-to-treat; MDS, myelodysplastic syndrome; UCBU, unmanipulated cord blood unit

Reviewer comment: *There were four subjects in the UCBU arm who were intended to receive double CBU and were listed in the dataset under "CBU intended uncorrected" to have received single CBU, and under "CBU intended corrected" to have received double CBU:*

- (b) (6) *(received OOS CBU due to site error and was excluded from the AT population)*
- (b) (6)
- (b) (6)
- (b) (6)

The Applicant clarified in response to IR that the difference between the uncorrected and corrected values reflects an error in data entry at the time of enrollment and thus a discrepancy between the source documents and the CRF. Therefore, all subjects in the UCBU arm who had an intended double cord transplant (as reflected in source documents and corrected CBU number) received two CBUs, and all subjects with an intended single cord transplant received one CBU.

The demographics and baseline disease characteristics were similarly distributed across the ITT population and were well balanced in the two arms, specifically for those factors used for minimization.

As anticipated, most subjects received CBUs that were HLA mismatched at two loci, reflecting the utility of CBT as a mismatched unrelated stem cell source.

Overall, the data presented illustrate that those enrolled in Study P0501 fairly represent the general U.S. population with hematologic malignancies who are in need for HSCT.

6.1.10.1.3 Subject Disposition

The first subject's consent was provided on 20 December 2016 and the first subject was randomized on 9 January 2017. The last subject's visit was on 15 April 2021. The cutoff date for this analysis was 29 April 2021. Subjects were enrolled across 33 sites globally.

A schematic of the overall disposition of study subjects is presented in Figure 3. Of the 155 subjects who provided informed consent, 125 were randomized, while 30 subjects were considered screen failures due to disease characteristics or relapse (n=13), medical conditions (n=8), protocol logistics/donor preference (n=4), CBU selection considerations (n=3), and/or voluntary withdrawal (n=2).

Of the 125 enrolled subjects who comprised the ITT population, 62 subjects were randomized to the omidubicel treatment group and 63 subjects were randomized to the UCBU group. Subjects randomized to omidubicel were transplanted within a median of 42 days (range 16 to 90), compared to 26 days (range 15 to 89) for the UCBU group.

The TP comprised 59 subjects in the omidubicel treatment group and 58 subjects in the UCBU group. Eight subjects in the ITT population were excluded from the TP because they did not receive either omidubicel or UCBU within 90 days following randomization. Three subjects from

the omidubicel treatment group and five subjects from the UCBU treatment group were excluded. The most frequent reason was relapse: two subjects in the omidubicel arm and three subjects in the UCBU arm relapsed prior to transplantation and were not able to receive a transplant within 90 days of randomization.

The omidubicel AT population comprised 52 subjects randomized to and treated with omidubicel. The UCBU AT population comprised 56 subjects: 55 randomized to and treated with UCBU, and one subject randomized to omidubicel who received UCBU. This subject (b) (6) (b) (6) was randomized to omidubicel but was transplanted with UCBU because of a manufacturing failure. Nine subjects in the TP were excluded from the AT population because they received a graft that was not within specifications. Six subjects randomized to the omidubicel treatment group were excluded from the AT population; three received an OOS omidubicel product, and three received an UCBU that did not meet protocol-specified criteria for CBU selection.

Overall, 10 subjects randomized to omidubicel and eight subjects randomized to UCBU were not transplanted per protocol. Of these subjects, five in each arm (8%) did not receive a transplantation within the protocol-defined timelines, or received a transplantation with a different graft source, due to their disease status (i.e., disease relapse) or a medical condition precluding their transplantation, or because of the investigator's choice. In addition, in the UCBU arm, three subjects were transplanted with CBUs that did not meet the protocol-defined CBU requirements, as a result of safety or logistical issues that precluded the use of the CBUs originally assigned to them.

On the omidubicel arm, five subjects (8%) could not receive omidubicel according to the protocol specifications due to manufacturing failures. Three of these subjects received omidubicel that did not meet product specifications under FDA approval, and two subjects were transplanted with backup CBUs.

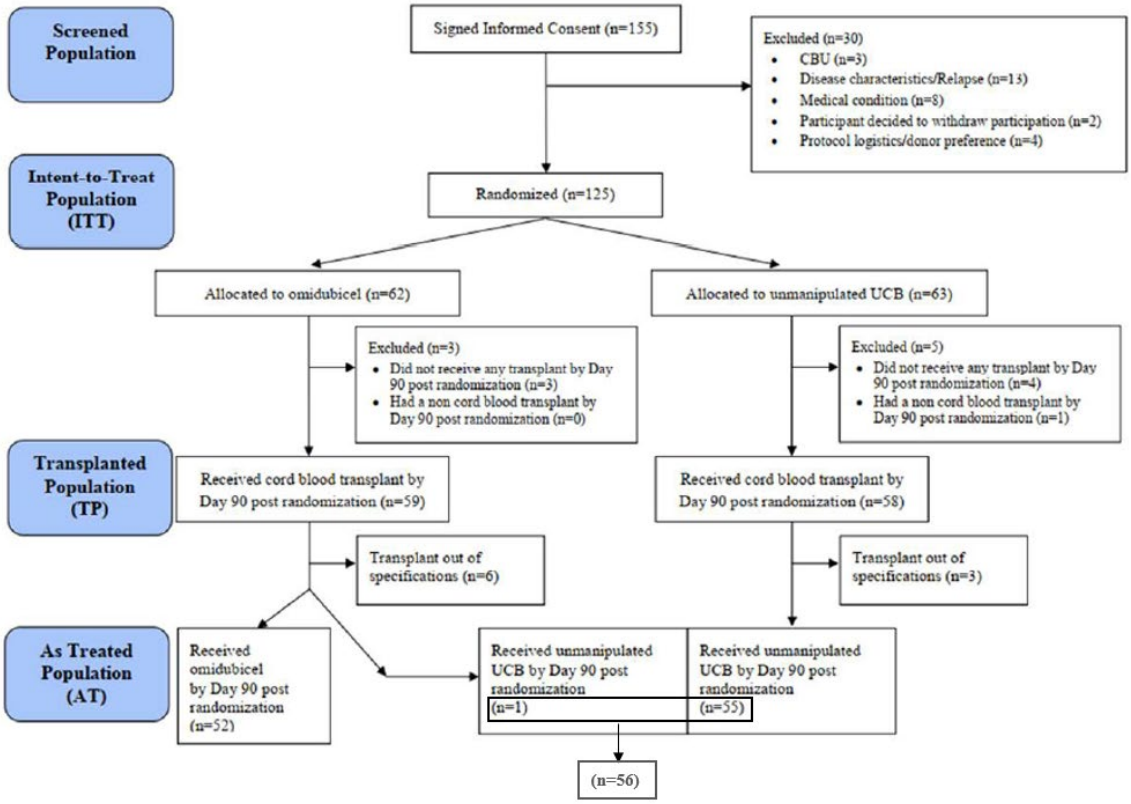
There were 15 subjects (six randomized to omidubicel and nine randomized to UCBU) who did not receive the specific CBU originally selected. The reasons for not receiving the intended CBU were largely related to logistical (e.g., delay in shipment, manufacturing failure) or clinical considerations (e.g., clinical condition precluding the use of myeloablative conditioning regimen, higher cell numbers in the back-up units).

All subjects were followed until completion of Month 15 follow-up or death except for two subjects who withdrew consent for further follow-up prior to study completion: one subject was not transplanted and withdrew consent 210 days following randomization, and one subject was withdrawn after 12 months following transplant due to lack of compliance and relocation. In the ITT population, 17 of 62 (27%) subjects in the omidubicel arm and 24 of 63 (38%) subjects in the UCBU arm died.

The median follow-up for the ITT population was 422.5 days (13.9 months) for the omidubicel arm and 429 days (14.1 months) for the UCBU arm.

Reviewer comment: *Randomization assignments and subjects' disposition were well-balanced across geographical regions.*

Figure 3. Study P0501 Flow Diagram



Source: Adapted from BLA 125738/0 CSR Section 10.1 Figure 2
Abbreviations: CBU, cord blood unit; n, number of subjects in each group; UCB, umbilical cord blood

Table 15, Table 16, and Table 17 summarize subjects in the ITT population who were excluded from the TP, subjects in the TP who were excluded from the AT population, and subjects in the AT population who received UCBU instead of omidubicel, respectively.

Table 15. Study P0501: Subjects in ITT Population Excluded From TP

Excluded From TP Randomized Treatment Group	Subject ID	Reason	Specified Reason
Did not receive any transplant by Day 90 post-randomization	-	-	-
Omidubicel	(b) (6)	Relapse	Relapsed disease
Omidubicel		Medical condition	Consolidation therapy due to MRD+ finding followed by sinus infection
Omidubicel		Relapse	Relapsed disease
UCBU		Relapse	Relapsed disease
UCBU		Relapse	Relapsed disease
UCBU		Relapse	AML relapse and refractory
UCBU		Medical condition	Delayed transplant- too necrotic in BM and MRD+
Had a non-cord blood transplant by Day 90 post-randomization	-	-	-
UCBU	(b) (6)	Investigator Decision	Received a mismatched unrelated donor transplant due to concerns for liver toxicity

Source: FDA analysis ADSL dataset, CSR
Abbreviations: AML, acute myelogenous leukemia; BM, bone marrow; ITT, intent-to-treat; MRD, minimal residual disease; TP, transplanted population; UCBU, unmanipulated cord blood unit

Table 16. Study P0501: Subjects in TP and Excluded From AT Population

Excluded From AT Population	Randomized Treatment Group	Treatment Received	Subject ID	Reason
Investigator decision to pursue a different transplant / CBU does not meet protocol requirements	Omidubicel	UCBU	(b) (6)	Due to issues with shipping the selected CBU to the Production facility, the physician investigators determined the subject could not wait for omidubicel production for study transplant. Per PI discretion, subject was removed from study-specific procedures. A single CBU was transplanted but it did not meet criteria for single cord transplant. HLA match was 4/6 and CD34 dose was 1.3×10^5cells/kg

Excluded From AT Population	Randomized Treatment Group	Treatment Received	Subject ID	Reason
Product OOS / CBU does not meet protocol requirements	Omidubicel	UCBU	(b) (6)	The subject was randomized to receive omidubicel but was infused with a double UCBU infusion instead. The unit sent for production had a harvest TNCC below specification (4.2×10^8 cells). Processed unit was discarded, and physician investigator decided the subject could not wait for another production cycle to receive transplant. Subject received double cord transplant but neither unit met protocol criteria. Unit 1 TNCC was 1.40×10^9 and Unit2 CD34 count was 7.08×10^6.
Investigator decision to pursue a different transplant / CBU does not meet protocol requirements	Omidubicel	UCBU	(b) (6)	The treating physician decided the subject was not suitable to be a research study subject (subject was consented by a different physician). Subject removed from study-specific procedures. Subject received a double CBU transplant per standard of care at UMN. Given single cord transplant that did not meet protocol criteria. HLA match was 4/6 and CD34 dose was 0.9×10^5/kg and TNC dose was 2.8×10^7/kg
Product OOS	Omidubicel	Omidubicel	(b) (6)	After the harvest of omidubicel CF, it was determined that the TNC was 6.7×10^8 cells. Per the protocol, the TNC for the final omidubicel CF must be $\geq 8.0 \times 10^8$ cells. The product met all other FPQC tests and release criteria. The FDA agreed to transplantation of this OOS product.
Product OOS	Omidubicel	Omidubicel	(b) (6)	After the harvest of omidubicel CF, it was determined that the TNC was 6.5×10^8 cells. Per the protocol, the TNC for the final omidubicel CF must be $\geq 8.0 \times 10^8$ cells. The product met all other FPQC tests and release criteria. The FDA agreed to transplantation of this OOS product.

Excluded From AT Population	Randomized Treatment Group	Treatment Received	Subject ID	Reason
Product OOS	Omidubicel	Omidubicel	(b) (6)	After the harvest of omidubicel CF, it was determined that the TNC was 5.2×10^8 cells. Per the protocol, the TNC for the final omidubicel CF must be $\geq 8.0 \times 10^8$ cells. The product met all other FPQC tests and release criteria. The FDA agreed to transplantation of this OOS product.
CBU does not meet protocol requirements	UCBU	UCBU	(b) (6)	Subject should have received double cord but received single instead. HLA match was 4/6 and Unit 1 CD34 dose was 1.4×10^5/kg. This was site error and is recorded as a protocol deviation.
CBU does not meet protocol requirements	UCBU	UCBU	(b) (6)	CBU1 was replaced because original cord was unavailable. Neither cord of the double cord transplant met TNCC criteria of $\geq 1.8 \times 10^9$. Unit 1 TNCC was 1.36×10^9 and Unit 2 TNCC was 1.51×10^9.
CBU does not meet protocol requirements	UCBU	UCBU	(b) (6)	Post thaw testing revealed CBU1 had 60% viability. CBU replaced but neither CBU infused met protocol criteria. Unit1 TNCC was 1.62×10^9 and Unit 2 CD34 count was 3.50×10^6 and Unit 2 TNCC was 1.698×10^9.

Source: FDA analysis ADSL dataset, CSR
Abbreviations: AT, as-treated; CBU, cord blood unit; CF, cultured fraction; FPQC, final process quality controls; HLA, human leukocyte antigen; OOS, out-of-specification; PI, principal investigator; TNC, total nucleated cell; TNCC, total nucleated cell count; TP, transplanted population; UCBU, unmanipulated cord blood unit; UMN:, University of Minnesota

Table 17. Study P0501: Subjects in AT Population Who Received UCBU Instead of Omidubicel

Randomized Treatment Group	Treatment Received	Subject ID	Reason
Omidubicel	UCBU	(b) (6)	Initial unit sent for production had a TNCC below specification. Processed unit was discarded, and a second unit was selected for shipment. The second unit sent was found to have a CFU count OOS. The processed unit was discarded, and physician investigator decided the subject could not wait for another production cycle to receive transplant. The subject was transplanted with UCBU.

Source: FDA analysis ADSL dataset, CSR
Abbreviations: AT, as-treated; CBU, cord blood unit; CFU, colony forming units; OOS, out-of-specification; TNCC, total nucleated cell count; UCBU, unmanipulated cord blood unit

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

All randomized subjects (N=125) were included in the ITT population, which was used for the primary analysis of the primary endpoint.

Primary Endpoint: Time to Neutrophil Engraftment Following Transplantation

The time to neutrophil engraftment was defined as achieving an ANC ≥0.5 × 10^9/L on three consecutive measurements on different days with subsequent donor chimerism (≤10% host cells by peripheral blood chimerism or BM chimerism if peripheral blood chimerism is not available) at any time on or after the day of engraftment up to either Day 100 post-transplant, date of relapse, date of secondary graft failure, or date of death, whichever comes first. The first day of the three measurements was designated as the day of neutrophil engraftment and must have occurred on or before 42 days post-transplant.

Primary graft failure was defined as failure to achieve neutrophil engraftment by Day 42. Secondary graft failure comprised documented neutrophil engraftment, followed by ANC <0.5 × 10^9/L for three or more consecutive laboratory values on separate days, with marrow cellularity <5%, without subsequent improvement occurring either spontaneously or after growth factor treatment. Infusion of an additional stem cell product after documented neutrophil engraftment was considered secondary graft failure.

Based on updated data submitted under the major amendment:

Additional missing laboratory assessments were identified and were included as major and minor protocol deviations. Overall, 39 minor laboratory assessment protocol deviations related to ANC data were newly identified in 27 subjects from 14 sites; 7 major protocol deviations were newly identified in 7 subjects from 6 sites. The Applicant clarified that MPDs included deviations that could potentially affect human subject protection or reliability of trial results. This included deviations in documentation of laboratory results with the potential to impact the primary endpoint.

Newly identified MPDs:

- Subject (b) (6) (assigned to UCBU arm): ANC recovered on Day 32; however, there were seven CBCs prior to that day that were missed, so engraftment date could have been 1 to 10 days earlier. Based on the updated ADLB dataset, however, ANC was 434 on Day 29. Therefore, the earliest ANC recovery would have been Day 30.
- The other six subjects had a difference of 1 day and were balanced between the two treatment arms.

Reviewer comment: *The newly identified deviations were balanced between the two arms and did not significantly impact the efficacy analyses.*

Discrepancies were identified in ANC recovery based on the calculation of ANC from new values in the Supplemental Laboratory Assessment Forms when compared to the day of neutrophil recovery reported in the Hematopoiesis Form, as submitted in the Study P0501 CSR (see Table 18 below). Overall, discrepancies were identified in 16 subjects across 11 sites: 9 sites in the U.S. (14 subjects), 1 in Brazil, and 1 in Israel. There were 10 discrepancies in subjects treated with UCBU and 6 in subjects treated with omidubicel. No site had more than two subjects with a discrepancy. Note that the adjudicated ANC recovery day for Subject (b) (6) was the same as what the Applicant reported despite the discrepancies identified.

Table 18. Study P0501: Summary of Discrepancies in Neutrophil Recovery in the ITT Population

Subject ID	Treatment Arm	ANC Recovery Per the Applicant Date/Day[a]	ANC Recovery Per FDA Adjudication Date/Day[a]	Comments[b]
(b) (6)	UCBU	(b) (6) (35)	(b) (6) (34)	Discrepancy in new lab data Manual ANC (0.4998, 0.522, 1132) for (b) (6)
(b) (6)	UCBU	(b) (6) (26)	(b) (6) (25)	Discrepancy in new lab data ANC (11045) for (b) (6)
(b) (6)	UCBU	(b) (6) (14)	(b) (6) (13)	Discrepancy in new lab data ANC (0.50974) for (b) (6)
(b) (6)	Omidubicel	(b) (6) (35)	(b) (6) (35)	Error in previously locked Visit 028 Form: review of lab data showed ANC <0.5 on (b) (6). Locked form had ANC data from (b) (6) erroneously entered for (b) (6) ANC (0.3978) on (b) (6)

Subject ID	Treatment Arm	ANC Recovery Per the Applicant Date/Day[a]	ANC Recovery Per FDA Adjudication Date/Day[a]	Comments[b]
(b) (6)	UCBU	(b) (6) (14)	(b) (6) (15)	Error in previously locked Visit 014 Form: neutrophil percentage field was not entered on (b) (6) ANC 0.6 was entered in comment field. ANC (0.5004) on (b) (6) .
(b) (6)	UCBU	(b) (6) (17)	(b) (6) (18)	Automated ANC (0.5) vs. manually calculated ANC (0.46) for (b) (6)
(b) (6)	Omidubicel	(b) (6) (9)	(b) (6) (10)	Automated ANC (0.5) vs. manually calculated ANC (0.4992) for (b) (6)
(b) (6)	Omidubicel	(b) (6) (15)	(b) (6) (16)	Automated ANC (0.5) vs. manually calculated ANC (0.496) for (b) (6)
(b) (6)	Omidubicel	(b) (6) (7)	(b) (6) (8)	Automated ANC (0.5) vs. manually calculated ANC (0.497) for (b) (6)
(b) (6)	Omidubicel	(b) (6) (28)	(b) (6) (29)	Automated ANC (0.5) vs. manually calculated ANC (0.462) for (b) (6)
(b) (6)	UCBU	(b) (6) (24)	(b) (6) (22)	Automated ANC (0.49) vs. manually calculated ANC (0.516) for (b) (6) Manually calculated ANC on (b) (6) was 0.648
(b) (6)	Omidubicel	(b) (6) (15)	(b) (6) (17)	Automated ANC (0.5) vs. manually calculated ANC (0.495) for (b) (6)
(b) (6)	UCBU	(b) (6) (16)	(b) (6) (17)	Automated ANC (0.5) vs. manually calculated ANC (0.39) for (b) (6)
(b) (6)	UCBU	(b) (6) (30)	(b) (6) (31)	Automated ANC (0.5) vs. manually calculated ANC (0.456) for (b) (6)
(b) (6)	UCBU	(b) (6) (26)	(b) (6) (27)	Automated ANC (0.6) vs. manually calculated ANC (0.3) for (b) (6)
(b) (6)	UCBU	(b) (6) (22)	(b) (6) (24)	Automated ANC (0.5) vs. manually calculated ANC (0.495) for (b) (6)

Source: FDA analysis, ADLB dataset, Response to IRs
a. From day of transplant, which is Day 0
b. ANC units in cells × 10^9/L
Abbreviations: ANC, absolute neutrophil count; FDA, U.S. Food and Drug Administration; ITT, intent-to-treat; UCBU, unmanipulated cord blood unit

While evaluating ANC recovery without taking into consideration the donor chimerism data, one additional subject was identified:

- Subject (b) (6)
  - Planned/actual treatment arm: omidubicel/omidubicel
  - ANC recovery date (day): (b) (6) (12)
  - Donor chimerism: 82,16, and 12% on Days 14, 21, and 27, respectively
  - The subject had blasts on peripheral blood smear on (b) (6) (Day 18). BM confirmed MDS relapse on (b) (6) (Day 27).

