Application Type	Original BLA
STN	125738/0
CBER Received Date	June 1, 2022
PDUFA Goal Date	May 1, 2023
Division / Office	DRPM/OTAT
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Priority Review	Yes
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Review Completion Date / Stamped Date	
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	John Scott, Ph.D., Director Division of Biostatistics
Applicant	Gamida Cell Ltd.
Established Name	Omidubicel
(Proposed) Trade Name	OMISIRGE
Pharmacologic Class	Nicotinamide modified allogeneic hematopoietic progenitor cell therapy derived from cord blood
Formulation(s), including Adjuvants, etc	A single dose consists of: • Cultured Fraction (CF): At the time of cryopreservation, the CF contains 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 suspended in approximately 10% dimethyl sulfoxide (DMSO). • Non-cultured Fraction (NF): At the time of cryopreservation, the NF contains a minimum of 4.0×10^8 total viable cells with a minimum of 2.4×10^7 CD3+ cells suspended in approximately 10% DMSO.
Dosage Form(s) and Route(s) of Administration	Cell suspension for intravenous infusion
Dosing Regimen	Single dose
Indication(s) and Intended Population(s)	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.

TABLE OF CONTENTS

GLOSSARY 4

1. EXECUTIVE SUMMARY 5

2. CLINICAL AND REGULATORY BACKGROUND 6
2.1 Disease or Health-Related Condition(s) Studied 6
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s) 6
2.4 Previous Human Experience with the Product (Including Foreign Experience) 7
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission 8

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES 9
3.1 Submission Quality and Completeness 9
3.2 Compliance With Good Clinical Practices And Data Integrity 10

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW 10
5.1 Review Strategy 10
5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review 10
5.3 Table of Studies/Clinical Trials 10
5.4 Consultations 11
5.4.2 External Consults/Collaborations 11
5.5 Literature Reviewed 12

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS 12
6.1 Study P0501 12
6.1.1 Objectives (Primary, Secondary, etc) 12
6.1.2 Design Overview 12
6.1.3 Population 12
6.1.4 Study Treatments or Agents Mandated by the Protocol 14
6.1.6 Sites and Centers 14
6.1.8 Endpoints and Criteria for Study Success 14
6.1.9 Statistical Considerations & Statistical Analysis Plan 15
6.1.10 Study Population and Disposition 23
6.1.11 Efficacy Analyses 26
6.1.12 Safety Analyses 32

10. CONCLUSIONS 33
10.1 Statistical Issues and Collective Evidence 33
10.2 Conclusions and Recommendations 34

Glossary

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALL	Acute Lymphocytic Leukemia
AML	Acute Myelogenous Leukemia
ANC	Absolute Neutrophil Count
AT	As-Treated
BLA	Biologics License Application
CBC	Complete Blood Count
CBT	Cord Blood Transplant/Transplantation
CB(U)	Cord Blood (Unit)
CDRH	Center of Device and Radiological Health
CF	Cultured Fraction
CIBMTR	Center for International Blood and Marrow Transplant Research
CML	Chronic Myelogenous Leukemia
CSR	Clinical Study Report
FDA	Food and Drug Administration
GvHD	Graft versus Host Disease
HLA	Human Leukocyte Antigens
HPC	Hematopoietic Progenitor Cell
HSCT	Hematopoietic Stem Cell Transplant
IR	Information Request
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent(ion)-to-treat
IV	Intravenous(ly)
MDS	Myelodysplastic Syndrome
(M)MUD	(Mis)Matched Unrelated Donor
NAM	Nicotinamide
NF	Non-cultured Fraction
PI	Package Insert
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCT	Stem Cell Transplant
SP	Safety Population
TEAE	Treatment Emergent Adverse Event
TNC	Total nucleated cell count
TP	Transplant Population
UCB(U)	Unmanipulated Cord Blood (Unit)
US	United States
WBC	White Blood Count

WR	Written Response

1. EXECUTIVE SUMMARY

This is an original Biologics Licensing Application (BLA) for the applicant's nicotinamide modified allogeneic hematopoietic progenitor cell therapy derived from cord blood with the proposed trade name OMISIRGE (also referred to by its established name, omidubicel, in this review), 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. Omidubicel is a single ex vivo expanded cord blood unit (CBU) given intravenously (IV) as a single dose consisting of a cultured fraction and a non-cultured fraction. In support of this BLA, Gamida Cell submitted the results from the pivotal study, P0501, a multi-center, open-label, randomized clinical trial designed to evaluate the safety and efficacy of omidubicel transplantation compared to the standard single or double unmanipulated cord blood unit (UCBU) transplantation in 125 subjects with hematologic malignancies.