Reviewer comment: *The reviewer considers this subject* (b) (6) *to have achieved the definition of ANC recovery despite the subsequent documented relapse 15 days later. This subject is included in FDA's analysis of the ANC recovery. The statistical reviewer agreed to include this subject in the evaluation of ANC recovery.*

While evaluating delayed ANC recovery (i.e., occurring after the Day 42 post-transplant cutoff), two additional subjects were identified:

- **Subject** (b) (6) Based on additional information from the clinical site obtained in response to the IR, the Applicant clarified that the subject had a documented ANC recovery on Day 45 of 0.752 $\times 10^9$/L. The subject continued to have ANC recovery through Day 57, and he died due to respiratory failure in setting of acute GvHD on Day 58. The subject was receiving GCSF (double dose at 600 µg daily) for approximately 2 weeks until Day 51. Per protocol, GCSF should have been stopped on Day 49 (See Section 6.1.4). The reviewer considers not stopping the GCSF to be a protocol violation. Despite stopping the GCSF on Day 51, the subject's ANC didn't drop below 1.00. Therefore, the reviewer doesn't consider this violation to have impacted the ANC recovery. This was also supported by the successful donor chimerism.
- **Subject** (b) (6) In the ADLB dataset, the subject had leukocytes reported as 0.1 × 10^9/L on Day 43 following transplantation. There were no other reported leukocytes or ANCs reported after Day 43, as the subject was considered to have primary graft failure (PGF). However, in the CSR the narrative stated that "The PGF event was reported as resolved on (b) (6) (Day 55) which was the date of neutrophil engraftment." The Applicant submitted data from the clinical site that showed an ANC of 0.51, 0.98, and 1.28 × 10^9/L on Days 55, 56, and 57, respectively.

Reviewer comment: *These two subjects were not considered in FDA's evaluation of ANC recovery because they occurred after Day 42 post-transplant. As stated in the description of Study P0501, the data in the study were collected more frequently during the time period of the prespecified primary endpoint of the study, which was 42 days. Following that, the data were not as rigorously captured. Specifically, daily CBCs were not required to be tested after primary graft failure, according to the protocol (Amendment VI, Section 7.9.1, "Scheduled Daily*

Assessments Post Transplant up to ANC Engraftment or Primary Graft Failure," and Section 7.9.6, "Early Withdrawal from Follow-up.") Furthermore, the SAP used Day 43 as the assigned analysis day on which the primary endpoint was not met. Therefore, FDA's review of efficacy was based on the follow-up period of 42 days following transplantation.

There were 15 subjects (5 randomized to the omidubicel arm and 10 to the UCBU arm) who did not achieve ANC recovery. Table 19 provides a summary of these subjects.

Table 19. Study P0501: Subjects not Achieving ANC Recovery in the ITT population

Subject ID	Treatment Arm Planned Actual	Comments
(b) (6)	UCBU UCBU	No neutrophil recovery by (and including) Day 42. Subject died on Day 44.
(b) (6)	UCBU Not treated	Subject did not receive any transplant by Day 90 post-randomization due to disease relapse.
(b) (6)	UCBU Not treated	Subject did not receive any transplant by Day 90 post randomization due to disease relapse.
(b) (6)	Omidubicel Not treated	Subject did not receive any transplant by Day 90 post-randomization due to disease relapse.
(b) (6)	UCBU UCBU	No neutrophil recovery by (and including) Day 42. Subject had PGF on Day 42. No evidence of disease relapse. He received a second haploidentical transplant from his mother on Day 44.
(b) (6)	UCBU UCBU	No neutrophil recovery by (and including) Day 42.
(b) (6)	UCBU Not Treated	Subject did not receive any transplant by Day 90 post-randomization due to disease relapse.
(b) (6)	Omidubicel Omidubicel	Subject received second transplant on or prior to Day 42 (On Day 40) without prior neutrophil recovery
(b) (6)	UCBU UCBU	Death on or prior to Day 42 without prior neutrophil recovery. Subject died on Day 22.
(b) (6)	Omidubicel Omidubicel	Subject received second transplant on or prior to Day 42 (On Day 36) without prior neutrophil recovery. Product was OOS
(b) (6)	UCBU Not Treated	Subject did not receive any transplant by Day 90 post-randomization. Delayed transplant due to BM necrotic and MRD+.
(b) (6)	UCBU UCBU	Subject received second transplant on or prior to Day 42 without prior neutrophil recovery
(b) (6)	Omidubicel Not Treated	Subject did not receive any transplant by Day 90 post-randomization. Subject died on Day 34.

Subject ID	Treatment Arm Planned Actual	Comments
(b) (6)	Omidubicel UCBU	No neutrophil recovery by (and including) Day 42. Product was OOS. The subject was randomized to receive omidubicel but was infused with a double UCBU infusion instead. The unit sent for production had a harvest TNCC below specification (4.2×10^8 cells). Processed unit was discarded, and physician investigator decided the subject could not wait for another production cycle to receive transplant. PGF was on Day 42 and the event was reported as resolved on Day 55 (b) (6) which was the date of neutrophil recovery. There was no treatment given for the graft failure. A deviation was recorded for the GCSF treatment, as it was erroneously held between Days 7 and 17.
(b) (6)	UCBU UCBU	No neutrophil recovery by (and including) Day 42. Subject received additional transplant on Day 43.

Source: FDA analysis ADLB, ADSL datasets, CSR, narratives
Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; CBU, cord blood unit; GCSF, granulocyte colony stimulating factor; ITT, intent-to-treat; MRD, minimal residue disease; OOS, out-of-specification; PGF, primary graft failure; TNCC, total nucleated cell count; UCBU, unmanipulated cord blood unit

In addition, four subjects (three in the omidubicel arm and one in the UCBU arm) were not included in the ANC recovery population due to competing risks:

- Subject (b) (6) was randomized to receive omidubicel and had disease relapse
- Subject (b) (6) was randomized to receive omidubicel however did not get transplanted within 90 days.
- Subject (b) (6) was randomized to receive omidubicel and had disease relapse
- Subject (b) (6) was randomized to receive UCBU and had disease relapse

In summary: 54 (87%) subjects in the omidubicel arm and 52 (83%) in the UCBU arm achieved neutrophil recovery.

Chimerism Assays and CDRH Consult

The clinical review team asked the Applicant to provide details of the chimerism assays used during the clinical trial and consulted the Center for Devices and Radiological Health (CDRH) for input on the adequacy of these assays to determine when donor chimerism is ≤10%.

Neutrophil engraftment was defined per protocol and per the SAP as achieving an ANC ≥0.5 × 10^9/L on three consecutive measurements on different days with subsequent donor chimerism (≤10% host cells by peripheral blood chimerism or BM chimerism if peripheral blood chimerism was not available) at any time on or after the day of engraftment up to the earlier of Day 100 (+/- 14 days) following transplant, date of relapse, date of secondary graft failure, or date of death. The first day of the three measurements was designated the day of neutrophil engraftment and

must have occurred on or before 42 days post-transplant (and prior to infusion of any additional stem cell product). Chimerism was measured at Days 21, 42, 100, 180, and 365 following transplantation.

Reviewer comment: *Subject* (b) (6) *had ANC recovery on Day 27 and chimerism testing was performed on Day 105, which showed successful donor engraftment. The Applicant clarified in response to the IR that the protocol allowed a visit window of +/- 14 days for the Day 100 visit.*

The Applicant provided data regarding: the statement of intended use, confirmation of a process for reagent control, instruments/kit/reagents used, sample handling, method of validation, as well as accuracy, precision, sensitivity, and specificity data. The statement of intended use was as follows: The chimerism assay is performed for the evaluation of donor-recipient chimerism following hematopoietic stem cell transplant.

The Applicant indicated that while commercial test kits are available, there are currently no FDA-approved tests for chimerism, and there are no established guidelines for chimerism analysis methodology, indications, or timepoints. Heterogeneity in chimerism practices among transplant programs was recently demonstrated in the results of a 2019 survey of 108 CIBMTR institutions (Blouin and Askar 2022). All survey respondents reported engraftment monitoring as a primary indication for chimerism testing. Most programs also indicated using chimerism testing for detection of relapse and for planning of immunotherapy. Most programs identified the laboratories performing the chimerism testing as academic/university hospital-based (79%); the rest were identified as non-academic, such as hospital-based labs (13%), reference/private labs (6%), or government labs (5%). (b) (4) analysis was the most common method reported (82%); (b) (4) was used by 23% and (b) (4) (b) (4) methods by 7%.

CDRH stated that, consistent with the survey results in CIBMTR institutions, the majority of laboratories in Study P0501 (26/27) reported using (b) (4) One laboratory at site SGH01 in Singapore used (b) (4) (variable number tandem repeats). One site (CHC01, City of Hope, CA) used (b) (4) for one subject before switching to (b) (4) for the remaining subjects. In 25 laboratories, commercially available kits were used, while 2 laboratories developed and validated their own system (SGH01, Singapore; PMC01/UTR01, the Netherlands). The most commonly used kit manufacturer was (b) (4) (54%) followed by (b) (4) (29%). The minor cell population detection limit was 1 to 5% for all methods reported.

CDRH noted that the limit of detection for the chimerism assays used was 5% or below and the limit of quantification (LOQ) values ranged between 1 and 5%.

Reviewer comment: *Based on the CDRH consult, the clinical reviewer concludes that if the chimerism values were reported as 10% or below, they could not have been higher than 11%. CDRH agreed with the clinical reviewer's interpretation. Therefore, the results of the chimerism tests can be relied on when analyzing the prespecified primary endpoint of the study.*

Neutrophil Engraftment vs. Neutrophil Recovery

The clinical review team considers the term “neutrophil engraftment” to be inaccurate because it is the transplanted stem cells that engraft and reconstitute the various hematopoietic cell types. Engraftment is the process by which HSCT home to BM niches where they proliferate to generate the hematopoietic cell subtypes (neutrophils, platelets, and red blood cells). Thus, it is not the neutrophils that are transplanted and later engrafted. In addition, the term engraftment needs confirmation of donor chimerism, which generally occurs later in the course of transplantation, and the combination of chimerism by Day 100 and neutrophil recovery by Day 42 does not clearly describe clinical benefit. Therefore, the reviewer recommends that the primary basis for efficacy be based on ANC recovery and incidence of infection (discussed below). Reliance on ANC recovery for regulatory decision-making would be conditional on the study first meeting its primary objective.

Efficacy Results

The study met its prespecified primary endpoint by demonstrating that the time to neutrophil engraftment was shorter in the omidubicel arm compared to the UCBU arm ($p<0.001$). The median time to neutrophil engraftment was 12 days (95% CI: 10, 16) for the omidubicel group, and 22 days (95% CI: 19, 25) for the UCBU group, being shorter in the omidubicel group by 10 days (95% CI: 5, 14; Bootstrap). Successful neutrophil engraftment by 42 days post-transplant was achieved in 86% of subjects in the omidubicel arm, compared to 83% of subjects who received UCBU. All cumulative incidence incorporated adjustment for competing risks.

Neutrophil Recovery With 42 Days of Follow-Up Without Regard to Chimerism

FDA considers time to ANC recovery with 42 days of follow-up from the day of transplantation to partially reflect clinical benefit for patients with hematologic malignancies undergoing UCBT.

Based on FDA adjudication, the median time to neutrophil recovery was 12 days (95% CI: 10, 15) for the omidubicel group and 22 days (95% CI: 19, 25) for the UCBU group, being shorter in the omidubicel group by 10 days (95% CI: 6, 14; bootstrap). Successful ANC recovery was achieved in 87% of subjects in the omidubicel arm, compared to 83% of subjects who received UCBU.

The review team concluded that because the study met its primary objective, analysis of ANC recovery can be used to inform regulatory decision making.

Reviewer comment: *The statistical reviewer also calculated the difference in median time to neutrophil recovery and neutrophil engraftment by the rerandomization method which were 10 days (95% CI: 6.6, 12.6; rerandomization) and (95% CI: 6.6, 12.7; rerandomization); respectively. For greater consistency, the statistical reviewer recommended to present the bootstrap 95% CIs in the USPI since the CI for the median time to neutrophil recovery and secondary endpoint are also calculated using the bootstrap approach.*

6.1.11.2 Analyses of Secondary Endpoints

Incidence of Grade 2/3 Bacterial or Invasive (Grade 3) Fungal Infections through 100 Days Following Transplantation

In response to IR, the Applicant clarified that for the efficacy analyses, the criteria used for infection grading was based on the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Technical Manual of Procedures (MOP) (BMT CTN 2013). The BMT CTN MOP was developed in 2011 by a consensus panel of experts in infectious diseases and HSCT and had been modified from infection grading validated by Cordonnier et al (Cordonnier et al. 2006). Anatomical classification of infection may be less relevant in HSCT. For example, fever of unknown origin and cutaneous coagulase-negative staphylococcal infection are associated with low mortality in HSCT, while cutaneous or perineal fungal infection are associated with high mortality. This grading system is considered the standard for clinical trials in HSCT including all BMT CTN trials. In general, patients undergoing allogeneic HSCT have a high rate of infections; however, only some infections have an impact on mortality. Therefore, combining infections from a particular organ system using the Common Terminology Criteria for Adverse Events (CTCAE) classification may serve to dilute the impact of clinically significant infections in HSCT.

The BMT CTN MOP uses a three-level grading system to describe severity, based on the expected rate of mortality for each type of infection. During the clinical trial, treated Grade 1 and all Grades 2 to 3 infections were reported on the BMT CTN Infection Form, while untreated Grade 1 infections were not reported. See Table 51 in the Appendix for the BMT CTN infection grading criteria.

Grade 2/3 bacterial or Grade 3 fungal infections by 100 days post-transplant were observed in 39% of subjects in the omidubicel arm and 60% of subjects in the UCBU arm, with an absolute difference of 22% (95% CI: 4, 39).

Days Alive and Out of Hospital (OOH) in the First 100 Days Following Transplantation

A day alive and OOH was defined as a full day (calendar day) in which the subject was alive and not hospitalized. Partial days alive and OOH, such as the day of admission, day of discharge, and day of death, did not count as a day alive and OOH. The day of transplant did not count as a day alive and OOH, regardless of whether the subject was treated as an inpatient or outpatient. Subjects who were not transplanted by Day 90 post-randomization were assigned a value of zero for total days alive and OOH. Duration of primary hospitalization was defined as the total number of days from transplant to first discharge from the hospital. Subjects transplanted as outpatients were assigned a duration of zero days.

Days alive and OOH was calculated by subtracting the total number of days in the hospital during the first 100 Days post-transplant from 100 (for subjects alive at 100 Days) or from the day of death (for subjects who died in the first 100 days). None of the subjects in this study were transplanted as outpatients.

Subjects randomized to receive omidubicel had more days alive and OOH (median =60.5) than subjects randomized to receive UCBU (median =48), with an absolute difference of 12.5% (95% CI: -2, 32.5). Table 20 and Table 21 present information on the number of days alive and OOH in the first 100 days following transplant in the ITT population. Details on reason for hospitalization were provided in response to the IR and were largely due to infection, GvHD, and disease relapse.

Table 20. Study P0501: Days Alive and Out of Hospital in the First 100 Days Following Transplantation in the ITT Population

Randomized Treatment Group	Not Transplanted by Day 90 Post-Randomization[a] (n)	100 Days of Follow-up Post-Transplant (n)	Died Within First 100 Days (n)
Omidubicel	3	53	6
UCBU	4	49	10

Source: FDA analysis ADHO dataset
a. For this group, days alive and out of hospital are assigned as 0.
Abbreviations: ITT, intent-to-treat; UCBU, unmanipulated cord blood unit

Table 21. Study P0501: Statistical Test of Days Alive and Out of Hospital in the First 100 Days Following Transplantation in the ITT Population

Randomized Treatment Group	N	Min	Lower Quartile	Median	Upper Quartile	Max
Omidubicel	62	0.0	33.0	60.5	76.0	89.0
UCBU	63	0.0	6.0	48.0	67.0	84.0

Data Source: FDA analysis ADHO dataset
Abbreviations: ITT, intent-to-treat; UCBU, unmanipulated cord blood unit

Reviewer comment: *The reviewer notes that the secondary endpoint of days OOH should be interpreted with caution, given that whether subjects are hospitalized could depend on several factors that are less objective, such as the judgment of the treating physician, the geographic location, etc.*

Platelet Engraftment by 42 Days Following Transplantation

Platelet engraftment was defined as the first day of a minimum of three consecutive measurements on different days such that the subject has achieved a platelet count >20 × 10^9/L with no platelet transfusions during the preceding 7 days (counting day of engraftment as one of the preceding 7 days). The first day of the three measurements was designated the day of platelet engraftment and had to occur prior to any infusion of a second stem cell product.

Platelet engraftment by Day 42 was achieved in 34 (55%) subjects randomized to receive omidubicel compared to 22 (35%) subjects in those randomized to receive UCBU. The absolute difference in incidence was 20% (rerandomization 95% CI: 3%, 35%).

Reviewer comment: *The concern with using the term "platelet engraftment" is similar to that of the use of "neutrophil engraftment." See discussion above.*

Platelet engraftment by Day 42 is not an accepted or established platelet recovery endpoint for regulatory decision making. Therefore, these data will not be included in the USPI.

6.1.11.3 Subpopulation Analyses

Exploratory, unadjusted subgroup analyses of ANC recovery with 42 days of follow-up according to several key baseline demographic and disease characteristics are presented in Table 22 and show a consistent trend for decreased time to neutrophil recovery across subgroups in subjects who received omidubicel compared to those who received UCBU.

Table 22. Study P0501: Subgroup Analyses of Neutrophil Recovery With 42 Days of Follow-Up in the ITT

Subgroup Category Randomized Treatment Group	Number of Subjects in Subgroup	Neutrophil Recovery %	Median Time to Neutrophil Recovery (95% CI)
Age (years)	-	-	-
12-17			
Omidubicel	8	87.5%	11 days (7, 19 days)
UCBU	6	66.7%	25 days (16, 29 days)
18-39			
Omidubicel	23	78.3%	10 days (8, 20 days)
UCBU	23	87.0%	21 days (19, 26 days)
40-65			
Omidubicel	31	93.6%	12 days (9, 16 days)
UCBU	34	82.4%	22 days (18, 27 days)
Gender	-	-	-
Male			
Omidubicel	32	87.5%	11 days (10, 17 days)
UCBU	40	80.0%	24 days (20, 27 days)
Female			
Omidubicel	30	86.7%	12 days (8, 16 days)
UCBU	23	87.0%	18 days (16, 24 days)

Subgroup Category Randomized Treatment Group	Number of Subjects in Subgroup	Neutrophil Recovery %	Median Time to Neutrophil Recovery (95% CI)
Race/ethnicity	-	-	-
Asian/any ethnicity			
Omidubicel	7	85.7%	8 days (7, 19 days)
UCBU	10	90.0%	19 days (16, 32 days)
Black/any ethnicity			
Omidubicel	11	90.9%	10 days (8, 14 days)
UCBU	9	100.0%	17 days (14, 24 days)
White/Hispanic			
Omidubicel	5	100.0%	11 days (8, 20 days)
UCBU	5	100.0%	18 days (14, 26 days)
White/Non-Hispanic or unknown			
Omidubicel	30	90.0%	13 days (8, 18 days)
UCBU	32	75.0%	24 days (21, 31 days)
Other, including unknown			
Omidubicel	9	66.7%	13 days (9, 20 days)
UCBU	7	71.4%	20 days (16, 20 days)
Geographic region	-	-	-
Europe			
Omidubicel	12	75.0%	12 days (7, 35 days)
UCBU	11	81.8%	22 days (17, 32 days)
U.S.			
Omidubicel	42	88.1%	12 days (10, 15 days)
UCBU	45	82.2%	22 days (19, 27 days)
Other (Brazil, Singapore, Israel)			
Omidubicel	8	100.0%	8 days (7, 19 days)
UCBU	7	85.7%	18 days (16, 32 days)
Disease risk	-	-	-
Low			
Omidubicel	15	93.3%	15 days (10, 18 days)
UCBU	15	73.3%	21 days (17, 40 days)
Moderate			
Omidubicel	27	88.9%	12 days (9, 16 days)
UCBU	25	88.0%	20 (17, 27 days)
High/very high			
Omidubicel	20	80.0%	10 days (7, 35 days)
UCBU	23	82.6%	24 days (20, 26 days)
Intended CB transplant	-	-	-
Single			
Omidubicel	20	85.0%	10 days (8, 20 days)
UCBU	21	81.0%	18 days (17, 27 days)
Double			
Omidubicel	42	88.1%	13 days (10, 16 days)
UCBU	42	83.3%	22 days (19, 26 days)

Subgroup Category Randomized Treatment Group	Number of Subjects in Subgroup	Neutrophil Recovery %	Median Time to Neutrophil Recovery (95% CI)
Disease	-	-	-
ALL			
Omidubicel	20	85.0%	13 days (8, 20 days)
UCBU	21	85.7%	25 days (19, 29 days)
AML			
Omidubicel	27	88.9%	12 days (10, 17 days)
UCBU	33	78.8%	19 days (18, 24 days)
CML			
Omidubicel	4	100.0%	8 days (6, 12 days)
UCBU	2	50.0%	22 days (22, 22 days)
MDS			
Omidubicel	6	83.3%	14 days (8, 35 days)
UCBU	3	100.0%	24 days (17, 27 days)
Lymphoma			
Omidubicel	3	100.0%	9 days (8, 19 days)
UCBU	2	100.0%	24 days (24, 26 days)
Other rare disease			
Omidubicel	2	50.0%	7 days (7, 7 days)
UCBU	2	100.0%	16 days (16, 22 days)
HCT-specific co-morbidity index	-	-	-
0			
Omidubicel	12	83.3%	13 days (8, 35 days)
UCBU	14	64.3%	26 days (17, 32 days)
1-2			
Omidubicel	19	84.2%	14 days (8, 18 days)
UCBU	16	87.5%	18 days (16, 26 days)
3+			
Omidubicel	31	90.3%	11 days (9, 14 days)
UCBU	33	87.9%	22 days (19, 25 days)

Source: Stats reviewer
Abbreviations: ANC, absolute neutrophil count; UCBU, unmanipulated cord blood unit

A summary of the subgroup analysis for the key secondary endpoint of BMT CTN Grade 2/3 bacterial or fungal infections through Day 100 following transplantation is shown below and demonstrates a lower incidence of Grade 2/3 infections across subgroups in subjects who received omidubicel compared to those who received UCBU.

Table 23. Study P0501: Subgroup Analyses of BMT CTN Grade 2/3 Bacterial or Grade 3 Fungal Infections Through Day 100 Following Transplantation in the ITT

Subgroup Category Randomized Treatment Group	Omidubicel n/N (%)	UCBU n/N (%)
Age (years)		
12-17	2/8 (25)	3/6 (50)
18-39	12/23 (52)	18/23 (78)
40-65	10/31 (32)	17/34 (50)

Subgroup Category Randomized Treatment Group	Omidubicel n/N (%)	UCBU n/N (%)
Gender		
Male	14/32 (44)	21/40 (53)
Female	10/30 (33)	17/23 (74)
Race/ethnicity		
Asian/any ethnicity	3/7 (43)	8/10 (80)
Black/any ethnicity	6/11 (55)	6/9 (67)
White/Hispanic	3/5 (60)	3/5 (60%)
White/Non-Hispanic or unknown	10/30 (33)	16/32 (50)
Other, including unknown	2/9 (22)	5/7 (71)
Geographic region		
Europe	4/12 (33)	6/11 (55)
U.S.	17/42 (40)	26/45 (58)
Other (Brazil, Singapore, Israel)	3/8 (38%)	6/7 (86)
Disease risk		
Low	8/15 (53)	9/15 (60)
Moderate	10/27 (37)	16/25 (64)
High/very high	6/20 (30)	13/23 (57)
Intended CB transplant		
Single	7/20 (35)	13/21 (62)
Double	17/42 (40)	25/42 (60)
Disease		
ALL	7/20 (35)	12/21 (57)
AML	12/27 (44)	22/33 (67)
CML	1/4 (25)	1/2 (50)
MDS	2/6 (33)	2/3 (67)
Lymphoma	1/3 (33)	0/2 (0)
Other rare disease	1/2 (50)	1/2 (50)
HCT-specific co-morbidity index		
0	5/12 (42)	10/14 (71)
1-2	7/19 (37)	10/16 (63)
3+	12/31 (39)	18/33 (55)

Source: FDA Review

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BMT CTN, Blood and Marrow Transplant Clinical Trials Network; CB, cord blood; CML, chronic myelogenous leukemia; HCT, hematopoietic cell transplantation; ITT, intent-to-treat; MDS, myelodysplastic syndrome; UCBU, unmanipulated cord blood unit

6.1.11.4 Dropouts and/or Discontinuations

Eight subjects discontinued/withdrew from study assessments (seven who were transplanted within 90 days following randomization and one who was not transplanted by Day 90). See Table 24 for details. Also, see Section 6.1.10 Study Population and Disposition.

Table 24. Study P0501: Withdrawal From Study Assessments

Subject ID	Treatment Planned Received	Days From Transplant to Withdrawal From Study Assessments/Tests	Primary Reason for Withdrawal
(b) (6)	Omidubicel Omidubicel	31	Physician decision: primary graft failure.
(b) (6)	UCBU Other donor	49	Physician decision: per investigator discretion
(b) (6)	UCBU UCBU	403	Physician decision: subject non-compliance
(b) (6)	UCBU UCBU	144	Physician decision: Principal investigator withdrew subject from study
(b) (6)	UCBU UCBU	307	Withdrawal by subject
(b) (6)	Omidubicel UCBU	-9	Physician decision: transplant in other study
(b) (6)	Omidubicel UCBU	-21	Physician decision: psychological
(b) (6)	UCBU Not treated by Day 90	266[a]	Withdrawal by subject

Source: FDA analysis ADSL dataset
a. Days from randomization to withdrawal
Abbreviations: UCBU, unmanipulated cord blood unit

6.1.11.5 Exploratory and Post Hoc Analyses

ANC Recovery Within 42 days of Follow-Up Post-Transplant in the Per-Protocol Population (i.e., AT or SP):

Additional analysis was performed in subjects in the AT population who received a transplant that met protocol specifications and were grouped according to the actual treatment received. Ninety-four percent of subjects who received omidubicel achieved ANC recovery with 42 days of follow-up compared to eighty-nine percent of subjects who received UCB. Similar to the results in the ITT population, with a median time to ANC recovery of 10 days (95% CI: 8, 12) for the omidubicel group, and 20 days (95% CI: 18, 24) for the UCBU group, the time to neutrophil recovery in the AT population was shortened by omidubicel transplantation compared to UCBU (being shorter in the omidubicel group by 10 days (95% CI: 7, 14; Bootstrap).

Incidence of Grade 2/3 Bacterial and Grade 3 Fungal Infections in the Per-Protocol Population

The incidence of Grade 2/3 bacterial and Grade 3 fungal infections through Day 100 following transplantation was 35% in subjects who received omidubicel compared to 61% in subjects who received UCBU.

Delayed Neutrophil Recovery (ANC Recovery at Any Time Following Transplantation and Without Regard to Chimerism) in the ITT Population

The incidence of delayed neutrophil recovery was similar between arms. One subject in each arm had documented neutrophil recovery after Day 42:

- (b) (6) – UCBU arm – neutrophil recovery on Day 45
- (b) (6) – omidubicel arm – neutrophil recovery on Day 55

Use of the Product With Leukodepleting In-Line Filer

Eleven subjects in the SP were infused with omidubicel using an in-line filter. Efficacy outcomes in these subjects were similar to those of the overall group of subjects treated with omidubicel.

Non-Relapse Mortality or Transplant-Related Mortality

NRM was analyzed at 130 days, 210 days, and 15 months following randomization with secondary analysis at 100 days, 180 days, and 1 year following transplantation (see Table 25).

Table 25. Study P0501: Non-Relapse Mortality (ITT Population, %)

Timepoint	Omidubicel	UCBU
130 days post-randomization	6	14
100 days post-transplantation	10	13
210 days post-randomization	11	24
180 days post-transplantation	11	22
15 months post-randomization	15	29
1 year post-transplantation	15	29

Source: FDA analysis, CSR
Abbreviations: ITT, intent-to-treat; UCBU, unmanipulated cord blood unit

Patient-Reported Outcome Data

Patient-reported HQL outcomes were assessed during the study using two measures: the Functional Assessment of Cancer Therapy – Bone Marrow Transplantation (FACT-BMT) and the EQ-5D. These were assessed at screening and at Days 42, 100, 180, and 365 following transplantation.

The FACT-BMT is a self-administered instrument designed to assess multidimensional aspects of the QOL in BMT patients. It consists of the 27-item FACT-General that evaluates the HQL of patients receiving treatment for cancer and the 23-item Bone Marrow Transplantation Subscale that addresses disease and treatment-related questions specific to BM transplant. The FACT-General assesses four primary dimensions of QOL, including physical, social/family, emotional, and functional well-being.

The EQ-5D descriptive system consists of five dimensions (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) for which subjects choose one of three responses. The responses record three levels of severity (no problems, some or moderate problems, or extreme problems).

Per the Applicant, subjects randomized to omidubicel scored higher on QOL at various post-transplant visits compared to subjects randomized to UCBU. However, none of these differences were tested for statistical significance.

Reviewer comment: *The patient-reported outcome data were reviewed but were insufficient to support any labeling claims.*

6.1.12 Safety Analyses

6.1.12.1 Methods

The study follow-up period was until 15 months post-randomization and 1-year post-transplantation. The median duration of follow-up for the SP was 14 months (range: 1 to 19 months) post-transplantation.

AEs were coded using the MedDRA version 23. AE severity was graded using the National Cancer Institute CTCAE version 4.03 with the following two exceptions:

- Infections: Infections were graded by two grading systems:

- BMT CTN grading criteria (Grades 1 to 3): used for evaluation of efficacy outcomes (for details, see Section 6.1.11.2 Analyses of Secondary Endpoints). These infections were reported in the clinical events analysis and clinical classification analysis (ADCE) dataset.
- CTCAE grading (Grades 1 to 5): Infections meeting the criteria for SAE were also graded using CTCAE. Adverse event analysis (ADAE) dataset contains only infections meeting the criteria for SAE.

- GvHD:

- Acute GvHD was graded per Przepiorka et al.(Przepiorka et al. 1995).
- Chronic GvHD was graded according to NIH Consensus Criteria (Jagasia et al. 2015).

  GvHD data were provided in tumor response and clinical classification analysis (ADRS) dataset.

AEs were collected/reported as either:

- Anticipated Events Post-Transplant: These events were collected as described in the protocol (per the Applicant, in order to minimize the burden on investigational sites) and were summarized by severity and time period and described by the MedDRA system organ class (SOC), preferred term (PT), and relationship to the study product. Maximum

toxicity severity for a subject was summarized for each period and for the entire 42-day period.

- Unanticipated Events Post-Transplant: Unanticipated AEs were events not listed in the protocol and were described by the MedDRA SOC, PT, severity, seriousness, and relationship to the study product.

Notably, in ADAE data file, AEs with Grade 0 corresponded to no event. Furthermore, the variable AETOXGR (reflecting AE toxicity grade): “Grade 1 or 2” was collected as a single category and therefore it is not discernable from the collected data whether the event was specifically Grade 1 or Grade 2. Grades 1 or 2 were recorded as Grade 2 in the dataset.

The Toxicity Form included a visit day rather than a calendar date. The visit day denoted the number of days following transplant and reflected the occurrence of an expected AE in the 7-day period prior to that day. These events were reported as the highest grade over a specified time interval (typically 1 week).

Visit intervals used for the Transplant Toxicity Summary Form were:

- Conditioning to transplant
- Transplant and 24 hours post-transplant (Days 0 and 1)
- Days 2 to 7
- Weekly through Day 42

For AEs captured in the Adverse Event Visit Log, and for SAEs, actual event dates were captured, and visit intervals were not reported. If no entry appears in the “Visit” column, it means that the AE was an SAE or a non-serious AE captured in the Adverse Event Visit Log (events through Day 42 that were not on the common events list, and all Grade 3 or higher events after Day 42).

To summarize, the ADAE dataset included:

- All SAEs
- All AEs through Day 42 post-transplantation
- Only Grades 3 or higher after Day 42

The ADAE dataset included only infections meeting the criteria for SAE, and the reviewer based the efficacy and safety analyses of infections on the ADCE dataset, which used the BMT CTN grading system. Efficacy analyses were reported for the ITT population and the safety analyses were reported for the SP.

Therefore, during the period from Day 43 through the end of study, Grade 3 to 5 AEs, infections, and all SAEs were reported individually (ADAE and ADCE datasets) and GvHD (ADRS dataset) was graded at every study visit. Grade 1 to 2 non-SAEs were not reported during this period.

The LB and ADLB datasets included only laboratory data that were required to be documented on the Laboratory Assessment Form, which included CBCs, WBC differential, and blood chemistries at Days -1, 0, 7, 14, 21, 28, 35, 42, 56, 70, 100, 180, 270, and 365 post-transplant. Any additional interval laboratory data were considered by the Applicant to not be valuable in the interpretation of the study data or contribute to the overall assessment of safety and

efficacy. In response to the IR that triggered the issuance of a major amendment, the Applicant submitted updated laboratory datasets, which included the lab data that were performed but were not reported since the protocol did not mandate report of these labs. Clinically significant laboratory abnormalities were reported as AEs.

Notably, throughout the review memo, several AEs are presented as grouped terms as defined by the reviewer. The complete list of FDA's grouped terms for all treatment-emergent adverse events (TEAEs) is presented in Table 52 in the Appendix. Unless otherwise specified, all analyses and tables were generated by the FDA review team.

Reviewer comment: *Due to the limitations of AE collection and reporting during the study, Section 6 of the USPI describing the adverse reactions (ARs) will list only Grade 3 and higher ARs rather than ARs of all grades. Grade 3 and higher AEs were more reliably collected. Infections will be reported as per the BMT CTN grading criteria since data collection by these criteria were more complete; only infections meeting the criteria for SAE were reported by CTCAE grade in the ADAE datasets.*

6.1.12.2 Overview of Adverse Events

Safety events were reported as of the cutoff date for the data analysis (29 April 2021). The safety evaluation in this review considers all AEs that occurred or worsened after transplantation to be TEAEs regardless of how the investigator attributed them. The immediate post-transplant period encompasses the start of the transplant infusion up through 24 hours after the end of the transplant infusion.

An overview of TEAEs by treatment group for the SP is provided in Table 26.

Table 26. Study P0501: TEAEs in the Safety Population

AE Grade	Omidubicel N=52 n (%)	UCBU N=56 n (%)
All-Grade AEs	52 (100)	56 (100)
Grade 3-5 AEs	51 (98)	53 (95)
Grade 1-4 AEs	40 (77)	36 (64)
Grade 3-4 AEs	39 (75)	33 (59)
Grade 3	32 (62)	23 (41)
Grade 4	7 (13)	10 (18)
SAEs	47 (90)	51 (91)

Source: FDA analysis ADAE, ADSL datasets
Abbreviations: CBU, cord blood unit; AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UCBU: unmanipulated cord blood unit

The incidence of TEAEs is presented by SOC. Table 27 below details AEs by SOC that occurred in ≥10% of subjects. The most common non-laboratory CTCAE Grade 3 or higher TEAEs occurring in >10% of subjects treated in the omidubicel treatment arm include: pain

(33%), mucosal inflammation (31%), hypertension (25%), gastrointestinal toxicity (19%), dysphagia (12%), hemorrhage (12%), respiratory failure (12%), and renal impairment (12%).

Table 27. Study P0501: Treatment-Emergent Adverse Events (TEAE) in ≥10% of Safety Population by System Organ Class

TEAE	Omidubicel N=52 Grade 1-5 n (%)	Omidubicel N=52 Grade 3-5 n (%)	UCBU N=56 Grade 1-5 n (%)	UCBU N=56 Grade 3-5 n (%)
Any TEAE	52 (100)	51 (98)	56 (100)	53 (95)
General disorders and administration site conditions	-	-	-	-
Pyrexia	42 (81)	1 (1.9)	54 (96)	6 (11)
Pain	41 (79)	17 (33)	43 (77)	10 (18)
Mucosal inflammation	39 (75)	16 (31)	47 (84)	19 (34)
Fatigue (GT)	31 (60)	2 (3.8)	42 (75)	12 (21)
Edema (GT)	25 (48)	1 (1.9)	37 (66)	4 (7)
Chills	19 (37)	0	32 (57)	0
Disease recurrence (GT)	8 (15)	8 (15)	6 (11)	5 (9)
Gastrointestinal disorders	-	-	-	-
Gastrointestinal toxicity	40 (77)	10 (19)	48 (86)	19 (34)
Vomiting	33 (63)	3 (6)	40 (71)	2 (3.6)
Dysphagia	17 (33)	6 (12)	21 (38)	7 (12)
Constipation	12 (23)	0	21 (38)	0
Dyspepsia	12 (23)	0	12 (21)	0
Abdominal distension	10 (19)	0	16 (29)	1 (1.8)
Skin and subcutaneous tissue disorders	-	-	-	-
Rash (GT)	22 (42)	0	30 (54)	1 (1.8)
Dry skin	21 (40)	1 (1.9)	10 (18)	1 (1.8)
Skin hyperpigmentation	16 (31)	0	15 (27)	0
Skin ulcer	4 (8)	0	6 (11)	1 (1.8)
Vascular disorders	-	-	-	-
Hypertension	29 (56)	13 (25)	37 (66)	21 (38)
Hemorrhage (GT)	25 (48)	6 (12)	34 (61)	10 (18)
Hypotension	16 (31)	2 (3.8)	19 (34)	5 (9)
Respiratory, thoracic and mediastinal disorders	-	-	-	-
Cough (GT)	14 (27)	0	30 (54)	0
Dyspnoea	13 (25)	4 (8)	26 (46)	9 (16)
Respiratory failure (GT)	8 (15)	6 (12)	26 (46)	17 (30)
Nervous system disorders	-	-	-	-
Dysgeusia	15 (29)	0	9 (16)	0
Dizziness	10 (19)	0	13 (23)	0
Tremor	8 (15)	0	12 (21)	1 (1.8)
Somnolence	7 (13)	1 (1.9)	12 (21)	0

TEAE	Omidubicel N=52 Grade 1-5 n (%)	Omidubicel N=52 Grade 3-5 n (%)	UCBU N=56 Grade 1-5 n (%)	UCBU N=56 Grade 3-5 n (%)
Psychiatric disorders	-	-	-	-
Insomnia	24 (46)	1 (1.9)	26 (46)	2 (3.6)
Anxiety	15 (29)	1 (1.9)	21 (38)	3 (5)
Depression	13 (25)	0	16 (29)	2 (3.6)
Investigations	-	-	-	-
Weight decreased	23 (44)	3 (6)	21 (38)	0
Cardiac disorders	-	-	-	-
Arrhythmia	24 (46)	0	30 (54)	1 (1.8)
Metabolism and nutrition disorders	-	-	-	-
Dehydration	11 (21)	3 (6)	10 (18)	2 (3.6)
Hypokalaemia	6 (12)	6 (12)	5 (9)	5 (9)
Hyperglycaemia	4 (8)	4 (8)	8 (14)	8 (14)
Immune system disorders	-	-	-	-
Hypersensitivity	4 (8)	0	10 (18)	1 (1.8)
Musculoskeletal and connective tissue disorders	-	-	-	-
Muscular weakness	16 (31)	1 (1.9)	22 (39)	2 (3.6)
Injury, poisoning and procedural complications	-	-	-	-
Vascular access complication	1 (1.9)	0	7 (12)	1 (1.8)
Renal and urinary disorders	-	-	-	-
Renal impairment (GT)	9 (17)	6 (12)	3 (5)	3 (5)
Eye disorders	-	-	-	-
Dry eye	6 (12)	0	10 (18)	0

Source: FDA analysis ADAE, ADSL datasets
Abbreviations: TEAE, treatment-emergent adverse event; UCBU, unmanipulated cord blood unit

Reviewer comment: *Infections and GvHD were excluded from Table 26 and Table 27 above because the ADAE dataset did not adequately capture these events. Infections were reported in the ADCE dataset and GvHD data were reported in the ADRS dataset. See Section 6.1.12.5 for review of infections and GvHD in the SP.*

6.1.12.3 Deaths

A total of 42 deaths were reported during the study follow-up. Seventeen deaths occurred in subjects randomized to omidubicel, and 25 deaths occurred in subjects randomized to UCBU. Of these, two subjects in the omidubicel arm and three subjects in the UCBU arm died of disease relapse before transplantation.

In the SP, deaths were reported for 12 (23%) subjects treated with omidubicel and 20 (36%) subjects treated with UCBU. Among subjects treated with omidubicel, common causes of death were infections, acute GvHD, and relapse (n=3 for each). 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 (n=6); respiratory disorders (n=6; including hypoxic respiratory failure, acute respiratory distress syndrome (ARDS), idiopathic pneumonia, and pulmonary organ failure); disease relapse (n=4); and GvHD (n=3). One subject died of VOD. Table 28 and Table 29 below provide the incidence of all deaths in the SP and the deaths that occurred in the omidubicel arm in the SP, respectively.

Table 28. Study P0501: Deaths in the Safety Population

Adverse Event	Omidubicel N=52 n (%)	UCBU N=56 n (%)
Deaths	12 (23)	20 (36)

Source: FDA analysis ADAE, ADSL, ADDD datasets
Abbreviation: UCBU, unmanipulated cord blood unit

Table 29. Study P0501: Deaths in the Omidubicel Treatment Arm in the Safety Population

Subject ID	Primary Cause of Death	Death Day	Adverse Reaction (Y/N)
(b) (6)	Acute GvHD	31	Y
	Infection, organism not identified (sepsis)	52	Y
	Organ failure, VOD/SOS	59	Y
	Acute GvHD	61	Y
	Acute GvHD	92	Y
	TTP/TMA	93	Y
	Pulmonary hemorrhage	103	Y
	Infection, organism not identified (sepsis)	133	Y
	Suicide in setting of disease relapse	191	N
	Infection, bacterial	192	Y
	Disease relapse	241	N
	Disease relapse	334	N

Source: FDA Analysis. ADSL, ADAE, ADDD datasets, Narratives, CRF, CSR
Abbreviations: GvHD, graft versus host disease; SOS, sinusoidal obstruction syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VOD, veno-occlusive disease

Reviewer comment: *Not including AEs in setting of disease relapse, nine (17%) subjects died due to ARs: infection (6%, n=3), acute GvHD (6%, n=3), pulmonary hemorrhage (2%, n=1), thrombotic thrombocytopenic purpura/thrombotic microangiopathy (2%, n=1), and VOD/SOS (2%, n=1). Fatal adverse reactions occurred in 29% of subjects treated with UCBU, including infection/sepsis (11%), respiratory disorders (11%), GvHD (5%), and VOD/SOS (2%). These fatal ARs will be included in Section 6 of the USPI.*

Deaths After Main Study Follow-Up as of Data Cutoff (29 April 2021)

Subjects who consented to the LTFU sub-study of this protocol were followed for up to 5 years post-transplant to report new deaths and other major outcomes occurring during standard of care follow-up. As of the data cutoff, eight subjects had died:

- Omidubicel arm

- (b) (6) Died at 16 months due to viral encephalitis.
- (b) (6) **:** Died at 19 months due to relapse. Relapse occurred on the primary study at Month 9.
- (b) (6) Died at 20 months due to PTLD. Secondary causes included multi-system organ failure and bacterial infection.
- (b) (6) Died at 21 months due to relapse. Secondary causes included viral and bacterial infections. Relapse occurred on the primary study at Month 3.
- (b) (6) Died at 23 months due to viral infection.
- (b) (6) Died at 27 months due to multi-system organ failure. Relapse reported at Month 23.