The prespecified primary efficacy endpoint was time to neutrophil engraftment, defined as achieving neutrophil recovery (an absolute neutrophil count (ANC) ≥ 0.5×10^9/L on 3 consecutive measurements on different days) with subsequent donor chimerism following transplantation. Within the intent-to-treat (ITT) population, the median times to neutrophil engraftment were 12 days and 22 days for the omidubicel and the UCBU groups, respectively. Omidubicel transplantation shortened the median time to neutrophil engraftment by 10 days (95% CI: 6.6, 12.7; $p < 0.001$).

However, the clinical review team determined during review that the efficacy of omidubicel should be established based on time to neutrophil recovery following transplantation and incidence of bacterial or fungal infections (one of the three key secondary endpoints). The median time to neutrophil recovery was the same as that of neutrophil engraftment with 10 days difference between the two groups (95% CI: 6.6, 12.7). Incidence of bacterial or fungal infections was 38.7% in the omidubicel group and 60.3% in the UCBU group, a reduction of 21.6% for the omidubicel group (95%CI: 4, 39). For the other two key secondary endpoints, the proportion of subjects achieving platelet engraftment by Day 42 was 54.8% in the omidubicel group, compared to 34.9% in the UCBU group. The absolute difference in incidence was 19.9% (95% CI: 2.3%, 37.4%). Compared to UCBU, transplantation with omidubicel was associated with a higher probability of more time alive and out of hospital in the first 100 days following transplantation. The difference in median days alive and out of the hospital was 12.5 days (95% CI: -2, 32.5). Similar results were observed within the as-treated (AT) population.

A total of 42 deaths were reported, of which 17 occurred in the omidubicel group and 25 occurred in the UCBU group. Treatment emergent serious adverse events (SAEs) occurred in 47 subjects treated with omidubicel and 51 treated

with UCBU. Among the subjects who received omidubicel, 4% experienced primary graft failure, 15% acute Grade 3-4 GvHD, 35% chronic GvHD, and 15% disease relapse. Among the subjects who received UCBU, 11% experienced primary graft failure, 20% acute Grade 3-4 GvHD, 25% chronic GvHD, and 11% disease relapse. Safety analysis did not show any substantial differences in deaths or non-fatal serious adverse events between the omidubicel and UCBU groups.

I verified the primary efficacy and key secondary analyses results for study P0501 as prespecified in the Statistical Analysis Plan (SAP). Post-hoc analyses were performed for the median time to neutrophil recovery by Day 42 post-transplantation. The statistical evidence supports approval of the omidubicel in reducing the time to neutrophil recovery and the incidence of infection in adult and pediatric subjects (12 years and older) with hematologic malignancies following transplantation.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hematologic malignancies are cancers that begin in the blood-forming tissues such as the bone marrow. The uncontrolled growth of abnormal cells disrupts the normal production and function of the normal blood cells. Hematologic malignancies include acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML), and lymphomas.

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

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy to treat hematologic malignancies. In most settings, best results are offered by human leukocyte antigens (HLA) identical sibling transplantation; however, more than two-thirds of subjects awaiting HSCT lack a suitable matched related donor. When a matched related donor is not available, HSCTs with unrelated donor grafts are the only option. For subjects without a suitable matched related donor or matched unrelated donor (MUD), there are three alternative sources for stem cells: mismatched unrelated donor (MMUD), haploidentical (haplo)-related donor, and umbilical cord blood (UCB).