- UCBU arm

- (b) (6) **:** Died at 28 months due to relapse.
- (b) (6) Died at 34 months from fungal infection (pulmonary aspergillosis). Relapse diagnosed on day of death.

6.1.12.4 Nonfatal Serious Adverse Events

An SAE was defined as an AE that met at least one of the following serious criteria:

- Fatal
- Life-threatening (places the subject at immediate risk of death)
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

Among the SP, SAEs occurred in 47 (90%) subjects in the omidubicel arm and 51 (91%) in the UCBU arm. SAEs occurring in ≥1% of subjects are presented in Table 30 below.

Table 30. Study P0501: Non-Laboratory Serious Treatment-Emergent Adverse Events Occurring in ≥1% of Safety Population

SAEs	Omidubicel N=52 Grade 1-5 n (%)	UCBU N=56 Grade 1-5 n (%)
Any SAE	47 (90)	51 (91)
Infections and infestations	-	-
Viral infection (GT)	15 (29)	11 (20)
Infections – pathogen unspecified (GT)	11 (21)	18 (32)
Bacterial infection (GT)	4 (8)	1 (1.8)
Cerebral toxoplasmosis	1 (1.9)	0
Fungal infection (GT)	0	1 (1.8)
Immune system disorders	-	-
Graft versus host disease in gastrointestinal tract	5 (10)	6 (11)
Acute graft versus host disease	5 (10)	2 (3.6)
Graft versus host disease	4 (8)	5 (9)
Graft versus host disease in skin	2 (3.8)	0
Acute graft versus host disease in intestine	1 (1.9)	0
Chronic graft versus host disease	0	1 (1.8)
Respiratory, thoracic and mediastinal disorders	-	-
Respiratory failure (GT)	2 (3.8)	10 (18)
Bronchospasm	1 (1.9)	1 (1.8)
Pulmonary embolism	1 (1.9)	1 (1.8)
Laryngeal oedema	1 (1.9)	0
Pneumonia aspiration	1 (1.9)	0
Idiopathic interstitial pneumonia	0	1 (1.8)
Idiopathic pneumonia syndrome	0	1 (1.8)
Pleural effusion	0	1 (1.8)
Renal and urinary disorders	-	-
Renal impairment (GT)	7 (13)	2 (3.6)
Gastrointestinal disorders	-	-
Diarrhea (GT)	2 (3.8)	3 (5)
Gastrointestinal disorder	1 (1.9)	1 (1.8)
Nausea	1 (1.9)	1 (1.8)
Dysphagia	1 (1.9)	0
Abdominal pain (GT)	1 (1.9)	2 (3.6)
Chronic gastritis	1 (1.9)	0
Food poisoning	0	1 (1.8)
Gastric perforation	0	1 (1.8)
Constipation	0	1 (1.8)
Inflammatory bowel disease	0	1 (1.8)
General disorders and administration site conditions	-	-
Disease recurrence (GT)	8 (15)	6 (11)
Pyrexia	5 (10)	3 (5)
Mucosal inflammation	1 (1.9)	0
Edema (GT)	1 (1.9)	1 (1.8)
Multiple organ dysfunction syndrome	0	2 (3.6)
Fatigue (GT)	0	1 (1.8)

SAEs	Omidubicel N=52 Grade 1-5 n (%)	UCBU N=56 Grade 1-5 n (%)
Injury, poisoning and procedural complications	-	-
Transplant failure	3 (6)	5 (9)
Femoral neck fracture	2 (3.8)	0
Infusion related reaction	0	1 (1.8)
Blood and lymphatic system disorders	-	-
Febrile neutropenia	3 (6)	0
Thrombotic microangiopathy	1 (1.9)	4 (7)
Nervous system disorders	-	-
Dysarthria	1 (1.9)	0
Facial paresis	1 (1.9)	0
Syncope	0	1 (1.8)
Cerebral infarction	0	1 (1.8)
Investigations	-	-
Pulmonary function test decreased	1 (1.9)	0
Metabolism and nutrition disorders	-	-
Dehydration	1 (1.9)	0
Failure to thrive	0	1 (1.8)
Psychiatric disorders	-	-
Anxiety	1 (1.9)	1 (1.8)
Mental status changes	1 (1.9)	1 (1.8)
Suicide attempt	1 (1.9)	0
Hepatobiliary disorders	-	-
Venoocclusive liver disease	2 (3.8)	4 (7)
Vascular disorders	-	-
Hemorrhage (GT)	4 (8)	6 (11)
Hypertension	1 (1.9)	1 (1.8)
Vena cava thrombosis	1 (1.9)	0
Hypovolaemic shock	0	1 (1.8)
Cardiac disorders	-	-
Cardiac failure	0	1 (1.8)
Congenital, familial and genetic disorders	-	-
Acquired chromosomal abnormality	0	1 (1.8)
Musculoskeletal and connective tissue disorders	-	-
Osteonecrosis	0	1 (1.8)

Source: FDA analysis: ADAE, ADSL datasets
Abbreviation: SAE, serious adverse event; UCBU, unmanipulated cord blood unit

6.1.12.5 Adverse Events of Special Interest

Most common adverse events of special interest (AESIs) that occurred in subjects treated with omidubicel included: infection (49; 94%), GvHD (32; 62%), and infusion reaction (29;56%).

Infections

The incidence of infections per BMT CTN in the SP is listed in Table 31 below. Sixty-five percent of subjects receiving omidubicel had at least one bacterial infection of any grade

compared to 80% of subjects receiving UCBU. Twenty-one percent of subjects receiving omidubicel had at least one fungal infection of any grade compared to 27% of subjects receiving UCBU.

Seventy-five percent of subjects receiving omidubicel had at least one viral infection of any grade compared to 80% in the subjects receiving UCBU. Grade 2/3 viral infections were observed in 29 (56%) subjects receiving omidubicel compared to 33 (59%) subjects receiving UCBU. These infections included viral reactivation (e.g., cytomegalovirus, human herpesvirus 6 [HHV6], etc.).

Reviewer comment: *Viral infections could be considered an indirect measure of lymphocyte reconstitution following transplantation. In Study P0501, the incidence of viral infection was similar between the two treatment arms.*

Table 31. Study P0501 Infections per BMT CTN Criteria in the Safety Population (N=108)

Infection Type	Omidubicel N=52 Grade 1-3 n (%)	Omidubicel N=52 Grade 2 n (%)	Omidubicel N=52 Grade 3 n (%)	UCBU N=56 Grade 1-3 n (%)	UCBU N=56 Grade 2 n (%)	UCBU N=56 Grade 3 n (%)
Any infection	49 (94)			56 (100)		
Viral infection	39 (75)	25 (48)	4 (8)	45 (80)	18 (32)	15 (27)
Bacterial infection	34 (65)	14 (27)	4 (8)	45 (80)	26 (46)	13 (23)
Non-microbiologically defined infection	18 (35)	8 (15)	5 (10)	14 (25)	6 (11)	5 (9)
Fungal infection	11 (21)	2 (4)	3 (6)	15 (27)	0 (0)	10 (18)
Parasitic/protozoal infection	2 (4)	0	2 (4)	0	0	0

Source: FDA analysis ADCE, ADSL datasets
Abbreviation: UCBU, unmanipulated cord blood unit

Febrile Neutropenia

In response to IR, the Applicant clarified that there were no AEs in the ADAE dataset with the PT "neutropenia" or "neutrophil count decreased" as all subjects in the study were expected to have neutropenia as a result of the myeloablative conditioning regimen administered prior to transplant. Therefore, neutropenia was not reported by investigators as an AE. In addition, common AEs were reported as associated with a visit day. For example, fever that occurred on Day 10 was reported on Visit Day 14, which encompassed the time period between Day 8 and Day 14 post-transplant. Furthermore, Grade 1 and 2 AEs were not collected after Day 42. Therefore, it not possible to identify all subjects who had true febrile neutropenia by identifying subjects who had overlapping AE of fever in the setting of neutropenia (as defined by ANC <1,000 per CTCAE criteria).

Graft Failure

Primary graft failure was defined as failure to achieve an ANC equal to or greater than 0.5 $x10^9$/L by Day 42 after transplantation.

Infusion of a second stem cell product on or prior to Day 42 was considered primary graft failure, unless the transplantation is received after documented neutrophil engraftment, which was considered secondary graft failure, even if it occurred on or prior to Day 42.

Primary graft failure occurred in one (2%) subject treated with omidubicel, compared to six (11%) subjects receiving UCBU.

The following subject in the SP treated in the omidubicel arm had primary graft failure:

- (b) (6) Subject had no ANC recovery and received a second transplant from a haploidentical donor on Day 40 with subsequent engraftment.

The following six subjects in the SP treated in the control arm had primary graft failure:

- (b) (6) Subject had no ANC recovery by (and including) Day 42.
- Subject had no ANC recovery by (and including) Day 42.
- Subject had no ANC recovery by (and including) Day 42.
- Subject died prior to ANC recovery.
- Subject received second transplant prior to ANC recovery.
- Subject had no ANC recovery by (and including) Day 42.

Secondary graft failure comprised documented neutrophil recovery and donor chimerism, followed by severe neutropenia (<0.5 × 10^9/L for three or more consecutive laboratory values on separate days) with marrow cellularity <5%, without subsequent improvement. One subject (b) (6) treated with omidubicel had a secondary graft failure approximately 6 months following transplantation, concurrent with a diagnosis of disease relapse.

GvHD

Among subjects in the SP who were transplanted with omidubicel, 32 (62%) subjects reported Grade II to IV acute GvHD. In the control group, 24 (43%) subjects reported Grade II to IV acute GvHD. Grade III to IV acute GvHD was reported in 8 (15%) subjects treated with omidubicel and 12 (21%) subjects in the control arm.

Chronic GvHD was reported in 18 (35%) subjects treated with omidubicel and in 14 (25%) subjects treated with UCBU. Mild, moderate, and severe chronic GvHD were in 6 (12%), 10 (19%), and 2 (4%) subjects treated with omidubicel and in 3 (5%), 9 (16%), and 2 (4%) subjects in the control arm, respectively.

Reviewer comment: *The higher incidence of Grade II to IV acute GvHD in the treatment arm may be explained by the earlier neutrophil recovery in this arm compared to the control arm. Notably, Grace III to IV acute GVHD was lower in the omidubicel arm compared to the control arm. However, a final conclusion cannot be made because the study was not designed or powered to detect a difference in GvHD incidence between the two arms.*

Eight out of the 11 (73%) subjects who received omidubicel with in-line filter developed acute GvHD. Seven subjects had Grade II and one subject had Grade III acute GvHD. Although the rates of acute GvHD were higher than observed in the SP, the small numbers in this subgroup do not allow for any definitive conclusions. Nevertheless, omidubicel should be administered without an in-line filter, which is reflected in the USPI.

Infusion Reaction

Infusion reactions were defined as any AE occurring or worsening within 24 hours of transplant regardless of whether the transplant product was determined to cause the AE. This conservative approach and broad definition were intended to ensure that potential safety signals immediately following the infusion were not missed.

Infusion reaction occurred in 29 (56%) subjects in the omidubicel arm and in 40 (71%) subjects in the control arm. Grade 3 to 4 infusion reaction occurred in 9 (17%) subjects in the omidubicel arm and in 12 (21%) subjects in the control arm. See Table 32 below.

The most common infusion reactions included hypertension, mucosal inflammation, arrhythmia, and fatigue. The most common Grade 3 to 4 infusion reaction event was hypertension, reported in three (6%) subjects treated with omidubicel and nine (16%) subjects treated with UCBU. Grade 3 to 4 infusion reactions occurring in more than one omidubicel subject were hypertension, mucosal inflammation, hypotension, gastrointestinal toxicity, and dysphagia. Two subjects in the omidubicel arm had Grade 4 infusion reactions; in both cases, the events began prior to transplantation (dyspnea in the setting of sepsis and mucosal inflammation in the setting of mucositis); however, they worsened during the 24 hours following infusion and were therefore considered infusion reactions.

Serious hypersensitivity reactions, including anaphylaxis, may be due to DMSO, residual gentamicin, Dextran 40, human serum albumin, or bovine material in omidubicel.

Table 32. Study P0501: Infusion Reactions in the Safety Population

Infusion Reaction Type	Omidubicel N=52 n (%)	UCBU N=56 n (%)
Any infusion reactions	29 (56)	40 (71)
No infusion reactions	23 (44)	16 (29)
Grade 3-4 infusion reactions	9 (17)	12 (21)

Source: FDA analysis
Abbreviation: UCBU, unmanipulated cord blood unit

Disease Relapse of Underlying Hematologic Malignancy

Disease relapse occurred in 11 (21%) subjects treated with omidubicel compared to seven (13%) subjects treated with UCBU. This analysis was based on review of the datasets and the narratives.

***Reviewer comment**:* Although the analysis shows a numerical difference between arms in the occurrence of relapse, the difference is < 10% and the study population is very heterogeneous with regard to hematologic malignancy diagnoses and disease-specific risk factors (including risk categorization and baseline disease status (i.e., subjects in remission vs overt disease)). The safety population included subjects with acute leukemia in CR1 to CR3, MDS with ≤10% blasts, CML of varying phase, and lymphoma in CR, partial response, or stable disease. There were more subjects in the omidubicel arm who were not required to be in remission at baseline than in the UCBU arm (i.e., subjects with MDS and CML: 17% vs 10%, respectively) which could impact the risk of relapse. Therefore, no conclusions can be drawn regarding the observed small numerical difference in relapse rate.

Malignancies of Donor Origin

No cases of new malignancies were reported during the 1-year follow-up of this study. However, during the LTFU period, two subjects treated with omidubicel and one subject treated with UCBU developed new malignancies.

The two subjects treated with omidubicel developed PTLD:

- (b) (6) The subject was diagnosed with monomorphic PTLD, diffuse large B-cell lymphoma (activated B-Cell type), 523 days following transplantation. She was treated with rituximab initially, and subsequently with lenalidomide, cyclophosphamide with dexamethasone, ibrutinib, and brentuximab. However, the disease progressed, and she died 603 days following transplantation.
- (b) (6) The subject was diagnosed with monomorphic PTLD Epstein-Barr virus (EBV)-positive diffuse large B-cell lymphoma 615 days following transplantation. He was

treated with rituximab and radiation therapy. Subsequent follow-up indicated remission with negative EBV with no sign of progression up to the last follow-up.

The one subject treated with UCBU developed new leukemia:

- (b) (6) The subject had a history of ALL. Approximately 35 months following transplantation, the subject was diagnosed with new leukemia. Testing indicated 100% donor chimerism.

Reviewer comment: *Note that one subject* (b) (6) *developed a clonal T-cell expansion during the first year post-transplant. The subject's lymphocytosis remained unchanged over time. She was under observation for her lymphocytosis, including monitoring of T-cell clones every 6 months and scans as indicated clinically. Repeat CT scans of the chest, abdomen, and pelvis continued to show no lymphadenopathy. The Clonal T-Cell Expansion event was subsequently considered resolved without any treatment.*

PTLD is a known complication of transplantation that occurs in subjects following HSCTs. Transplant with mismatched unrelated donor and cord blood is associated with a greater risk of PTLD, due to low numbers and naïve nature of infused T-cells. PTLD in the HSCT setting are usually associated with EBV infection. Donor cell-derived leukemias are a known complication of allogeneic HSCT.

Engraftment Syndrome (ES)

Per ADAE dataset, suspected ES occurred in two subjects:

- (b) (6) Treated with UCBU, developed Grade 1/2 ES between Days 15 and 17.
- (b) (6) Treated with UCBU, developed Grade 1/2 ES between Days 49 and 57. The subject died on Day 98 due to septic shock.

However, based on the narratives, these subjects did not have a confirmed diagnosed of ES.

6.1.12.6 Clinical Test Results

Table 33 below presents laboratory abnormalities that occurred in ≥10% of subjects in any arm. The most common Grade 3 to 4 laboratory abnormalities reported in subjects treated with omidubicel were neutropenia, lymphopenia, thrombocytopenia, anemia, increased alanine aminotransferase, increased aspartate aminotransferase, and hyperbilirubinemia.

Table 33. Study P0501: Laboratory Abnormalities in ≥10% of Subjects in the Safety Population

Laboratory Abnormality	Omidubicel N=52 Grade 1-4 n/N-evaluable (%)	Omidubicel N=52 Grade 3-4 n/N-evaluable (%)	UCBU N=56 Grade 1-4 n/N-evaluable (%)	UCBU N=56 Grade 3-4 n/N-evaluable (%)
Chemistry				
Magnesium (Mg/Dl) – decreased	49/52 (94)	2/52 (3.8)	51/56 (91)	1/56 (1.8)
Aspartate aminotransferase (U/L) – increased	29/52 (56)	7/52 (13)	34/56 (61)	4/56 (7)
Alanine aminotransferase (U/L) – increased	29/52 (56)	7/52 (13)	32/56 (57)	5/56 (9)
Creatinine (Mg/Dl) – increased	26/52 (50)	2/52 (3.8)	32/56 (57)	1/56 (1.8)
Bilirubin (Mg/Dl) – increased	22/52 (42)	6/52 (12)	34/56 (61)	12/56 (21)
Alkaline phosphatase (U/L) – increased	22/52 (42)	0/52 (0)	30/56 (54)	1/56 (1.8)
Magnesium (Mg/Dl) – increased	8/52 (15)	1/52 (1.9)	16/56 (29)	5/56 (9)
Hematology				
Neutrophils (10^9/L) – decreased	50/52 (96)	50/52 (96)	51/56 (91)	51/56 (91)
Lymphocytes (10^9/L) – decreased	49/52 (94)	49/52 (94)	51/56 (91)	51/56 (91)
Platelets (10^9/L) – decreased	47/52 (90)	47/52 (90)	49/56 (88)	49/56 (88)
Leukocytes (10^9/L) – decreased	46/52 (88)	46/52 (88)	50/56 (89)	50/56 (89)
Hemoglobin (G/Dl) – decreased	46/52 (88)	41/52 (79)	50/56 (89)	49/56 (88)

Source: FDA analysis, ADLB and ADSL datasets
Notes: Denominators for laboratory analyses are based on subjects with a baseline and at least one on-study value. Subject must have had at least one grade worsening on study to be counted in analyses and only worst grade will be included in the analyses.
Analysis imputed baseline toxicity grade from the first day of conditioning chemotherapy
Some subject-tests have multiple baseline records on baseline day
Abbreviation: UCBU, unmanipulated cord blood unit

Reviewer comment: *The incidence of laboratory abnormalities was similar between arms and did not indicate a potential safety issue beyond the known toxicity prevalent in subjects with underlying severe hematologic malignancies with prior treatments, undergoing myeloablative conditioning followed by HSCT. The USPI will only include chemistry laboratory abnormalities as they are more informative in this population undergoing transplantation.*

6.1.12.7 Dropouts and/or Discontinuations

See Section 6.1.11.4

Day 120 Safety Update:

The Day 120 safety update report was received on 29 September 2022 under Amendment #26 (SN 0027). The data cutoff date was 5 August 2022.

The report included safety data for 87 subjects who were ongoing at the time of the BLA submission cutoff, and five new subjects treated with omidubicel. Of the 87 subjects whose follow-up was ongoing, 57 subjects were transplanted with omidubicel and 30 subjects with

UCBU. LTFU data on 62 subjects (32 transplanted with omidubicel and 30 transplanted with UCBU) from Study P0501_LTF were also included. In addition, the report included follow-up data from 13 ongoing subjects and 5 new subjects who were treated under the expanded access Study P0701. The five new subjects were transplanted with omidubicel product manufactured at KGI, the commercial manufacturing facility for omidubicel. Safety and efficacy in subjects treated with product manufactured at KGI were described separately.

The median follow-up for the 62 subjects ongoing in Study P0501_LTF was 3 years (range 2 to 3 years) post-transplant. The distribution of subject follow-up is summarized in Table 34 below. Between 21 October 2021 and 5 August 2022, 32 omidubicel subjects were ongoing; 1 subject (b) (6) withdrew from the study. Of the 30 UCBU subjects in the study, 1 subject withdrew (b) (6) , 1 subject was lost to follow-up (b) (6) and 1 subject died (b) (6)

Table 34. Study P0501_LTFU Post-Transplant Follow-up (Data cutoff: 05 Aug 2022)

Treatment Arm	N	Year 2 (n)	Year 3 (n)	Year 4 (n)	Year 5 (n)
Omidubicel	32	14	11	7	0
UCBU	30	13	8	9	0
Total	62	27	18	16	0

Source: Day 120 Safety Study Report Study
Note: "Year" refers to the year of follow-up post-transplant. Subjects are in "Year 2" during the period >1.
Abbreviations: LTFU, long-term follow-up; N, total number of subjects; n, number of subjects per group; UCBU, unmanipulated cord blood unit.