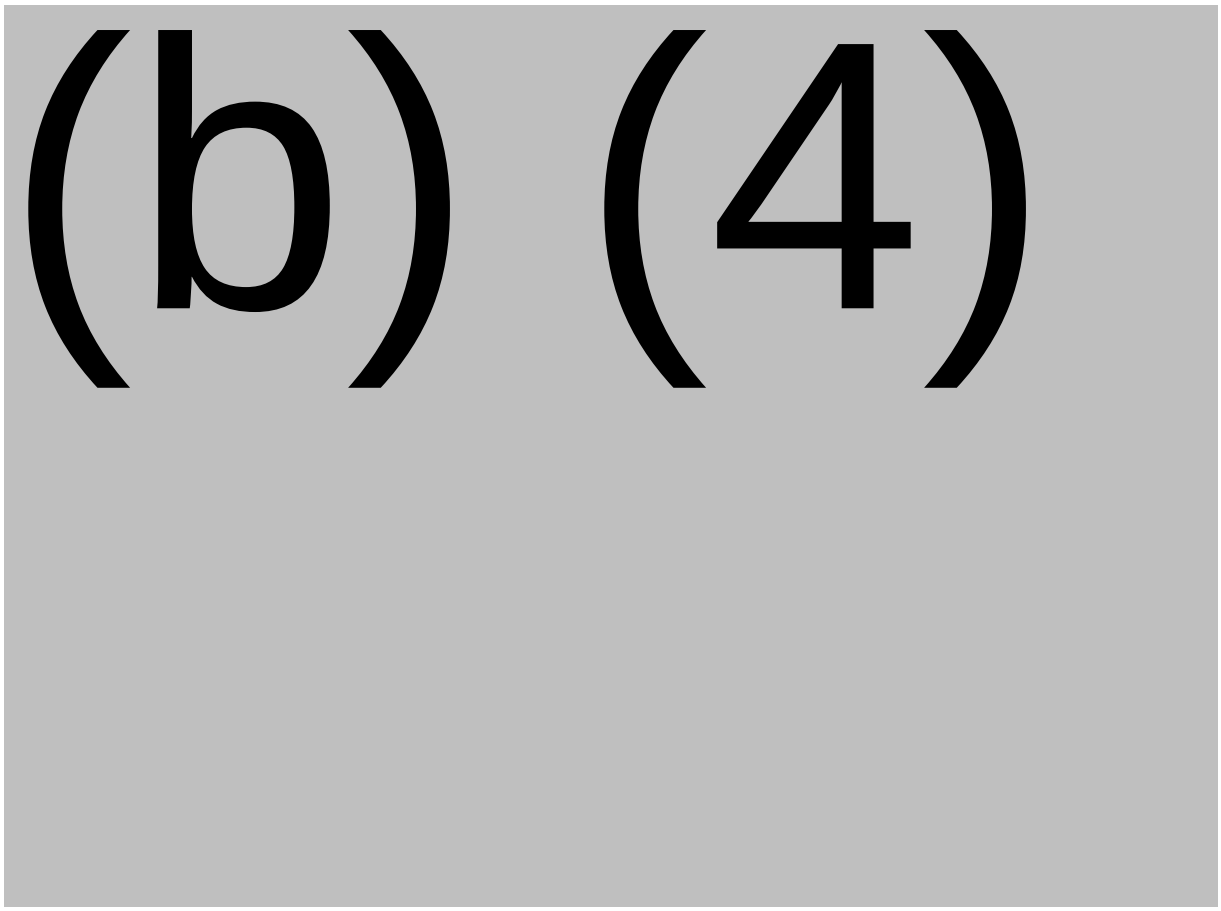
The use of UCB is less stringent in its matching requirements which allows for a higher probability of finding a match with the recipient. However, UCB usually has a low stem cell dose available for transplantation, which can compromise the chances of engraftment and contribute to delayed hematopoietic recovery and poor clinical outcomes.

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

Omidubicel has not been approved anywhere. The applicant has previously conducted early phase clinical studies on omidubicel in subjects with hematologic malignancies following myeloablative therapy.

1. An open-label, single arm, Phase I/Pilot study (P0101) evaluating the safety of co-transplantation of omidubicel and UCBU was completed in 11 subjects with hematologic malignancies. Infusion of omidubicel was well tolerated with no grade 4 infusion toxicity. All 11 subjects achieved neutrophil engraftment with a median time of 12.5 days post-transplantation. Two deaths were reported because of complications that arose during the study, neither of which were considered to be related to omidubicel.

2. An open-label, single arm, Phase I/II study (P0301) evaluating the safety and efficacy of omidubicel transplantation was completed in 38 subjects with hematologic malignancies. Among the 38 subjects, 36 subjects received a single unit of omidubicel, and 2 subjects received omidubicel and UCBU. Neutrophil engraftment was achieved in 94% of the subjects with a median time of 11.5 days. Sixteen deaths were reported, of which 8 were associated with transplant complications.



(b) (4)

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

The clinical development program of omidubicel for treatment of hematologic malignancies was under IND 14459. There were multiple pre-submission and post-submission interactions between the applicant and the FDA.

Regulatory history with statistical implications is summarized below:

Pre-submission

1. On December 14, 2015, in an End of Phase 2 meeting via written response (WR), the FDA recommended formal hypothesis testing for each of the secondary endpoints, ranked hierarchically based on clinical importance.
2. On June 12, 2017, in a Type B meeting on the breakthrough designation and analysis plan, the FDA acknowledged the sponsor's difficulty in analyzing the key secondary endpoints due to limited sample size and event rates. For the primary analysis, the FDA recommended a competing risk model in addition to the Mann-Whitney analysis. The sponsor proposed the Gehan-Wilcoxon analysis for competing risks. On the acceptability of the SAP, the FDA responded that two Phase 3 studies are generally required for licensure. A single pivotal study might be accepted only if the results show a highly significant treatment effect on the primary efficacy endpoint that is also consistent across relevant subgroups.
3. On January 12, 2021, in a Type B meeting via WR, the FDA recommended all subjects treated with omidubicel be included in the Integrated Summary of Safety (ISS). Analyses should be conducted for key demographic populations and for different patient populations of interest. The ISS SAP should include detailed analyses for Treatment Emergent Adverse Events (TEAE), Adverse Events of Special Interest (AESI), Adverse Events (AE), Serious Adverse Events (SAE), clinical laboratory abnormalities, and deaths. For the Integrated Summary of Efficacy (ISE), the FDA recommended any subject missing primary endpoint data be imputed as a non-engrafter for analysis.
4. On November 9, 2021, a pre-BLA meeting under IND14459 was held with the FDA to discuss the filing strategy for omidubicel.

Post-submission

5. The BLA was submitted on a rolling basis. Throughout the review process, multiple amendments were submitted in response to FDA IRs:
    a. On July 6, 2022, under amendment 10, Gamida Cell submitted the ADAM programs and Tables, Figures, and Listings programs for Study P0501, ISE, and ISS.

b. On November 8, 2022, under amendment 33, Gamida Cell submitted updated lb.xpt and adlb.xpt data files to include all complete blood counts (CBCs) (with white blood count (WBC) differential when indicated) that were performed per protocol but were not documented in the original case report forms (CRFs) and provided details on chimerism assays.
c. On November 15, 2022, under amendment 36, Gamida Cell submitted updated data file adlb.xpt to include ANCs for all CBCs that were performed, flagging variable for automated vs manually calculated ANCs, and flagging variable for discrepancies in the calculation of ANCs. The adtteu dataset was also manually updated to correct the time to neutrophil engraftment based on errors noted when comparing the date of engraftment from the laboratory forms to the date of engraftment from the hematopoiesis forms. However, the applicant only corrected the subjects who had incorrect dates entered on the hematopoiesis forms. This amendment was designated as a major amendment on 11/18/2022.
d. On December 13, 2022, under amendment 41, Gamida Cell submitted updated adlb.xpt.
e. On March 6, 2023, under amendment 54, Gamida Cell submitted the code used to calculate the 95% confidence interval (CI) by re-randomization method.
f. On March 20, 2023, under amendment 57, Gamida Cell provided clarifications on the analyses of secondary endpoints and statistical methodology in the SAP.
g. On March 24, 2023, under amendment 60, Gamida Cell provided clarifications on the statistical methodology in the SAP.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission quality of this BLA was poor. The applicant did not submit the analysis programs and laboratory data containing information on donor chimerism assays required for the adjudication of the primary efficacy endpoint during the initial BLA submission. The applicant later submitted the analysis programs in amendment 10. The primary efficacy data were inconsistent between the automated and manually calculated neutrophil counts. The applicant submitted the updated efficacy and laboratory datasets in amendment 36, which was designated as a major amendment. However, the updated efficacy and laboratory datasets did not fully resolve the neutrophil count discrepancy for all subjects. Discrepancy of the data was ultimately resolved and adjudicated internally within the FDA review team. The applicant did not submit all analysis programs used to produce the results in the initial BLA submission, which required several IRs to resolve. These issues presented great challenges to the completion of the statistical review.