No secondary graft failure was reported in either treatment group. One new case (b) (6) (b) (6) of mild chronic GvHD was reported in the omidubicel group (N=32) during Year 3 post-transplant. Two new cases of chronic GvHD were reported in the UCBU group (N=30): one mild chronic GvHD in Year 2 and one moderate GvHD in Year 4. Disease relapse was reported in one subject in each treatment group between (b) (6) , transplanted with omidubicel, with AML who relapsed 969 days post-transplant, and (b) (6) transplanted with UCBU with hepatosplenic T-cell lymphoma, who initially relapsed 575 days post-transplant, and relapsed for a second time at 1,176 days post-transplant; the subject died on Day 1,206 post-transplant). There were no deaths reported in the omidubicel group and no new reports of malignancies of donor origin in either arm.

Overall, the report did not identify new or unexpected safety findings.

6.1.13 Study Summary and Conclusions

Efficacy and safety were based on Study P0501, an open-label, multicenter, international, Phase 3, randomized study of HSCT with omidubicel versus one or two UCBU in subjects with hematologic malignancies for whom allogeneic HSCT is recommended.

Efficacy:

The efficacy of omidubicel was established based on the results of the randomized Study P0501, in which subjects 12 to 65 years old with hematologic malignancies who underwent myeloablative conditioning followed by transplantation with omidubicel had a shorter time to neutrophil recovery with 42 days of follow-up (median 12 days versus 22 days; absolute

difference -10 days [95% CI: -16, -6]) and a lower incidence of BMT CTN Grade 2/3 bacterial or Grade 3 fungal infection through Day 100 after transplantation (39% versus 60%; absolute difference 22% [95% CI: 4, 39]) compared to subjects transplanted with UCBU.

A treatment effect was observed across the subpopulation analyses.

Safety:

The SP in Study P0501 included 108 subjects: 52 subjects were treated with omidubicel and 56 subjects with UCBU.

- Deaths were reported in 23% of subjects who received omidubicel compared to 36% who received UCBU.
  - Fatal AR (excluding AEs leading to death in setting of disease relapse):
    - Omidubicel (17%): infection 6% (n=3), acute GVHD 6% (n=3), organ failure in setting of VOD/SOS 2% (n=1), Thrombotic thrombocytopenic purpura (TTP)/Thrombotic microangiopathy (TMA) 2%(n= 1), and pulmonary hemorrhage 2% (n=1)
    - UCBU (29%): infection or septic shock 11% (n=6), respiratory disorders 11% (n=6; including hypoxic respiratory failure, ARDS, idiopathic pneumonia, and pulmonary organ failure), and GvHD 5% (n=3). One subject (2%) died of VOD.
- SAEs occurred in 90% (47/52) of subjects who received omidubicel compared to 91% (51/56) of subjects who received UCBU.
- Grade 3 or higher TEAEs occurred in 51 (98%) and 53 (95%) subjects treated with omidubicel and UCBU, respectively.
- The most common non-laboratory Grade 3 or higher TEAEs occurring in >10% of subjects treated in the 1) omidubicel-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 2) 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 AESIs that occurred in subjects treated with omidubicel 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%]).
- Primary graft failure occurred in one (2%) subjects treated with omidubicel, 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 omidubicel arm were numerically higher than or similar to the UCBU arm at all timepoints.

Table 35. Documented Donor Chimerism >90% by Day

Documented Donor Chimerism >90% on or Before:	Omidubicel N=52	UCBU N=56
Day 28	45 (87%)	36 (64%)
Day 42	50 (96%)	47 (84%)
Day 100	50 (96%)	52 (93%)

Source: FDA analysis
Abbreviation: UCBU, unmanipulated cord blood unit

- Relapse of underlying hematologic malignancy was numerically higher in subjects treated with omidubicel: 21% compared to 13% 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, no conclusions can be drawn regarding the observed small numerical difference in relapse rate.

- 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 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 (Przepiorka et al. 1995) Grade II to IV occurred in 62% of subjects treated with omidubicel versus 43% of subjects treated with UCBU. Acute GvHD Grade III to IV occurred in 15% versus 21% of subjects in the omidubicel and UCBU arms, respectively.
- Chronic GvHD (NIH Consensus Criteria) was reported in 35% of subjects treated with omidubicel and 25% of subjects treated with UCBU. Mild, moderate, and severe cGVHD were reported in 12%, 19%, and 4% of subjects who received omidubicel, and 5%, 16%, and 4% of subjects who received UCBU.

- Two subjects treated with omidubicel, and one subject treated with UCBU developed new malignancies, which included PTLD and new leukemia.
- As discussed in Section 4.4.2, in Study P0501, a total of 37 subjects were included in an immune reconstitution sub-study of which 17 were transplanted with omidubicel and 20 with UCBU. The recovery of CD4+ and CD8+ T cells were significantly higher in the omidubicel group on Days 7 and 14 than 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 omidubicel and UCBU-treated groups.

In conclusion, Study P0501 met its protocol-specified primary endpoint of time to neutrophil recovery with subsequent donor chimerism in subjects treated with omidubicel compared with UCBU. Time to neutrophil recovery by 42 days following transplantation and the incidence of Grade 2/3 bacterial and Grade 3 fungal infections were reduced in the omidubicel arm compared to the UCBU arm. The safety profile of omidubicel is acceptable for the intended population. The major risks can be mitigated through labeling, including notice of cord blood-specific risks such as infusion reaction, GvHD, graft failure, and malignancies of donor origin. Overall, the analyses demonstrate no detriment in the graft function of omidubicel compared to UCBU.

7. Integrated Overview of Efficacy

7.1 Indication #1

7.1.1 Methods

The Applicant proposed the indication: (b) (4) ”

The proposal was based on the results of Study P0501, a randomized Phase 3 trial of omidubicel versus UCBU in subjects with hematologic malignancies. The primary endpoint was described as time to neutrophil engraftment following transplantation, defined as achieving an 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. Several issues with the clinical development program were identified.

First, FDA generally requires multiple adequate and well-controlled trials to support an approval. The Applicant conducted one other study, a Phase 1/2 study (P0301) of single-unit omidubicel (the proposed administration in the USPI) in subjects with hematologic malignancies. This study is described briefly under Additional Efficacy Considerations below. However, given differences in study design and data collection/submission, the primary efficacy results could not be independently verified and pooling for the efficacy analysis is not appropriate. Therefore, the integrated review of effectiveness will focus on results from Study P0501.

Second, Study P0501 was not designed in a manner that allows any conclusions to be drawn regarding the efficacy of omidubicel for the proposed indication for (b) (4) (b) (4) To support an indication for treatment of (b) (4) the study would need to be designed appropriately to show an effect on the disease(s) in question. For example, for subjects with AML in remission at the start of study, a study designed to demonstrate an effect on overall survival might be reasonable to support an indication for treatment of the disease. For patients with overt MDS at the start of study, a study designed to demonstrate an effect on durable CR or OS might support an indication for treatment of the disease. Study P0501 enrolled a population with heterogeneous hematologic malignancy diagnoses and disease statuses (with or without achieving remission prior to transplantation) at enrollment and did not study any endpoints relevant to the treatment effect of omidubicel on the

malignancies. Therefore, the study cannot be used to support a treatment indication (b) (4)
(b) (4)

Third, the primary endpoint of the study was "time to neutrophil engraftment following transplantation". Use of the term "neutrophil engraftment" is a misnomer since neutrophils are not transplanted; rather, it is the stem cells that are transplanted, which then engraft and reconstitute the hematopoietic cell lines. As discussed in Section 6.1.11.1, the Applicant defined this endpoint as the earliest of 3 consecutive measurements of ANC ≥ 0.5 Gi/L occurring on or before 42 days post-transplantation with subsequent donor chimerism >90% by Day 100. Although neutrophil recovery within 42 days of transplantation is a reasonable expectation of benefit for transplantation with an UCB cell source (i.e., failure to achieve neutrophil recovery in this time frame is considered primary graft failure), donor chimerism is considered a metric of safety. In clinical practice, donor chimerism following stem cell transplantation is conducted at multiple time points during the first year to monitor engraftment and to guide potential prophylactic or salvage strategies in the event of graft failure or disease relapse. Thus, the prespecified primary endpoint is 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); the clinical benefit of this set of parameters combined in a single endpoint is unclear.

Assessment of the efficacy of other cord blood products has been based on hematopoietic reconstitution (i.e., recovery of all three hematopoietic cell lines – neutrophils, platelets, and erythrocytes). Neutrophil recovery and time to neutrophil recovery represent an early component of hematopoietic reconstitution following SCT. However, recovery of platelets and erythrocytes are expected to occur later than neutrophil recovery, and laboratory data collection beyond Day 42 on this trial was insufficient to reliably assess recovery of these two cell lines. Neutrophil recovery alone would not be sufficient to characterize the clinical benefit of omidubicel. Nonetheless, neutrophils are the primary mediators of the immune response against bacterial and fungal pathogens, and neutrophil recovery is associated with a decrease in the risk of serious and life-threatening infections. FDA considers a reduction in infections to be evidence of direct clinical benefit for interventions affecting myelopoiesis. Analysis of the incidence of BMT CTN Grade 2/3 bacterial and invasive (or Grade 3) fungal infections in the first 100 days following transplantation was a prespecified key secondary endpoint and can be considered direct evidence of clinical benefit.

The review team concluded that as long as the study met the primary objective, the issues with Study P0501 discussed above did not negate the use of an analysis of time to neutrophil recovery with 42 days of follow-up together with the incidence of infection to inform regulatory decision-making.

7.1.2 Demographics and Baseline Characteristics

See Section 6.1.10.

7.1.3 Subject Disposition

See Section 6.1.10.

7.1.4 Analysis of Primary Endpoint(s)

The primary analysis of the primary endpoint compared the distribution of times to engraftment between the two treatment groups based on the Mann-Whitney test statistic. Based on Noether's formula using a two-sided significance level of 5%, a sample size of 45 subjects had a power of 0.9 to demonstrate probability P = 0.78 that a subject treated with omidubicel has a shorter engraftment time than a subject treated with UCBUU. To provide a more robust assessment of the primary endpoint and more extensive safety database, a total sample size of 120 was determined to have > 0.99 power for the primary endpoint.

Chimerism testing in Study P0501 was performed locally using either commercially available test kits (25 laboratories) or laboratory-developed systems (two laboratories) and was defined as the presence of ≤10% host cells. CDRH was consulted for their input on these tests and concluded that based on the laboratories' reports of the lower LOQ, which ranged between 1% and 5%, the assays were able to distinguish between subject samples that had ≤10% versus >11% host cells.

For assessment of neutrophil recovery, the date of the first of the three consecutive recorded ANC ≥0.5 Gi/L was considered the date of recovery. FDA independently adjudicated time to neutrophil recovery with 42 days of follow-up with subsequent >90% donor chimerism by Day 100. The median time to neutrophil recovery with 42 days of follow-up was 12 days (95% CI: 10, 16) in the omidubicel 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.

FDA regarded time to neutrophil recovery with 42 days of follow-up without consideration of subsequent chimerism to be informative of clinical benefit when evaluated together with incidence of infection (see below). Using this definition, one additional subject was identified in the omidubicel arm who achieved neutrophil recovery on Day 12. The median time to neutrophil recovery was estimated by the Kaplan-Meier approach, and the 95% confidence intervals were estimated using the bootstrap method. The median time to neutrophil recovery with 42 days of follow-up was 12 days (95% CI: 10, 15) in the omidubicel arm compared to 22 days (95% CI: 19, 25) in the UCBU arm. The absolute difference between arms showed a 10-day shorter time to neutrophil recovery in the omidubicel arm (95% CI: 6, 14). FDA noted that the median time to neutrophil recovery in the UCBU arm of Study P0501 was consistent with those reported in labeling for other cord blood products.

7.1.5 Analysis of Key Secondary Endpoint

A reduction in infection is considered direct evidence of clinical benefit for interventions that affect myelopoiesis. The key secondary endpoint of Study P0501 was the incidence of BMT CTN Grade 2/3 bacterial or Grade 3 fungal infections from randomization through Day 100 following transplantation. Thirty-nine percent of subjects in the omidubicel arm experienced a Grade 2/3 bacterial or Grade 3 fungal infection compared to 60% in the UCBU arm ($p =0.016$). This represents a 22% lower incidence of these infections in the omidubicel arm (95% CI: 4, 39).

A summary of bacterial and fungal infections by maximum grade through the first 100 days post-transplantation is shown below. Fatal infections/sepsis were reported in three subjects who received omidubicel and six subjects who received UCBU.

Table 36. Study P0501: Bacterial and Fungal Infections by Maximum Grade through Day 100 Following Transplantation (ITT)

Infection Type	Max Grade 1 Omidubicel N=62	Max Grade 1 UCBU N=63	Max Grade 2 Omidubicel N=62	Max Grade 2 UCBU N=63	Max Grade 3 Omidubicel N=62	Max Grade 3 UCBU N=63
Bacterial	12 (19%)	9 (14%)	16 (26%)	29 (46%)	6 (10%)	9 (14%)
Fungal	6 (10%)	5 (8%)	0	0	4 (6%)	8 (13%)

Source: FDA Analysis based on ADCE.xpt
Abbreviations: UCBU, unmanipulated cord blood unit

7.1.6 Other Endpoints

The protocol and SAP listed several additional secondary endpoints including days alive and OOH in the first 100 days after transplantation, as well as platelet engraftment by Day 42.

- The median number of days alive and OOH in the first 100 days after transplantation was 60.5 days in the omidubicel arm and 48.0 days in the UCBU arm. While the endpoint was prespecified and the difference was considered statistically significant (adjusted p =0.01), days alive and OOH is a somewhat subjective measure since whether a subject is hospitalized for a given event depends on the judgement of the clinician and/or standard of care at the given institution. Although randomization may help balance some of these unknown factors, the review team considered this analysis to be supportive only and recommends against including days alive and OOH in the USPI.
- In Study P0501, 53% of subjects who received omidubicel achieved platelet "engraftment" by Day 42 compared to 35% in the UCBU arm. Although this observation indicates that a subset of subjects recovered platelets by Day 42, platelet engraftment by Day 42 is not an accepted measure of hematopoietic recovery following transplantation nor an accepted endpoint for interventions affecting thrombopoiesis. Therefore, it should not be included in the USPI.

7.1.7 Subpopulations

The demographics and baseline disease characteristics of the study population were described in Section 6.1.10.1.1 above. The study population was concluded to be representative of the intended population. Table 22.and Table 23 in Section 6.1.11.3 show the subpopulation analysis for time to neutrophil recovery with 42 days of follow-up and BMT CTN Grade 2/3 bacterial and Grade 3 fungal infection through Day 100 following transplantation. Although some subgroups have numbers too small to allow for a credible analysis, a treatment effect is noted across subpopulations. The review team concludes that the results support the intended population of patients 12 years and older with hematologic malignancies undergoing UCB transplantation.

7.1.8 Persistence of Efficacy

N/A

7.1.9 Product-Product Interactions

N/A

7.1.10 Additional Efficacy Analyses

Additional Studies

Study P0301 was a Phase 1/2 open-label, single-arm study of omidubicel in adolescent and adult subjects with hematologic malignancies undergoing allogeneic HSCT. There were multiple differences between this study and the pivotal Study P0501 that preclude pooling for efficacy analyses.

- Early in the review process of this BLA, there was a concern regarding the comparability of the investigational product used in Study P0301 to that used in Study P0501. Ultimately, and based on additional data submitted by the Applicant in response to IR, the CMC reviewer confirmed that the products used in both studies were considered comparable.
- The primary endpoint was the cumulative incidence of neutrophil engraftment, which differed from the time to neutrophil engraftment endpoint of Study P0501.
- Although the Applicant reported the results of exploratory and post hoc analyses of time to neutrophil engraftment for Study P0301 in the ISE, not all laboratory data were submitted to the BLA. Only selected CBCs demonstrating neutrophil recovery were included. Therefore, the results could not be independently verified, and the study was not considered informative with respect to the endpoint of time to neutrophil recovery in support of regulatory decision making.
- 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.

Dose/Dose Response

The analysis of dose/dose response is described in Section 4.4.2.

- A dose-response analysis of Study P0501 showed:

- The median TNC dose was 4.7 × 10^7cells/kg (range 1.7-12.4 × 10^7/kg) for omidubicel group and 3.4 × 10^7/kg (range 1.3-8.0 × 10^7/kg) for UCBU group.

- The median CD34+ cell dose was 9 × 10^6cells/kg (range 2-48 × 10^6/kg) for omidubicel group and 0.2 (range 0-0.8 × 10^6cells/kg) for UCBU group.
- The median time to neutrophil engraftment was 12 days for the omidubicel group, and 22 days for the UCBU group.
- Dose-efficacy assessment was conducted on log-transformed data using the linear model between-cell dose (TNC per kg and CD34+ cells per kg) and days to neutrophil engraftment or recovery.
- The linear-regression model showed association between cell dose tested (TNC/kg and CD34/kg) and the days to neutrophil recovery. The model suggests that days to neutrophil recovery decrease with an increase in cell dose.

- Based on data from Study P0501 and Study P0301, days to neutrophil recovery decreases with an increase in TNC and CD34+ cells while no relationship was identified between cell dose and platelet recovery.
- The clinical pharmacology review team concluded that the data support the proposed single dose administration of a minimum of 12 × 10^8 TNC (from both CF and NF), and a minimum of 9.2 × 10^7 CD34+cells (from CF).

7.1.11 Efficacy Conclusions

The efficacy of omidubicel was established based on the results of the randomized Study P0501, in which subjects 12 to 65 years old with hematologic malignancies who underwent myeloablative conditioning followed by transplantation with omidubicel had a shorter time to neutrophil recovery with 42 days of follow-up (median time to neutrophil recovery 12 days versus 22 days; absolute difference 10 days [95% CI: 6, 14]) and a lower incidence of BMT CTN Grade 2/3 bacterial or Grade 3 fungal infections through Day 100 following transplantation (39% versus 60%; absolute difference 22% [95% CI: 4, 39]) compared to subjects transplanted with UCB product. A treatment effect was observed across the subpopulation analyses.

Although the overall trial was considered positive, the design of the trial does not support the Applicant's proposed indication for (b) (4) Additionally, the prespecified primary endpoint was composite of efficacy and safety and did not clearly describe clinical benefit. This presented a challenge in determining an appropriate indication statement supported by the submitted data. However, 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 NRM in the early post-transplantation period and reducing the incidence of infection is considered direct evidence of clinical benefit for interventions affecting myelopoiesis. The study as designed demonstrates a clinically meaningful benefit with omidubicel 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 receiving MAC followed by UCBT. Therefore, the indication statement will be revised to reflect this assessment.

Although subjects >65 years old were not enrolled in Study P0501, given the mechanism of omidubicel, efficacy is expected to be similar across adults and may be extrapolated to the full adult population.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The ISS provides integrated analyses of all available safety data in the omidubicel development program to provide supportive evidence to the safety findings from Study P0501. The Applicant submitted the ISS, ISS SAP, and ISS datasets. The AdaM datasets were derived from each of the studies' SDTM v3.2 datasets. All studies had AEs coded with MedDRA version 23.

At a Type B ISS ISE meeting with FDA, it was agreed upon that safety data from subjects treated with OOS products were provided in an integrated dataset and as a narrative in the ISS but were not included in the tabulated safety summaries in the ISS report. The ISS safety assessment focused on data through 1-year post-transplant.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

As mentioned in Section 5.3, the omidubicel development program consisted of four clinical studies under IND #14459: GC P#01.01.020 (P0101), (b) (4), GC P#03.01.020 (P0301), and GC P#05.01.020 (P0501); and one study under IND #(b) (4) (b) (4) As defined in the ISS SAP, the ISS provides an integrated analyses of all available safety data in these five completed clinical studies, which are described in Table 37 and Table 38.

A sixth study, GC P#07.01.020, is ongoing. This study is an open-label, expanded access study of omidubicel for allogeneic transplantation in subjects with hematologic malignancies. As data from this study are not yet mature, these data were not included in the ISS.

An investigator-initiated IND (IND (b) (4)) includes Study IST (b) (4) which is a Phase 1/2 study of omidubicel in subjects with (b) (4) The Applicant does not maintain the IND nor the data for this study and, therefore, it was not included in the ISS.