3.2 Compliance With Good Clinical Practices And Data Integrity

The studies were conducted with good clinical practices. There were no issues with data integrity.

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

5.1 Review Strategy

The applicant submitted seven studies in support of this application. Two early phase studies (P0101 and P0301) and one pivotal Phase 3 study (P0501) submitted were for the indication that the applicant is seeking. This review memo focuses on the complete study report of the Phase 3 study P0501, but does not review the early phase studies and the other studies conducted for different indications.

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

The documents reviewed for the submission include:

- Original submission BLA 125738/0
  - Module 1.6 Meetings
- Amendment BLA 125738/1
  - Module 2.5 Clinical Overview
  - Module 2.7 Clinical Summary
  - Module 5.3.5.1 Study Reports of Controlled Clinical Studies
  - Module 5.3.5.2 Study Reports of Uncontrolled Clinical Studies
- Amendment BLA 125738/10
  - Module 5 Analysis programs
- Amendment BLA 125738/33
  - Module 5 Datasets
- Amendment BLA 125738/36
  - Module 5 Datasets
- Amendment BLA 125738/41
  - Module 1 Information amendment
  - Module 5 Datasets
- Amendment BLA 125738/54
  - Module 1 Information amendment
  - Module 5 Datasets
- Amendment BLA 125738/57
  - Module 1 Information amendment

5.3 Table of Studies/Clinical Trials

Table 1 provides an overview of the clinical studies conducted for the treatment of hematologic malignancies. This review focuses on the pivotal study P0501.

Table 1. Overview of clinical studies for treatment of hematologic malignancies.

Study Phase (Study Identifier)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)	Number of Patients	Primary Endpoint	Hypothesis testing
Phase III (P0501)	Evaluate safety and efficacy of omidubicel transplantation in patients with hematologic malignancies following myeloablative therapy	Open label, randomized study; sponsor blinded to treatment assignment	Single dose of omidubicel	125 patients; 62 patients randomized to omidubicel and 63 patients randomized to UCBU	Time to neutrophil engraftment by Day 42 following transplant.	Superiority
Phase I/II (P0301)	Evaluate safety and efficacy of omidubicel transplantation in patients with hematologic malignancies following myeloablative therapy	Open label, single arm study	Single dose of omidubicel	38 patients; 36 patients received omidubicel and 2 patients received omidubicel with UCBU	Incidence of neutrophil engraftment by Day 42 following transplant.	None
Phase I/Pilot (P0101)	Evaluate safety of omidubicel and unmanipulated CBU co-transplantation in patients with hematologic malignancies following myeloablative therapy	Open label single arm study	Single dose of omidubicel in combination with UCBU	11 patients	Proportion of subjects achieving neutrophil engraftment by Day 42 following transplant.	None

Source: Adapted from BLA 125738/1; Module 5.2, Tabular Listing of All Clinical Studies.

5.4 Consultations

5.4.2 External Consults/Collaborations

On December 19, 2022, the clinical review team consulted the FDA Center of Device and Radiological Health (CDRH) about the sensitivity of non-FDA approved chimerism assays in detecting less than or greater than 10% host cells used as part of the primary efficacy endpoint. On January 5, 2023, CDRH concluded that the chimerism assay data provided by the applicant should be sensitive for detecting ≤ 10% host cells.

5.5 Literature Reviewed

Sample size calculations were based on Noether's formula. Noether, G. E. (1987). Sample Size Determination for Some Common Nonparametric Tests. Journal of the American Statistical Association 82(398): 645-647.

6. Discussion of Individual Studies/Clinical Trials

6.1 Study P0501

The protocol for Study P0501 was titled "A Multicenter, Randomized, Phase III Registration Trial of Transplantation of NiCord, Ex Vivo Expanded, Umbilical Cord Blood-derived, Stem and Progenitor Cells, versus Unmanipulated Umbilical Cord Blood for Patients with Hematological Malignancies."

6.1.1 Objectives (Primary, Secondary, etc)

Primary Objective:

- Assess time to neutrophil engraftment following transplantation

Secondary Objectives:

- Assess incidence of grade 2/3 bacterial or invasive fungal infections by 100 days following transplantation
- Assess days alive and out of hospital in the first 100 days following transplantation
- Assess platelet engraftment by 42 days following transplantation

6.1.2 Design Overview

P0501 was an open-label, multicenter, randomized controlled study to evaluate safety and efficacy of omidubicel transplantation in patients with hematological malignancies. A total of 120 subjects were planned to be randomized in a 1:1 ratio to either omidubicel or UCBU treatment. Subjects were planned to be followed for up to 15 months post-randomization.

6.1.3 Population

Selected inclusion criteria:

1. Subjects must be 12-65 years of age at the time of randomization
2. Subjects with one of the following hematological malignancies:
    - Acute lymphoblastic leukemia (ALL) at one of the following stages:
        - High risk first complete morphologic remission (CR1), defined as one or more of the following:
            - The presence of adverse cytogenetics or adverse molecular changes.
            - Extreme leukocytosis at diagnosis (WBC >30,000/μl for B-ALL or >100,000/μl for T-ALL)
            - Failure to achieve complete morphologic remission after first induction therapy

- Evidence of minimal residual disease (MRD) at screening by flow cytometry or molecular testing
- Evidence of slow response to induction therapy, such as peripheral blood leukemic blasts one week after start of induction, or >10% leukemic blasts in bone marrow (BM) 2 weeks after start of induction
- Age older than 30 years at diagnosis

▪ Second or subsequent complete morphologic remission

- Acute myelogenous leukemia (AML) at one of the following stages:
  - ▪ First complete morphologic remission (CR1) that is NOT considered as favorable risk:
  - ▪ Patients in CR1 with one or more of the favorable risk criteria but with additional high-risk features may be considered eligible upon consultation with the study chairs.
  - ▪ Second or subsequent remission
- Chronic myelogenous leukemia (CML) at one of the following phases:
  - ▪ Chronic phase with one or more of the following characteristics:
    - ▪ Failure to achieve a primary hematological or cytogenetic response to either nilotinib or dasatinib
    - ▪ Intolerance to/failure of two tyrosine kinase inhibitors (TKI)
    - ▪ Any T315I mutation
    - ▪ Prior blast crisis
  - ▪ Accelerated phase with one or more of the following characteristics:
    - ▪ Newly diagnosed patients who do not achieve an optimal response to TKIs
    - ▪ TKI-treated patients who progress from chronic phase
  - ▪ Prior blast crisis (myeloid or lymphoid) currently in chronic phase or in complete morphologic or molecular remission
- CMMoL or MDS/CMMoL overlap with spleen size <13cm
- Myelodysplastic Syndrome (MDS) with history of one or more of the following:
  - ▪ International Prognostic Scoring System (IPSS) risk category of INT-1 or greater. MDS patients categorized as INT-1 on primary presentation must have life threatening neutropenia (ANC < 0.5x109/L) or thrombocytopenia (platelets < 30x109/L)
  - ▪ Revised International Prognostic Score System (IPSS-R) risk category of intermediate or greater
- Biphenotypic/undifferentiated/Prolymphocytic/Dendritic Cell Leukemias and Natural Killer Cell Malignancies in first or subsequent CR, adult T-cell leukemia/lymphoma in first or subsequent CR
- Lymphoma, meeting one or more of the following criteria:
  - ▪ Burkitt's lymphoma in second or subsequent CR

- OR High-risk lymphomas in first CR, including enteropathy-associated T cell lymphoma and hepatosplenic gamma delta T cell lymphoma
- OR Chemotherapy-sensitive (defined as at least stable disease) lymphomas that have failed at least 1 prior regimen of multi-agent chemotherapy and are not candidates for an autologous transplant.