Table 37. Clinical Studies in Subjects With a Diagnosis of Hematologic Malignancy in the Omidubicel Development Program That are Included in the ISS

Parameter	Details
Protocol Number / Phase	**GC P#01.01.020 (P0101) / Pilot Study**
Title	Allogeneic Stem Cell Transplantation of NiCord®, Umbilical Cord Blood-derived Ex Vivo Expanded Stem and Progenitor Cells, in Combination with a Second, Unmanipulated Cord Blood Unit in Subjects with Hematological Malignancies
Subjects in safety analysis set	N=11

Parameter	**Details**
Subject population	Subjects 18-65 years old with a diagnosis of a hematologic malignancy (ALL, AML, MDS, lymphoma) who are candidates for unrelated cord blood transplantation, with qualifying HLA-matched UCBU.
Treatment and follow-up	This is a single-arm, open-label study in which subjects were to receive both omidubicel and UCBU following conditioning therapy. Omidubicel and UCBU were to be transplanted on the same day. Subjects were followed for 6 months post-transplant with additional post-study follow-up through 1 year post-transplant.
Primary objective	To evaluate the safety of co-transplantation of omidubicel transplant and UCBU following conditioning therapy
Endpoints	Primary: Incidence and severity of acute toxicity associated with the infusion of omidubicel The proportion of subjects with neutrophil engraftment following co-transplantation of omidubicel and UCBU
Protocol Number / Phase	**GC P#03.01.020 (P0301) / Phase 1/2**
Title	Allogeneic Stem Cell Transplantation of NiCord®, Umbilical Cord Blood-derived Ex Vivo Expanded Stem and Progenitor Cells, in Adolescent and Adult Subjects with Hematological Malignancies
Subjects in safety analysis set	N=36
Subject population	Subjects 12-65 years old with a diagnosis of a hematologic malignancy (ALL, AML, CML, MDS, lymphoma) who are candidates for unrelated cord blood transplantation, with qualifying HLA-matched UCBU.
Treatment and follow-up	This is a single-arm, open-label study in which subjects were to receive omidubicel transplant following conditioning therapy. Subjects were followed for 1 year post-transplant.
Primary objective	To evaluate the safety and efficacy of omidubicel in subjects with hematological malignancies following conditioning therapy
Endpoints	Primary: Incidence of omidubicel-derived neutrophil engraftment Incidence of secondary graft failure at 180 days following transplant Secondary endpoints included: Incidence of acute GvHD Grade II-IV at 100 days Incidence of chronic GvHD at 180 days and at 1 year Primary and secondary graft failure Safety and tolerability of omidubicel transplantation
Protocol Number / Phase	**GC P#05.01.020 (P0501) / Phase 3**
Title	A Multicenter, Randomized, Phase 3 Registration Trial of Transplantation of NiCord®, Ex Vivo Expanded, Umbilical Cord Blood-derived, Stem and Progenitor Cells, versus Unmanipulated Umbilical Cord Blood for Subjects with Hematologic Malignancies
Subjects in safety analysis set	N=109 (52 omidubicel; 56 UCBU; 1 omidubicel off study)
Subject population	Subjects 12-65 years old with a diagnosis of a hematologic malignancy (ALL, AML, CML, MDS, lymphoma) who are candidates for unrelated CBT, with qualifying HLA-matched UCBU.

Parameter	Details
Treatment and follow-up	Subjects were to be randomized 1:1 to receive omidubicel or UCBU following conditioning therapy. Subjects will be followed for 1 year following transplant/15 months following randomization.
Primary objective	To compare the safety and efficacy of omidubicel to UCBU transplantation in subjects with hematologic malignancies, following myeloablative conditioning therapy
Endpoints	Primary: Time to neutrophil engraftment following transplant Secondary, Tertiary, and Exploratory Endpoints included: Infections, including Incidence of Grade 2/3 bacterial or invasive fungal infection by 100 days following transplant Grade 3 viral infections by 180 days and 1 year following transplant Primary and secondary graft failure Acute GvHD Grade II-IV and III-IV by 100 days following transplant Chronic GvHD by 180 days and 1 year following transplant Safety and tolerability of omidubicel transplant

Source: Adapted from ISS SAP Section 3 Table 1
Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CBT, cord blood transplantation; CML, chronic myeloid leukemia; GvHD, graft-versus-host disease; HLA, human leukocyte antigen; ISS, integrated summary of safety; MDS, myelodysplastic syndrome; UCBU, unmanipulated cord blood unit

Table 38. Clinical Studies in Subjects With a Diagnosis of (b) (4) in the Omidubicel Development Program That are Included in the ISS

(b) (4)

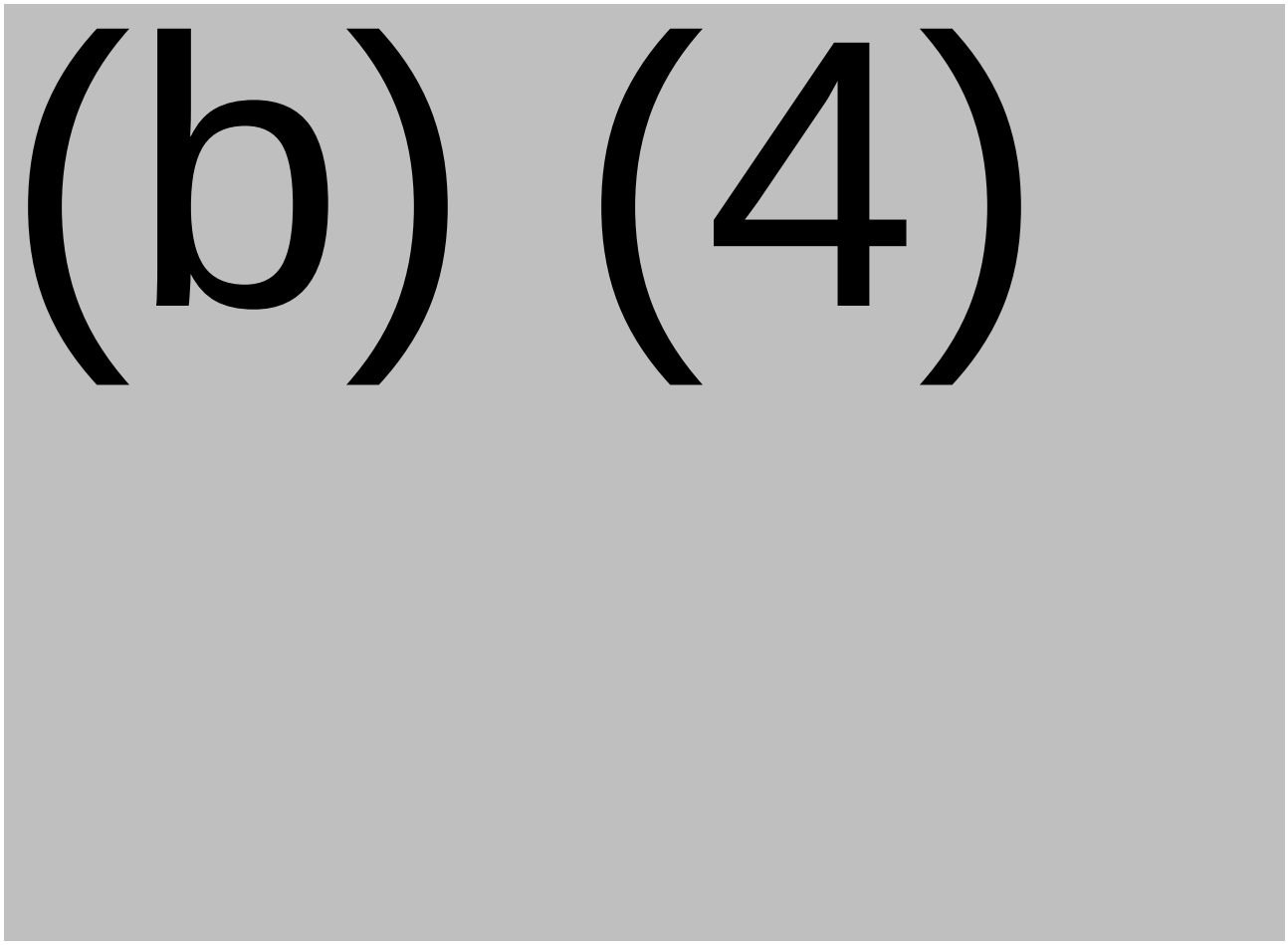


Table 39. Clinical Study Pools of Subject Populations of Interest

Indication	Omidubicel Alone	Omidubicel + UCBU	All Subjects
Hematologic Malignancy	P0501 (N=52)+ P0501 off study (N=1)+ P0301 (N=36) *Pool 1 (N=89)*	P0101 (N=11)	*Pool 2 (N=100)*
(b) (4)	(b) (4)	(b) (4)	(b) (4)
All Subjects	*Pool 4 (N=93)*	*Pool 5 (N=24)*	*Pool 6 (N=117)*

Source: ISS SAP Section 4.1 Table 2
Abbreviation: UCBU, unmanipulated cord blood unit

Table 40. Subject Population Pool Descriptions and Sample Sizes

Pool	Description	Sample Size
Pool 1	Subjects who received omidubicel alone for the treatment of hematologic malignancies	89
Pool 2	Subjects who received any omidubicel for treatment of hematologic malignancies	100
(b) (4)	(b) (4)	(b) (4)
Pool 4	Subjects who received omidubicel alone	93
Pool 5	Subjects who received omidubicel in combination with UCBU	24
Pool 6	All subjects who ever received omidubicel	117

Source: ISS SAP Section 4.1 Table 3
Abbreviation: UCBU, unmanipulated cord blood unit

The review focused on two Pools when analyzing the ISS data:

- **Pool 6** "ISS Safety analysis population" (N=117) represented all subjects who have received any omidubicel
  - This pool was used to describe Section 5, Warnings and Precautions (W&P), of the label.
- **Pool 1** "ISS Focused SP" (N=89) represented the subject population with the same indication that the Applicant is seeking for omidubicel in this application (i.e., omidubicel alone in subjects with underlying hematologic malignancies).

Data from an additional pool were also reviewed:

- **Pool 3** (N=17): Subjects who received any omidubicel for the treatment of hemoglobinopathies

In describing the safety findings in the ISS, data from both arms of Study P0501 were also included in all the tables. Note that the one P0501 subject who received omidubicel more than 90 days after randomization (i.e., considered as off study since it was outside of the protocol-specified window) was not included in the SP analysis set for the P0501 omidubicel alone arm, which was consistent with the SP analysis set definition in the individual CSR. However, this one subject was included in the subject population Pools 1, 2, 4, and 6 and was identified as P0501 off study in Table 39 above. Subjects who received an OOS product were not included in the safety analysis sets.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Throughout the development program, 144 subjects were exposed to omidubicel; 122 via completed clinical studies P0101, P0301, P0501, (b) (4), (b) (4) and 22 in ongoing studies P0701, and (b) (4) . Overall exposure included 118 subjects with hematologic malignancies, 17 subjects with SCD and 9 subjects with SAA. A total of 26 subjects were transplanted with omidubicel in combination with an UCBU, and 118 subjects were transplanted with single-unit omidubicel.

The ISS Safety Analysis Population was comprised of 117 subjects with a median age of 39 years (range 2 to 62 years). Fifty-nine (50.4%) subjects were male, and 68 (58.1%) subjects were White. Notably, 30.8% of the overall omidubicel population were Black, and over 40% of subjects were of diverse race or ethnicity subgroups. Fifteen (12.8%) subjects in the safety analysis population had SCD. Overall, 75% of subjects received a 4/6 HLA-matched graft, and 46.2% were treated with a total body irradiation (TBI) based conditioning regimen. The majority of subjects (59.6%) were located in the U.S. See Table 41 for detailed demographics of all pools.

Table 41. Demographic Characteristics in the ISS

		Clinical Study P0501		All Patients	Hematologic Malignancy		Any Indication		(b) (4)
		Omidubicel (N=52)	UCBU (N=56)	Safety Analysis Population[a] (Pool 6) (N=117)	Focused Safety Population[b] (Pool 1) (N=89)	Any Omidubicel (Pool 2) (N=100)	Single Unit Omidubicel (Pool 4) (N=93)	Omidubicel + UCBU (Pool 5) (N=24)	
Variable	**Characteristic**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Gender	Male	27 (51.9)	35 (62.5)	59 (50.4)	47 (52.8)	52 (52.0)	50 (53.8)	9 (37.5)	
	Female	25 (48.1)	21 (37.5)	58 (49.6)	42 (47.2)	48 (48.0)	43 (46.2)	15 (62.5)	
Age (years)	Median (Range)	40.0 (13, 62)	36.0 (13, 64)	39.0 (2, 62)	42.0 (13, 62)	44.0 (13, 62)	41.0 (2, 62)	16.0 (3, 61)	
Age Group	2-11 years	0 (0.0)	0 (0.0)	8 (6.8)	0 (0.0)	0 (0.0)	2 (2.2)	6 (25.0)	
	12-17 years	7 (13.5)	7 (12.5)	18 (15.4)	9 (10.1)	9 (9.0)	11 (11.8)	7 (29.2)	
	18-39 years	19 (36.5)	23 (41.1)	34 (29.1)	33 (37.1)	34 (34.0)	33 (35.5)	1 (4.2)	
	40-59 years	22 (42.3)	25 (44.6)	50 (42.7)	41 (46.1)	50 (50.0)	41 (44.1)	9 (37.5)	
	60-65 years	4 (7.7)	1 (1.8)	7 (6.0)	6 (6.7)	7 (7.0)	6 (6.5)	1 (4.2)	
Weight at Screening (kg)	Median (Range)	81.6 (42.8, 133.9)	73.8 (45.5, 132.9)	74.5 (14.2, 133.9)	77.1 (42.0, 133.9)	81.6 (42.0, 133.9)	75.8 (14.2, 133.9)	63.7 (16.0, 103.9)	
Ethnicity	Not Hispanic or Latino	38 (73.1)	45 (80.4)	102 (87.2)	74 (83.1)	85 (85.0)	78 (83.9)	24 (100.0)	
	Hispanic or Latino	9 (17.3)	6 (10.7)	10 (8.5)	10 (11.2)	10 (10.0)	10 (10.8)	0 (0.0)	
	Not Reported/ Unknown	5 (9.6)	5 (8.9)	5 (4.3)	5 (5.6)	5 (5.0)	5 (5.4)	0 (0.0)	
Race	White	31 (59.6)	29 (51.8)	68 (58.1)	61 (68.5)	68 (68.0)	61 (65.6)	7 (29.2)	
	Black	10 (19.2)	9 (16.1)	36 (30.8)	15 (16.9)	19 (19.0)	19 (20.4)	17 (70.8)	
	Asian	5 (9.6)	11 (19.6)	7 (6.0)	7 (7.9)	7 (7.0)	7 (7.5)	0 (0.0)	
	Other	6 (11.5)	7 (12.5)	6 (5.1)	6 (6.7)	6 (6.0)	6 (6.5)	0 (0.0)	
CMV Status	Positive	35 (67.3)	37 (66.1)	79 (67.5)	61 (68.5)	70 (70.0)	63 (67.7)	16 (66.7)	

		Clinical Study P0501		All Patients	Hematologic Malignancy		Any Indication		(b) (4)
		Omidubicel (N=52)	UCBU (N=56)	Safety Analysis Population[a] (Pool 6) (N=117)	Focused Safety Population[b] (Pool 1) (N=89)	Any Omidubicel (Pool 2) (N=100)	Single Unit Omidubicel (Pool 4) (N=93)	Omidubicel + UCBU (Pool 5) (N=24)	
Variable	**Characteristic**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
	Negative	17 (32.7)	16 (28.6)	37 (31.6)	27 (30.3)	29 (29.0)	29 (31.2)	8 (33.3)	
	Unknown	0 (0.0)	3 (5.4)	1 (0.9)	1 (1.1)	1 (1.0)	1 (1.1)	0 (0.0)	
Disease Type	AML	22 (42.3)	27 (48.2)	45 (38.5)	39 (43.8)	45 (45.0)	39 (41.9)	6 (25.0)	
	ALL	18 (34.6)	19 (33.9)	29 (24.8)	28 (31.5)	29 (29.0)	28 (30.1)	1 (4.2)	
	MDS	5 (9.6)	3 (5.4)	14 (12.0)	12 (13.5)	14 (14.0)	12 (12.9)	2 (8.3)	
	Other Hematologic Malignancy	7 (13.5)	7 (12.5)	14 (12.0)	10 (11.2)	12 (12.0)	12 (12.9)	2 (8.3)	
	Sickle Cell	0 (0.0)	0 (0.0)	15 (12.8)	0 (0.0)	0 (0.0)	2 (2.2)	13 (54.2)	
Disease Risk Index[c]	Low Risk	12 (23.1)	13 (23.2)	12 (22.6)	12 (22.6)	12 (22.6)	12 (22.6)	0 (0.0)	
	Intermediate Risk	22 (42.3)	23 (41.1)	23 (43.4)	23 (43.4)	23 (43.4)	23 (43.4)	0 (0.0)	
	High/ Very High Risk	18 (34.6)	20 (35.7)	18 (34.0)	18 (34.0)	18 (34.0)	18 (34.0)	0 (0.0)	
Donor – Recipient HLA Match for Omidubicel or First UCBU	4/6	37 (71.2)	42 (75.0)	88 (75.2)	64 (71.9)	72 (72.0)	68 (73.1)	20 (83.3)	
	5/6	14 (26.9)	13 (23.2)	26 (22.2)	22 (24.7)	25 (25.0)	22 (23.7)	4 (16.7)	
	6/6	1 (1.9)	1 (1.8)	3 (2.6)	3 (3.4)	3 (3.0)	3 (3.2)	0 (0.0)	
Conditioning Regimen	TBI - containing[d]	27 (51.9)	28 (50.0)	54 (46.2)	43 (48.3)	54 (54.0)	43 (46.2)	11 (45.8)	
	Non- TBI[e]	25 (48.1)	28 (50.0)	63 (53.8)	46 (51.7)	46 (46.0)	50 (53.8)	13 (54.2)	
Region	Europe	10 (19.2)	10 (17.9)	27 (23.1)	27 (30.3)	27 (27.0)	27 (29.0)	0 (0.0)	
	US	35 (67.3)	38 (67.9)	81 (69.2)	53 (59.6)	64 (64.0)	57 (61.3)	24 (100.0)	

		Clinical Study P0501		All Patients	Hematologic Malignancy		Any Indication		(b) (4)
		Omidubicel (N=52)	UCBU (N=56)	Safety Analysis Population[a] (Pool 6) (N=117)	Focused Safety Population[b] (Pool 1) (N=89)	Any Omidubicel (Pool 2) (N=100)	Single Unit Omidubicel (Pool 4) (N=93)	Omidubicel + UCBU (Pool 5) (N=24)	
Variable	**Characteristic**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
	Other	7 (13.5)	8 (14.3)	9 (7.7)	9 (10.1)	9 (9.0)	9 (9.7)	0 (0.0)	

Data Source: Appendix Table 3

N=number of patients in the safety population for a group; n=Number of patients with the characteristic

[a] Includes all patients who received omidubicel

[b] Includes all patients with hematologic malignancy who received single unit omidubicel

[c] Only patients in Study P0501 study are summarized. DRI was not reported in other studies.

[d] TBI containing conditioning regimen category include: TBI/Fludarabine; TBI/Fludarabine/Cyclophosphamide; TBI/Fludarabine/Thiotepa

[e] Non-TBI conditioning regimens include: busulfan/cyclophosphamide/fludarabine; busulfan/cyclophosphamide/horse ATG; busulfan/thiotepa/fludarabine; busulfan/clofarabine/fludarabine

Abbreviations: ALL: Acute lymphoblastic leukemia; AML: Acute myelogenous leukemia; CMV: Cytomegalovirus; DRI: Disease risk index; HLA: Human leukocyte antigen; MDS: Myelodysplastic syndrome; TBI: Total body irradiation; UCBU: Unmanipulated cord blood unit

Source: ISS Section 4 Table 7

Reviewer comment: *The demographic and baseline characteristics were consistent across pools, except the hemoglobinopathy population, which comprised pediatric subjects with a median age of 12 (range 2 to 16), all Black, with SCD.*

Overall, the baseline and disease characteristics reflect the general population in need of allogeneic HSCT, encompassing a broad range of ages, weights, diseases, as well as ethnicities; the ethnically diverse population has a need for alternative donor grafts, due to a lower probability of finding suitably matched donors available for transplantation in a timely manner.

8.2.3 Categorization of Adverse Events

Per the ISS SAP, endpoints for the evaluation of omidubicel safety included the following:

- Deaths
- TEAEs and SAEs
- ASEI:
  - Infusion reactions
  - Primary graft failure
  - Secondary graft failure
  - Infections
  - Grade II to IV and Grade III to IV acute GvHD
  - Chronic GvHD
- Clinical laboratory abnormalities

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

All studies were conducted between January 2011 and April 2021. Over this 9-year time period, data on the use and safety of omidubicel were accrued from the ongoing studies, consensus guidelines were updated, which caused standard of care to evolve, and safety event toxicity grading guidelines changed. Due to this evolving information, these five studies used various criteria for event collection and toxicity grading; specifically:

- Grade 1 to 2 anticipated AEs outside of SAEs, GvHD, and infections with onset more than 24 hours post-transplant were not collected in P0101 (b) (4) ; such events were collected in P0301, (b) (4) and P0501.
- In P0301 and P0101, anticipated AEs outside of SAEs, GvHD, and infections were graded as Grade 1, Grade 2, Grade 3, Grade 4, and Grade 5. In P0501, such events were graded as Grade 1 or 2, Grade 3, Grade 4, and Grade 5.
- In P0101, acute GvHD was graded per the Glucksberg Classification (Glucksberg et al. 1974), and in (b) (4) P0301, P0501, and (b) (4) per the Consensus Criteria (Przepiorka et al. 1995) .
- Chronic GvHD was graded per the criteria of Shulman et al (Shulman et al. 1980) in P0101, (b) (4) P0301, and (b) (4). Chronic GvHD was also graded per 2005 NIH consensus criteria in (b) (4), P0301, and (b) (4) (Filipovich et al. 2005). Chronic GvHD was graded per 2014 NIH consensus criteria (Jagasia et al. 2015) in P0501.

8.4 Safety Results

8.4.1 Deaths

A summary of deaths for the Safety Analysis Population (Pool 6, N=117), Focused SP (Pool 1, N=89), Study P0501 treatment groups, and (b) (4) subjects (Pool 3, N=17) is presented in Table 42.

In the Safety Analysis Population, 32 (27.4%) subjects died. In the Focused SP, 28 (31.5%) subjects died. Disease relapse/progression/persistence was the most common primary cause of death occurring in 12 (10.3%) subjects in the Safety Analysis Population and in 11 (12.4%) in the Focused SP. Other causes of death included infections and GvHD. Two pediatric subjects died, both with SCD: an 8-year-old subject who died of infection and a 16-year-old subject who died of GvHD.