3. Qualifying HLA-matched UCBU with sufficient pre-cryopreserved total nucleated cell dose and CD34+ cell dose. Details of the CBU criteria are described in Section 6.1.4.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Treated Arm
Investigational Product: Transplantation with omidubicel
Dose and Route of Administration: A single dose via IV

Control Arm:
Product: Transplantation with one or two unmanipulated cord blood units
Dose and Route of Administration: one or two CBUs via IV

All CBUs were required to be human leukocyte antigens (HLA)-matched at 4-6/6 HLA loci with the subject. Each CBU was required to contain a pre-cryopreserved (post-processing) total CD34+ cell count of at least 8×10^6, as well as a pre-cryopreserved (post-processing) total nucleated cell count (TNC) of at least 1.8×10^9, and a total nucleated cell dose of at least 1.5×10^7 TNC/kg body weight. One CBU was used for the omidubicel arm; a single or double unmanipulated cord blood transplant (CBT) was used for the control arm. In the case of double CBT, two CBUs were required to have a combined pre-cryopreserved (post-processing) total nucleated cell dose of $\geq 3 \times 10^7$ TNC/kg.

6.1.6 Sites and Centers

Subjects were enrolled across 33 sites globally, including 87 subjects from the United States (US), 23 from Europe, and 15 from Brazil, Israel, and Singapore.

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint:

- Time to neutrophil engraftment within 42 days post-transplantation
  - Neutrophil engraftment is defined as achieving an absolute neutrophil count (ANC) greater than or equal to 0.5 x 10^9/L on 3 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) any time on or after the day of engraftment up to the earlier of 100 days post-transplant, date of relapse, date of secondary graft failure, or date of death.

- The day of neutrophil engraftment is designated as the first of the 3 consecutive measurements, occurring on or before 42 days post-transplant and prior to any competing risks.

Key secondary endpoints:

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

Reviewer comment:
The clinical review team decided that efficacy of omidubicel will also be based on bacterial or fungal infections by 100 days because this endpoint represents a direct clinical benefit of the product. Although platelet engraftment by 42 days and days alive and out of hospital by 100 days were considered in the review of data, these are not endpoints that FDA has accepted for regulatory decision-making to include in labeling.

Other endpoint:

- Time to neutrophil recovery within 42 days post-transplantation
  - Neutrophil recovery is defined as achieving an absolute neutrophil count (ANC) greater than or equal to 0.5 x 10^9/L on 3 consecutive measurements on different days any time on or after the day of recovery up to the earlier of 100 days post-transplant, date of relapse, date of secondary graft failure, or date of death.

Reviewer comment:
The clinical review team decided that the primary evidence of efficacy for this BLA would be based on time to neutrophil recovery, instead of neutrophil engraftment, and incidence of infections. Neutrophil engraftment is defined as neutrophil recovery by 42 days and donor chimerism by 100 days post-transplantation. Neutrophil recovery reflects a component of hematopoietic reconstitution (on which cord blood efficacy is based) and is therefore a partial representation of clinical benefit in this setting. In the case of CBT, failure to achieve recovery by 42 days is considered graft failure or treatment failure. On the other hand, chimerism is a metric of safety. The pre-specified engraftment endpoint is therefore a composite of efficacy and safety endpoints with different timeframes of follow-up, and the direct clinical benefit of this combination assessment is unclear.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Treatment assignment:

Subjects were randomized in a 1:1 ratio to the omidubicel or UCBU treatment arm based on minimization. Minimization was designed to improve the balance of

the selected prognostic factors across the treatment groups. The minimization algorithm was based on these four factors:

1. Treatment center
    a. Approximately 10 treatment centers were expected
2. Disease risk group
    a. There were three levels: low risk, moderate risk, and high/very high risk, based on Armand et al. For subjects with rare disease types who were not classified by Armand et al., the disease risk was assigned by the site investigator.
3. Age group
    a. The age group factor had three categories: 12-17 years, 18-39 years and ≥40 years.
4. Intent to perform single vs double cord transplant
    a. The investigator for each subject made this decision based on the HLA match score and cell doses.