Table 42. Deaths in the ISS

	Clinical Study P0501		Safety Analysis Population[a] (Pool 6) (N=117)	Focused Safety Population[b] (Pool 1) (N=89)	(b) (4)
	Omidubicel (N=52)	UCBU (N=56)			
	n (%)	n (%)	n (%)	n (%)	n (%)
Deaths	12 (23.1)	20 (35.7)	32 (27.4)	28 (31.5)	

Source: ISS Section 5.1 Table 8
a. Includes all subjects who received omidubicel
b. Includes all subjects with hematologic malignancy who received single unit omidubicel
Abbreviations: ISS, integrated summary of safety; UCBU, unmanipulated cord blood unit

Table 43. Primary Cause of Death in the ISS

	Clinical Study P0501		Safety Analysis Population[a] (Pool 6) (N=117)	Focused Safety Population[b] (Pool 1) (N=89)
	Omidubicel (N=52)	UCBU (N=56)		
Primary Cause of Death	n (%)	n (%)	n (%)	n (%)
All Deaths	12 (23.1)	20 (35.7)	32 (27.4)	28 (31.5)
Disease relapse[c]	3 (5.8)	4 (7.1)	12 (10.3)	11 (12.4)
Infection	3 (5.8)	6 (10.7)	10 (8.5)	8 (9.0)
GvHD	3 (5.8)	3 (5.4)	6 (5.1)	5 (5.6)
Respiratory Disorder	1 (1.9)	6 (10.7)	1 (0.9)	1 (1.1)
Thrombotic microangiopathy	1 (1.9)	0 (0.0)	1 (0.9)	1 (1.1)
VOD/ SOS	1 (1.9)	1 (1.8)	1 (0.9)	1 (1.1)
Cardiogenic Shock	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.1)

(b) (4)

Source: Source: ISS Section 5.1 Table 9
a. Includes all subjects who received omidubicel
b. Includes all subjects with hematologic malignancy who received single unit omidubicel
c. Refers to disease relapse, progression or persistence
Abbreviations: GvHD, graft-versus-host disease; ISS, integrated summary of safety; N, total number of subjects in each respective population; n, total number of subjects deaths by primary cause within each population; SOS, sinusoidal obstruction syndrome; UCBU, unmanipulated cord blood unit; VOD, veno-occlusive disease

Reviewer comment: *The rates and causes of deaths were generally consistent across all subject population pools.*

8.4.2 Nonfatal Serious Adverse Events

For the Safety Analysis Population, SAEs were reported in 105 (89.7%) subjects. The most common events by SOC were infections and immune system disorders (which included GvHD and graft failure), occurring in 53 (45.3%) and 36 (30.8%) subjects, respectively. The most common events by PT were GvHD, reported in 15 (12.8%) subjects. For the Focused SP, SAEs occurred in 82 (92.1%) subjects. Infections and immune system disorders were reported most frequently, occurring in 43 (48.3%) and 29 (32.6%) subjects, respectively.

Table 44. SAEs in the ISS

	Clinical Study P0501		Safety Analysis Population[a] (Pool 6) (N=117)	Focused Safety Population[b] (Pool 1) (N=89)	(b) (4)
	Omidubicel (N=52)	UCBU (N=56)			
	n (%)	n (%)	n (%)	n (%)	
Patients with ≥1 SAE	47 (90.4)	51 (91.1)	105 (89.7)	82 (92.1)	

Source: ISS Section 5.1 Table 8
a. Includes all subjects who received omidubicel
b. Includes all subjects with hematologic malignancy who received single unit omidubicel
Abbreviations: ISS, integrated summary of safety; N, number of subjects in each population; n, number of subjects with event; SAE, serious adverse event; UCBU, unmanipulated cord blood unit

Reviewer comment: *The reported SAEs are known complications associated with HSCT conditioning and treatment.*

8.4.3 Study Dropouts/Discontinuations

Overall, 1 (0.9%) of the 117 subjects from the Safety Analysis Population (Pool 6) discontinued from the study; this was a subject in the UCBU treatment group of Study P0501.

8.4.4 Common Adverse Events

In the Safety Analysis Population (Pool 6, N=117), 114 (97.4%) subjects had at least 1 TEAE. All 89 subjects (100%) in the Focused SP had at least 1 TEAE. Since omidubicel is a single-use treatment, there were no TEAEs leading to discontinuation. In the Safety Analysis Population, the most common AEs were fever reported in 82 (70%) subjects, mucosal inflammation in 75 (64%) subjects, pain in 70 (60%) subjects and hypertension in 69 (59%) subjects. The most common Grade 3 to 5 events were hypertension in 42 (36%) subjects, mucosal inflammation in 34 (29%) subjects, and pain in 26 (22%) subjects.

Events generally occurred at similar rates across the different omidubicel subpopulations, with some differences resulting from variations in reporting across studies, mainly in Grade 1/2 events.

Table 45. TEAEs in the ISS

	Clinical Study P0501		Safety Analysis Population[a] (Pool 6) (N=117)	Focused Safety Population[b] (Pool 1) (N=89)	(b) (4)
	Omidubicel (N=52)	UCBU (N=56)			
	n (%)	n (%)	n (%)	n (%)	
Patients with ≥1 TEAE	52 (100.0)	56 (100.0)	114 (97.4)	89 (100.0)	

Source: ISS Section 5.1 Table 8
a. Includes all subjects who received omidubicel
b. Includes all subjects with hematologic malignancy who received single unit omidubicel
Abbreviations: ISS, integrated summary of safety; N, number of subjects in each population; n, number of subjects with event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UCBU, unmanipulated cord blood unit

8.4.5 Clinical Test Results

The Applicant provided analysis of shift tables from baseline visit to post-baseline visit. Overall, there was no difference between shifts in laboratory values in subjects who received either omidubicel or UCBU.

8.4.6 Systemic Adverse Events

N/A

8.4.7 Local Reactogenicity

N/A

8.4.8 Adverse Events of Special Interest

AESIs include infusion reactions, primary graft failure, secondary graft failure, infections, and acute and chronic GvHD. Table 46 provides a summary of AESIs.

Of the 117 subjects from the Safety Analysis Population (Pool 6):

- Infusion reactions of any severity occurred in 55 (47%) subjects. Grade 3 to 5 infusion reactions were reported in 18 (15.4%) subjects. A numerically lower rate of infusion reactions was reported in subjects treated with omidubicel compared to UCBU.
- Primary graft failure occurred in four (3%) subjects.
- Secondary graft failure occurred in five (4.3%) subjects.
- Acute GvHD was analyzed at 100 and 180 days following transplantation. Overall, 68 (58.1%) subjects had acute GvHD of Grade II to IV, and 20 (17.1%) subjects had acute GvHD of Grade III to IV.
- Chronic GvHD occurred in 41 (35.0%) subjects.
- Infections Grade 2/3 occurred in 94 (80.3%) subjects. Bacterial infections of any severity occurred in 76 (65.0%) subjects, and viral infections occurred in 95 (81.2%) subjects. See Table 47 for details regarding the incidence of infections.

- Malignancies of donor origin developed in three (3%) subjects:

- Two subjects (b) (6) and (b) (6) from Study P0501 developed PTLD in their LTFU (during their second year post-transplant)
- One subject from Study P0301 developed a new MDS during their LTFU, approximately 40 months post-transplant.

Among the subjects who received UCBU, one subject developed a leukemia of donor origin in their LTFU, approximately 35 months post-transplant.

Table 46. AESIs in the ISS

	Clinical Study P0501		Safety Analysis Population[a] (Pool 6) (N=117)	Focused Safety Population[b] (Pool 1) (N=89)
	Omidubicel (N=52)	UCBU (N=56)		
	n (%)	n (%)	n (%)	n (%)
Infusion reactions	29 (55.8)	40 (71.4)	55 (47.0)	51 (57.3)
Primary graft failure	2 (3.8)	6 (10.7)	7 (6.0)	5 (5.6)
Secondary graft failure	2 (3.8)	0 (0.0)	5 (4.3)	4 (4.5)
Acute GvHD Grades II-IV	32 (61.5)	24 (42.9)	68 (58.1)	50 (56.2)
Acute GvHD Grades III-IV	8 (15.4)	12 (21.4)	20 (17.1)	13 (14.6)
Chronic GvHD	18 (34.6)	14 (25.0)	41 (35.0)	34 (38.2)
Infections	49 (94.2)	56 (100.0)	112 (95.7)	85 (95.5)

(b) (4)

Source: ISS Section 5.1 Table 8 and ISS datasets
a. Includes all subjects who received omidubicel
b. Includes all subjects with hematologic malignancy who received single unit omidubicel
Note: See reviewer comment below regarding the correct incidence of primary graft failure
Abbreviations: AESIs, adverse events of special interest; GvHD, graft-versus-host disease; ISS, integrated summary of safety; N, number of subjects in each population; n, number of subjects with event; UCBU, unmanipulated cord blood unit

Reviewer comment: *Note that the text in the ISS report erroneously states: Overall, of the 117 patients from the Safety Analysis Population (Pool 6), 54 (46%) had an infusion reaction of any severity. However, the Applicant clarified that the ISS Appendix Table 206 is the correct one as the text within the ISS report was not updated.*

Subjects (b) (6) *had neutrophil recovery without subsequent donor chimerism, and therefore do not meet the definition of primary engraftment failure. As such, primary graft failure occurred in 4/117 (3%) subjects treated with omidubicel (Subject IDs:* (b) (6) (b) (6) *and in 3/89 (3%) subjects in the focused safety population "Pool 1"*

(Subject IDs: (b) (6) *and not as reported by the Applicant in* ***Table 46*** *above.*

Table 47. Infections per BMT CTN Criteria in the ISS Population

		Clinical Study P0501		Safety Analysis Population[a] (Pool 6) (N=117)	Focused Safety Population[b] (Pool 1) (N=89)	(b) (4)
		Omidubicel (N=52)	UCBU (N=56)			
		n (%)	n (%)	n (%)	n (%)	
All Infections	All Infections	49 (94.2%)	56 (100.0%)	112 (95.7%)	85 (95.5%)	
	Bacterial	37 (71.2%)	46 (82.1%)	76 (65.0%)	57 (64.0%)	
	Viral	41 (78.8%)	45 (80.4%)	95 (81.2%)	70 (78.7%)	
	Fungal	12 (23.1%)	16 (28.6%)	18 (15.4%)	15 (16.9%)	
	Parasitic/Protozoal	2 (3.8%)	0 (0.0%)	3 (2.6%)	3 (3.4%)	
	Non-microbiological	18 (34.6%)	14 (25.0%)	44 (37.6%)	37 (41.6%)	
Grade 2/3 Infections	All Infections	45 (86.5%)	53 (94.6%)	94 (80.3%)	75 (84.3%)	
	Bacterial	21 (40.4%)	40 (71.4%)	44 (37.6%)	30 (33.7%)	
	Viral	31 (59.6%)	33 (58.9%)	71 (60.7%)	54 (60.7%)	
	Fungal	6 (11.5%)	10 (17.9%)	10 (8.5%)	8 (9.0%)	
	Parasitic/Protozoal	2 (3.8%)	0 (0.0%)	3 (2.6%)	3 (3.4%)	
	Non-microbiological	13 (25.0%)	11 (19.6%)	22 (18.8%)	21 (23.6%)	
Grade 3 Infections	All Infections	18 (34.6%)	30 (53.6%)	37 (31.6%)	26 (29.2%)	
	Bacterial	5 (9.6%)	13 (23.2%)	11 (9.4%)	7 (7.9%)	
	Viral	4 (7.7%)	15 (26.8%)	16 (13.7%)	9 (10.1%)	
	Fungal	4 (7.7%)	10 (17.9%)	7 (6.0%)	5 (5.6%)	
	Parasitic/Protozoal	2 (3.8%)	0 (0.0%)	3 (2.6%)	3 (3.4%)	
	Non-microbiological	5 (9.6%)	5 (8.9%)	7 (6.0%)	6 (6.7%)	

Source: ISS Section 5.7.6 Table 75
a. Includes all subjects who received omidubicel
b. Includes all subjects with hematologic malignancy who received single unit omidubicel
Abbreviations: BMT CTN, Blood and Marrow Transplant Clinical Trials Network; ISS, integrated summary of safety; N, number of subjects in each population; n, number of subjects with event; UCBU, unmanipulated cord blood unit

Reviewer comment: *We noted that Grade III to IV acute GvHD in the hemoglobinopathy pool (Pool 3, N=17) was numerically higher, as it was observed in seven (41.2%) subjects. Overall, omidubicel treatment was associated with higher incidence of Grade II to IV acute GvHD and secondary graft failure, but Grade III to IV acute GvHD was similar across pools except for Pool 3 (subjects with* (b) (4) *, who had higher incidence of acute GvHD. This may be attributable to different demographic and baseline subject characteristics, including Black race,*

which has often been found to be associated with lower HLA matching between graft and recipient, or prior disease history including multiple red blood cell transfusions and immunologic reactivity (Parikh et al. 2021). However, due to the small number of subjects treated, definitive conclusions could not be made.

The AESIs in the Safety Analysis Population (Pool 6 N=117) will be included in Section 5 of the USPI.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Throughout the omidubicel clinical program, the dosing of omidubicel was assessed by the minimal cellularity required to release a product for infusion. Per the Applicant, the CD34+ doses provided by omidubicel were higher than UCBU in Study P0501 and comparable to CD34+ cell doses infused in peripheral blood transplants (Anasetti et al. 2012). CD3+ doses were low, however, when compared to UCBU transplant.

The Applicant did not provide specific analyses exploring adverse effect dose-response correlations.

The clinical pharmacology reviewer performed analyses on dose-safety relationship for omidubicel in Study P0501. See Table 48 and Table 49 for details. To summarize:

- No statistically significant relationship was identified for cell dose versus the selected AEs of GvHD, disease relapse, or primary graft failure (p>0.1).
- The TNC dose and CD34 cell dose were comparable between subjects with or without acute GvHD or chronic GvHD, or disease relapse.
- Data were insufficient to perform dose-response analysis for primary graft failure because only two subjects had primary graft failure, who both received a lower dose of CD34, suggesting that dose may play role in graft failure.

Table 48. Study P0501: Summary of Median (Min, Max) CD34 Dose per kg ($x10^6$) in Subjects With or Without AEs

AE	Without Event	With Event	P-Value
Acute GvHD (all grade)	7.4 (3.6, 47.6)	10.3 (2.1, 25.4)	0.33
Acute GvHD (Grade 3-4)	10.3 (2.1, 47.6)	8 (3.0, 25.4)	0.64
Chronic GvHD	9.8 (2.9, 27.8)	8.6 (2.1, 47.6)	0.64
Disease relapse	9.1 (2.1, 47.6)	8.8 (2.9, 15.9)	0.34
Primary graft failure*	10.3 (2.1, 47.6)	4.9 (4, 5.8)	-

Source: clinical pharmacology reviewer
Abbreviations: AE, adverse event; GvHD, graft-versus-host disease

Table 49. Study P0501: Summary of Median (Min, Max) TNC Dose per kg (x10^7) in Subjects With or Without AEs

AE	Without Event	With Event	P-Value
Acute GvHD (all grade)	4.6 (2.5, 12.4)	4.5 (1.7, 9.7)	0.18
Acute GvHD (Grade 3-4)	4.7 (1.7, 12.4)	4.3 (2.8, 9.1)	0.39
Chronic GvHD	4.7 (2.5, 12.1)	4.4 (1.7, 12.4)	0.91
Disease relapse	4.7 (1.7, 12.4)	5.3 (2.5, 10.3)	0.98
Primary graft failure*	4.7 (1.7, 12.4)	3.6 (2.5, 4.7)	-

Source: Clin Pharm reviewer
Abbreviation: AE, adverse event; GvHD, graft-versus-host disease; TNC, total nucleated cells

8.5.2 Time Dependency for Adverse Events

N/A

8.5.3 Product-Demographic Interactions

The Applicant assessed the safety outcomes by age group (including adolescents) and by gender. Overall, events were similarly distributed across the age subgroups and gender, although in some cases numbers were too small to draw definitive conclusions. No consistent adverse profile by age or by gender was observed.

Safety outcomes were also assessed by race subgroups. Both bacterial and viral infections occurred at higher rates in the Black and Asian race subgroups of the omidubicel groups; however, the limited numbers of subjects preclude a definitive conclusion. Rates of acute Grade II to IV GvHD were higher in Black subjects. Rates of Grade III to IV acute GvHD were higher in Black subjects with SCD, but not with hematologic malignancies.

Hepatic and renal impairment studies of omidubicel were not conducted. Subjects treated in the omidubicel studies were required to meet minimal hepatic and renal function requirements, to enable the myeloablative conditioning, because of its possible association with hepatic and renal toxicities, respectively.

8.5.4 Product-Disease Interactions

The underlying disease risk was not prospectively evaluated in studies of omidubicel except for Study P0501, where events were generally similarly distributed across the disease risk subgroups. While some events occurred at higher rates in the low-risk subgroup, numbers were too small to draw definitive conclusions. No consistent adverse profile by disease risk or by comorbidity index was observed.

8.5.5 Product-Product Interactions

No studies of drug interaction were performed with omidubicel.

8.5.6 Human Carcinogenicity

No in vivo carcinogenicity, mutagenicity, and fertility studies were conducted to evaluate the effects of omidubicel.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There has been no experience with overdose of omidubicel in human clinical trials.

8.5.8 Immunogenicity (Safety)

N/A

8.5.9 Person-to-Person Transmission, Shedding

N/A

8.6 Safety Conclusions

The primary data in support of safety came from Study P0501, in which 52 subjects with hematologic malignancies received transplantation with omidubicel while 56 subjects received UCBU. Data from an additional 37 subjects from other studies of single-unit omidubicel in subjects with hematologic malignancies were pooled and compared with the control arm of Study P0501 for some safety analyses where data were available. Data from all 117 subjects who received omidubicel for any indication (Pool 6) were also reviewed and will be included in Section 5 of the USPI when describing W&P.

Deaths during study follow-up occurred in 23% of subjects treated with omidubicel and 36% of subjects treated with UCBU in Study P0501. In the pooled population (Pool 6), 32% of subjects died. The most common causes of death in all subjects treated with omidubicel were relapse (10%), infection (9%), and GvHD (5%). In subjects who received UCBU, the most common causes of death were infection (11%), relapse (7%), and GvHD (5%).

Primary graft failure, defined as failure to achieve ANC ≥0.5 Gi/L by Day 42 after transplantation, was reported in 2% (1/52) of subjects treated with omidubicel and 11% (6/56) of subjects treated with UCBU in Study P0501. Primary graft failure was reported in 3% (3/89) of subjects in the Focused SP with underlying hematologic malignancies who received omidubicel alone (Pool 1) and in 3% (4/117) of all subjects who received omidubicel for any disease.

AESI in the safety analysis population (N=117) are summarized below:

- Infusion reactions of any severity occurred in 55 (47%) subjects. Grade 3 to 5 infusion reactions were reported in 18 (15.4%) subjects. A numerically lower rate of infusion reactions was reported in subjects treated with omidubicel compared to UCBU.
- The severity and incidence of infections was similar across pooled safety populations. Grade 2/3 bacterial infections occurred in 38%, fungal infections in 9%, and viral infections 61% of subjects.
- GvHD:
  - Acute GvHD occurred in 58% of subjects.
  - Chronic GvHD occurred in 35% subjects.
- Malignancies of donor origin developed in 3% of subjects and included PTLD and MDS.

As discussed in Section 6.1.13, a more comprehensive analysis of safety from Study P0501 showed no detriment in the graft function of omidubicel compared to UCBU including similar or better outcomes for graft failure, chimerism, disease relapse, and immune reconstitution coupled with a lower rate of Grade 3 viral infections.

The safety profile of omidubicel is acceptable for the intended population. The major potential risks can be mitigated through labeling, including notice of cord blood-specific risks.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

The Applicant stated that there are no available data with omidubicel use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with omidubicel to assess whether it can cause fetal harm when administered to a pregnant woman. There are no data on the effect of omidubicel on fertility.

9.1.2 Use During Lactation

There is no information regarding the presence of omidubicel in human milk, the effect on the breastfed infant, and the effect on milk production.

9.1.3 Pediatric Use and PREA Considerations

The safety and efficacy of omidubicel have been established in adolescents (12 to <17 years old). The results of Study P0501 suggest consistent efficacy across age groups studied, and a case could be made for extrapolation of efficacy to younger pediatric age groups. Eight pediatric subjects <12 years old with (b) (4) were exposed to omidubicel in Study (b) (4); however, due to differences in the treatment received (e.g., conditioning regimen with anti-thymocyte globulin (ATG), transplantation with both omidubicel + UCBU) and the underlying disease (b) (4) (b) (4) the safety of omidubicel in pediatric subjects <12 years old under the conditions to be prescribed could not be established. Therefore, the indication will be limited to patients 12 years and older.

Omidubicel is exempt from Pediatric Research Equity Act (PREA) requirements as it has orphan drug designation (ODD). Omidubicel was granted ODD on 23 May 2018 for “the treatment of myeloablation” and the indication was amended on 28 August 2018 to “enhancement of cell engraftment and immune reconstitution in subjects receiving hematopoietic stem cell transplant.” The ODD date remained as 23 May 2018.

During the IND investigations, the Applicant submitted an initial pediatric study plan (iPSP). However, on 4 December 2020, FDA communicated to the Applicant that “After the Pediatric Review Committee (PeRC) review of the iPSP, FDA agreed that omidubicel is exempt from PREA requirements, as it has been granted ODD for the proposed indication, and that it was not subject to the Research to Accelerate Cures and Equity for Children Act.” Therefore, an agreed iPSP was not required.

Reviewer comment: *Based on the clinical review team assessment, the indication that the team recommends omidubicel be approved for is encompassed under the broader ODD indication, as neutrophil recovery is considered to be a subset of immune reconstitution. The Office of Orphan Products Development confirmed on 14 February 2023 via email communication that the proposed indication of "reducing the time to neutrophil recovery and the incidence of infection in adults and pediatric subjects (12 years and older) with hematologic malignancies undergoing myeloablative conditioning regimen followed by umbilical cord blood transplantation" falls within the scope of the ODD indication of "enhancement of cell engraftment and immune reconstitution in subjects receiving hematopoietic stem cell transplantation." Therefore, the PREA exemption still stands and no PREA PMR is required.*

9.1.4 Immunocompromised Subjects

The population targeted for use is an immunocompromised population.

9.1.5 Geriatric Use

Clinical studies of omidubicel 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 MOA of omidubicel, efficacy is expected to be similar across all adults and may be extrapolated to the full adult population.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

N/A

10. CONCLUSIONS

Study P0501 provided evidence of efficacy for omidubicel in adult and adolescent (12 years and older) subjects with hematologic malignancies who are undergoing myeloablative conditioning regimen followed by UCBU transplantation. The safety profile is acceptable and consistent with known risks associated with other cord blood products.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Hematopoietic Stem Cell Transplantation

HSCT remains the only curative option for a substantial proportion of patients with various hematologic malignancies. However, many patients in need of HSCT do not have fully matched related donors and finding matched unrelated donors may be difficult, especially for patients with diverse racial and ethnic backgrounds. UCB is a readily available graft source with low immunogenicity which allows for less strict HLA matching than adult donor sources and expands the potential donor possibilities in patients who might not otherwise have an available

donor. However, use of UCBT has several major disadvantages including delayed hematopoietic recovery, increased graft failure, increased infection, and increased transplant-related mortality compared to transplantation with other donor sources. Furthermore, despite supportive care with growth factors and antimicrobial agents, deaths related to infection in the setting of severe neutropenia are a common cause of NRM in the post-transplantation period. Patients with hematologic malignancies are in need of an improved graft option that minimizes the disadvantages of standard UCBT including delayed neutrophil recovery and serious, life-threatening infections. There are currently no approved products that address these limitations of UCBT.

Evidence and Uncertainties

Study P0501 was a randomized, open-label, multicenter, Phase 3 study comparing transplantation of omidubicel to transplantation of one or two unmanipulated unrelated CBUs in subjects with hematologic malignancies for whom allogeneic HSCT is recommended. The primary endpoint of the study was time to neutrophil engraftment within 42 days with subsequent donor chimerism >90% by Day 100, and analysis of this endpoint showed an improvement in subjects who received omidubicel compared to those who received UCBU. Although the trial was considered positive, the major limitation of the study was that the primary endpoint was a composite of efficacy and safety and did not clearly describe clinical benefit for the intended population, nor did it support the Applicant's proposed indication (b) (4) (b) (4)
However, the clinical review team considered that neutrophil recovery reflected a component of hematopoietic recovery following transplantation and a reduction in infection has been accepted as direct evidence of clinical benefit for interventions affecting myelopoiesis. Therefore, the efficacy of omidubicel was established based on a reduction in the time to neutrophil recovery with 42 days of follow-up and a reduction in the incidence of Grade 2/3 or and Grade 3 fungal infections in subjects receiving omidubicel compared to subjects receiving UCBU. Transplantation with omidubicel was associated with a shorter time to neutrophil recovery (median 12 days versus 22 days; absolute difference 10 days [95% CI: 6, 14]), and a decreased incidence of BMT CTN Grade 2/3 bacterial or Grade 3 fungal infections through 100 days following transplantation (39% versus 60%; absolute difference 22% [95% CI: 4, 39]) compared to subjects transplanted with UCBU. These differences were considered clinically meaningful, and the indication statement was revised based on this evidence of effectiveness.

For this application, assessment of graft function was essential to ensure there was no detriment introduced by manipulation of the graft source. Analyses of graft failure, disease relapse, and immune reconstitution showed similar or slightly better outcomes in the omidubicel arm compared to the UCBU arm. High grade infections and Grade III to IV acute GVHD were numerically lower in subjects who received omidubicel. The safety profile of omidubicel was consistent with the known toxicities and complications following allogeneic HSCT with myeloablative conditioning therapy, and there was no detriment in safety with omidubicel compared to UCBU transplantation. The risks are similar to the risks associated with other cord blood products and include infusion reactions, GvHD, graft failure, and malignancies of donor origin. These risks can be managed by appropriate post-HSCT monitoring and routine pharmacovigilance.

Conclusions and Reasons

HSCT is the only curative option for a large proportion of patients with hematologic malignancies, but many patients are unable to find suitable donors. CBT offers a readily available donor source, but there are several disadvantages to its use, including delayed hematopoietic recovery and increased infections compared to transplantation with other donor sources. These limitations represent an unmet medical need.

Study P0501 met its primary objective. The study also showed a reduction in the time to neutrophil recovery and the incidence of BMT CTN Grade 2/3 bacterial or Grade 3 fungal infections in patients who received omidubicel compared to those who received UCBU. There was no evidence of detrimental effects on graft function, and the safety profile was consistent with the known toxicities following MAC and allogeneic HSCT. Thus, Study P0501 represents an adequate and well-controlled study that provided substantial evidence of effectiveness in the context of an acceptable safety profile in support of approval.

The data support an indication for omidubicel 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.

Table 50. Risk-Benefit Analysis Summary for Omidubicel

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients with hematologic malignancies have serious, life-threatening diseases. • Allogeneic HSCT is an established treatment for hematologic diseases that cannot be cured with conventional treatments. • CBT offers a readily available donor source for patients without a matched related or unrelated donor (MRD, MUD). This is option is especially critical for those patients with diverse ethnic/racial backgrounds for whom fewer matched donors are available. • Use of CBT is limited by delayed hematopoietic recovery and an increased risk of life-threatening or fatal infections compared to other donor sources.	• CBT offers an alternative graft option for patients with hematologic malignancies without a MRD or MUD, but use of CBT has significant disadvantages compared with other donor sources, including delayed hematopoietic recovery and increased infections/infection-related mortality.
Unmet Medical Need	• There are no approved HCP products that address these limitations of CBT. • Despite use of supportive care (e.g., GCSF, antibiotics/antifungals), serious and life-threatening infections in the setting of severe neutropenia remain a common cause of non-relapse mortality in the post-transplantation setting in general, and post-CBT in particular.	• Patients with hematologic malignancies in need of HSCT but without a matched donor are in need of an improved graft option that minimizes the disadvantages of standard UCBT including delayed neutrophil recovery and serious, life-threatening infections.
Clinical Benefit	• Study P0501 was an open-label, multicenter, international, Phase 3, randomized study of HSCT with omidubicel versus one or two UCBU in subjects 12 to 65 years old, with hematologic malignancies for whom allogeneic HSCT is recommended. • All subjects received prespecified chemotherapy- or radiation-based myeloablative conditioning regimen. • The study met its primary objective and was considered a positive trial. • Transplantation with omidubicel resulted in a shorter time to neutrophil recovery (median 12 days [95% CI: 10, 15] versus 22 days [95% CI: 19, 25]; absolute difference 10 days [95% CI: 6, 14]), and a decreased incidence of BMT CTN Grade 2/3 bacterial or Grade 3 fungal infections through Day 100 following transplantation (39% versus 60%; absolute difference 22% [95% CI: 4, 39]) compared to subjects transplanted with UCBU. • A treatment effect was observed across the subpopulation analyses.	• Study P0501 met its primary objective of reducing the time to neutrophil recovery with subsequent donor chimerism. • The clinical effectiveness of omidubicel was established based on the reduction of time to neutrophil recovery with 42 days of follow-up and reduction in the incidence of BMT CTN Grade 2/3 bacterial or Grade 3 fungal infections through Day 100 following transplantation.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	• Analyses of graft failure, disease relapse, and immune reconstitution showed similar or numerically better results in the omidubicel arm compared to the UCBU arm. • Major and clinically significant ARs associated with omidubicel included infusion reaction, GvHD, graft failure, and malignancies of donor origin. • The types and incidence of adverse reactions reported with omidubicel were similar to or less common than in subjects receiving UCBT.	• Overall, the analyses demonstrated no detriment in the graft function of omidubicel compared to UCBU. • The safety profile is acceptable for the intended population.
Risk Management	• The premedications and safety monitoring in Study P0501 were effective in mitigating serious potential toxicities. • Risks associated with transplantation with omidubicel and cord blood products can be addressed by standard post-HSCT safety monitoring, clear instructions in labeling, and routine pharmacovigilance.	• Because administration of omidubicel is associated with the known risks of cord blood products, inclusion of the boxed warnings and Warnings & Precautions of the HPC cord blood product class are warranted. • Routine pharmacovigilance will be implemented to monitor for potential risk of transmission of serious infections or rare genetic diseases.

Abbreviations: AE, adverse event; BMT CTN, Blood and Marrow Transplant Clinical Trials Network; CBT, cord blood transplantation; CI, confidence interval; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; HLA, human leukocyte antigen; PMR, post-marketing requirement; UCBU, unmanipulated cord blood unit

11.2 Risk-Benefit Summary and Assessment

The risks of omidubicel are associated with its MOA as a CBT product. These include infusion reaction, GvHD, graft failure, and malignancies of donor origin and can be managed by routine pharmacovigilance.

The evidence of clinical benefit of omidubicel is compelling, 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. The benefit risk of omidubicel is favorable in support of approval.

11.3 Discussion of Regulatory Options

Three regulatory options exist: regular approval, accelerated approval, and complete response.

In support of the marketing application, the Applicant submitted efficacy and safety data from the clinical Study P0501, as well as supplemental efficacy data from Study P0301 and safety data from the completed Studies P0101, P0301, P0501, (b) (4)

Substantial evidence of effectiveness in this application was established based on one adequate and well-controlled investigation supported by 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. This evidence of effectiveness is coupled with an acceptable safety profile that is similar to that observed following CBT.

The recommended dosing is a minimum of 12×10^8 TNC (from both CF and NF), and minimum of 9.2×10^7 CD34+cells (from CF).

11.4 Recommendations on Regulatory Actions

The review team recommends granting regular approval for omidubicel 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. The Applicant's proposed indication of (b) (4)

(b) (4) was considered unacceptable based on the review of the data.

11.5 Labeling Review and Recommendations

The review team recommended the following revisions to the Applicant's proposed label:

Indication:

- Revision of the indication statement to reflect the population studied and the clinical benefit observed during the study, which is the reduction in time to neutrophil recovery and reduction in the incidence of Grade 2/3 bacterial or Grade 3 fungal infection compared to UCBT.

  Reviewer comment*: During labeling negotiations, the Applicant stated that SCT is given for treatment of hematologic malignancies (and other diseases) and therefore, their proposed indication statement was valid. FDA reiterated that Study P0501 was not designed to demonstrate a treatment effect on an endpoint relevant to the hematologic malignancies. Indication statements for other cord blood labels are for use in a specific population with a condition rather than for treatment of a disease. In addition, the Applicant requested to not restrict the indication to patients planned for UCBT. However, FDA reiterated that Study P0501 was a comparison between omidubicel and UCB and the benefit of omidubicel was demonstrated in comparison to UCBT only. Therefore, the indication should be limited to those patients in whom an UCBT is planned.*

  FDA's revised indication statement is as follows:

  Omidubicel (OMISIRGE) is a nicotinamide modified allogeneic hematopoietic progenitor cell therapy derived from cord blood 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.

Administration

- Inclusion of specific premedication instructions used in Study P0501

Safety:

- Addition of Boxed Warning and modification to the W&P section to reflect that of cord blood. The USPI should carry all of the W&P section of the USPI of the NF, so that omidubicel is not falsely perceived to be safer than other approved cord blood products.

- The Boxed Warning will include infusion reactions, GvHD, graft failure, and ES.

- W&P will include infusion and hypersensitivity reactions, GvHD, graft failure, ES, malignancies of donor origin, and transmission of serious infections or rare genetic diseases.

- Section 6:

- Revise to clearly describe the safety findings, considering differences in severity grading for different ARs as well as the limitations of the data collection.
- Include only data from Study P0501 since this was a randomized trial and no new or more severe safety signals were identified in Study P0301.

Efficacy:

- Data solely from Study P0501 should be included in Section 14 of the USPI. Study P0301 should be removed.
- Efficacy of omidubicel is based on time to neutrophil recovery with 42 days of follow-up and incidence of BMT CTN Grade 2/3 bacterial or Grade 3 fungal infections through Day 100 following transplantation.
- Removal of results of time to platelets recovery and days alive and OOH.
- Removal of tertiary and exploratory endpoints.
- Removal of details that do not provide clinically meaningful information.

Patient Counseling Information:

- Add counseling information for all W&P.

Reviewer comment: *Labeling negotiations with the Applicant are ongoing at the time of completion of this review.*

11.6 Recommendations on Postmarketing Actions

The Applicant's proposed pharmacovigilance plan is adequate. Based on the review of the BLA submission, the reviewer doesn't recommend any clinical PMC or PMR studies.

APPENDICES

Table 51. Infection Grading per BMT CTN Grading Criteria

Type of infection/ severity grade	Grade 1	Grade 2	Grade 3
Bacterial infections	Bacterial focus NOS requiring no more than 14 days of therapy for treatment (e.g., urinary tract infection)	Bacteremia (except CoNS) without severe sepsis	Bacteremia with deep organ involvement (e.g., with new or worsening pulmonary infiltrates; endocarditis)
	Coag Neg Staph (S. epi), Corynebacterium, or Proprioniobacterium bacteremia	Bacterial focus with persistent signs, symptoms or persistent positive cultures requiring greater than 14 days of therapy	Severe sepsis with bacteremia
	Cellulitis responding to initial therapy within 14 days	Cellulitis requiring a change in therapy d/t progression Localized or diffuse infections requiring incision with or without drain placement	Fasciitis requiring debridement
		Any pneumonia documented or presumed to be bacterial	Pneumonia requiring intubation
			Brain abscess or meningitis without bacteremia
	C. Difficile toxin positive stool with diarrhea < 1L without abdominal pain (child < 20 mL/kg)	C. Difficile toxin positive stool with diarrhea ≥ 1L (child ≥ 20 mL/kg) or with abdominal pain	C. Difficile toxin positive stool with toxic dilatation or renal insufficiency with/without diarrhea
Fungal infections	Superficial candida infection (e.g., oral thrush, vaginal candidiasis)	Candida esophagitis (biopsy proven).	Fungemia including Candidemia
		Proven or probable fungal sinusitis confirmed radiologically without orbital, brain or bone involvement.	Proven or probable invasive fungal infections (e.g., Aspergillus, Mucor, Fusarium, Scedosporium).
			Disseminated infections (defined as multifocal pneumonia, presence of urinary or blood antigen, and/or CNS involvement) with Histoplasmosis,

Type of infection/ severity grade	Grade 1	Grade 2	Grade 3
			Blastomycosis, Coccidiomycosis, or Cryptococcus. *Pneumocystis jiroveci* pneumonia (regardless of PaO2 level)
Viral infections	Mucous HSV infection		
	Dermatomal Zoster with 2 or fewer dermatomes	VZV infection with 3 or more dermatomes	Severe VZV infection (coagulopathy or organ involvement)
	Asymptomatic CMV viremia untreated or a CMV viremia with viral load decline by at least 2/3 of the baseline value after 2 weeks of therapy	Clinically active CMV infection (e.g., symptoms, cytopenias) or CMV Viremia not decreasing by at least 2/3 of the baseline value after 2 weeks of therapy	CMV end-organ involvement (pneumonitis, enteritis, retinitis)
	EBV reactivation not treated with rituximab	EBV reactivation requiring institution of therapy with rituximab	EBV PTLD
	Adenoviral conjunctivitis asymptomatic viruria, asymptomatic stool shedding and viremia not requiring treatment	Adenoviral upper respiratory infection, or symptomatic viruria requiring treatment	Adenovirus with end-organ involvement (except conjunctivitis and upper respiratory tract)
	Asymptomatic HHV-6 viremia untreated or an HHV-6 viremia with a viral load decline by at least 0.5 log after 2 weeks of therapy	HHV-6 viremia without viral load decline 0.5 log after 2 weeks of therapy	Clinically active HHV-6 infection (e.g., symptoms, cytopenias)
	BK viremia or viruria with cystitis not requiring intervention	BK viremia or viruria with clinical consequence requiring prolonged therapy and/or surgical intervention	
Viral infections continued		Enterocolitis with enteric viruses Symptomatic upper tract respiratory virus	Lower tract respiratory viruses

Type of infection/ severity grade	Grade 1	Grade 2	Grade 3
	Viremia (virus not otherwise specified) not requiring therapy	Any viremia (virus not otherwise specified) requiring therapy	Any viral encephalitis or meningitis
Protozoal/Parasitic infections	Infection (not including toxoplasmosis or strongyloides) not requiring therapy	Infection (not including toxoplasmosis or strongyloides) requiring therapy	Infection causing severe sepsis CNS or other organ toxoplasmosis Strongyloides hyperinfection
Nonmicrobiologically defined infections	Uncomplicated fever with negative cultures responding within 14 days Clinically documented infection not requiring inpatient management	Pneumonia or bronchopneumonia not requiring mechanical ventilation Typhlitis	Any acute pneumonia requiring mechanical ventilation Severe sepsis without an identified organism
*Concomitant or multimicrobial infections are graded according to the grade of the infection with the higher grade of severity. **Therapy includes both PO and IV formulations			

Source: BLA 125738/0 Appendix 16.1.1 Protocol GC P#05.01.020 (Appendix G)
Abbreviations: BMT CTN, Blood and Marrow Transplant Clinical Trials Network; CoNS, coagulase-negative staphylococci; CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6; HSV, herpes simplex virus; IV, intravenous; NOS, not otherwise specified; PaO2, partial pressure of oxygen; PO, by mouth; PTLD, post-transplant lymphoproliferative disorders; VZV, varicella zoster virus

Table 52. FDA Grouped Terms

FDA Grouped Terms	FDA Preferred Terms
Abdominal pain	Abdominal pain
Bacterial infection	Clostridium difficile infection Enterobacter bacteraemia Pneumonia pseudomonal Staphylococcal bacteraemia Staphylococcal infection
Cough	Cough
Diarrhea	Colitis Diarrhoea
Disease recurrence	Acute lymphocytic leukaemia recurrent Leukaemia recurrent Myelodysplastic syndrome
Edema	Fluid overload Oedema Oedema peripheral

FDA Grouped Terms	FDA Preferred Terms
Fatigue	Asthenia
	Fatigue
Fungal infection	Pulmonary mucormycosis
Hemorrhage	Conjunctival haemorrhage
	Contusion
	Cystitis haemorrhagic
	Epistaxis
	Gastrointestinal haemorrhage
	Haematochezia
	Haematuria
	Haemorrhage
	Metrorrhagia
	Petechiae
	Pulmonary alveolar haemorrhage
	Rectal haemorrhage
	Subarachnoid haemorrhage
	Upper gastrointestinal haemorrhage
Infections – pathogen unspecified	Abdominal infection
	Anorectal infection
	Bacteraemia
	Device related infection
	Device related sepsis
	Encephalitis
	Gastrointestinal infection
	Infection
	Pneumonia
	Pyelonephritis
	Respiratory tract infection
	Sepsis
	Septic shock
	Skin infection
	Soft tissue infection
	Upper respiratory tract infection
	Urinary tract infection
Rash	Acne
	Erythema
	Pruritus
	Rash
	Rash erythematous
	Rash maculo-papular
	Rash papular
Renal impairment	Acute kidney injury
	Blood creatinine increased
	Renal failure
	Renal impairment

FDA Grouped Terms	FDA Preferred Terms
Respiratory failure	Acute respiratory distress syndrome
	Acute respiratory failure
	Hypoxia
	Respiratory distress
	Respiratory failure
Viral infection	Adenovirus infection
	BK virus infection
	Coronavirus infection
	COVID-19 pneumonia
	Cystitis viral
	Cytomegalovirus colitis
	Cytomegalovirus infection
	Cytomegalovirus infection reactivation
	Cytomegalovirus viraemia
	Encephalitis viral
	Herpes simplex oesophagitis
	Herpes zoster
	Herpes zoster cutaneous disseminated
	Herpes zoster reactivation
	Human herpesvirus 6 encephalitis
	Human herpesvirus 6 infection
	Human herpesvirus 6 infection reactivation
	Metapneumovirus infection
	Parainfluenzae virus infection
	Pneumonia adenoviral
	Polyomavirus viraemia
	Respiratory syncytial virus infection
	Varicella
	Viral infection.

Abbreviations: COVID-19, coronavirus disease 2019; FDA, U.S. Food and Drug Administration

Najat Bouchkouj, MD

Emily Jen MD, PhD

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Marc Theoret, MD

Division of Clinical Evaluation Hematology / Office of Clinical Evaluation / Office of Therapeutic Products:

Concurrence with OCE/clinical recommendation:

Tejashri Purohit-Sheth, MD