To implement the minimization randomization, a measure of treatment group imbalance was calculated for each new subject and the treatment assignment was made as follows:

- If $n_{omidubicel} < n_{UCBU}$ then assign to omidubicel with 90% probability
- If $n_{omidubicel} = n_{UCBU}$ then assign to omidubicel with 50% probability
- If $n_{omidubicel} > n_{UCBU}$ then assign to omidubicel with 10% probability,

where $n_{omidubicel}$ = count of those assigned to omidubicel in the subject's disease risk group + count of those assigned to omidubicel in the subject's age group + count of those assigned to omidubicel in the subject's center + count of those assigned to omidubicel where the intent was to perform a transplant of the same type (single or double) as the subject. Similarly, n_{UCBU} was calculated as the total counts of those assigned to UCBU at the same levels of the four factors as the subject.

Statistical hypothesis:
Null: There is no difference in time to neutrophil engraftment between the two arms
Alternative: There is a difference in time to neutrophil engraftment between the two arms

Sample size estimation:
Sample size calculations were based on Noether's formula, which requires specifying the probability P that an omidubicel subject has a shorter engraftment time than an UCBU subject. The estimate of P was based on 16 subjects treated with omidubicel and 152 subjects treated with UCBU from the Center for International Blood and Marrow Transplant Research (CIBMTR) database between 2010 and 2013. After factoring probabilities of subjects not receiving a

transplant and batch failures, the applicant estimated P to be between 0.72 and 0.78.

Assuming no loss to follow-up and using a two-sided test with a 5% significance level, a test under the null that $P = 0.50$ and an alternative that $P = 0.78$ required a total sample of size 45 for 90% power. Under an alternative of $P = 0.72$, the required total sample size was 72 for 90% power.

The study planned to enroll 120 subjects to provide an extensive safety database for omidubicel, to determine whether a difference exists between the two groups for the primary endpoint, and to reduce the chance of observing higher mortality in the omidubicel group than in the UCBU group.

In December 2017, the applicant planned to enroll a maximum of 30 subjects between 12 and 17 years old. Under the assumption that subjects in the younger age group had a median time to engraftment of 16 days compared to 22 days observed in the 152 CIBMTR subjects, enrolling 30 adolescents would have 97% power.

Analysis population:

- Intent-to-Treat (ITT) population included all randomized subjects, analyzed according to the assigned treatments. The primary efficacy endpoint and key secondary endpoints were based on the ITT population.
- As-treated (AT) population included the randomized subjects who received a cord blood transplant on or before 90 days post randomization, analyzed according to the treatment received. Subjects who received a cord blood transplant that was out of specifications were not included in the AT population. Analysis of the AT population was for supportive evidence.
- Transplant population (TP) included all randomized subjects who received a cord blood transplant on or before 90 days post randomization, analyzed according to the assigned treatments. Subjects who received a cord blood transplant that was out of specifications were included in the TP. Analysis of the TP was for the exploratory endpoints that depend on transplant.
- Safety population (SP) was identical to the AT population.

Statistical method:

Primary efficacy endpoint: Neutrophil engraftment

The test statistic P, the probability that the time to neutrophil engraftment is shorter in the omidubicel group than in the UCBU group, is defined as follows:

(b) (4)

where U is the Mann-Whitney test statistic based on the Wilcoxon sum of scores from the omidubicel group, W_N; n_N and n_C are the sample sizes in the omidubicel group and UCBU group, respectively.

To compute the p-value for the observed test statistic $\hat{P}$, a large number (S) of datasets were created using the re-randomization method and the P test statistic was calculated for each dataset (i.e., $P_1, P_2, \ldots, P_S$). The estimated p-value was the proportion of values that were greater than or equal to the maximum of ($\hat{P}, 1-\hat{P}$) plus the proportion that were less than or equal to the minimum of ($\hat{P}, 1-\hat{P}$). Here S was chosen to be 8000 so that the standard error of the estimated p-value was less than 0.0025 if the true p-value were 0.05. Each dataset was created by applying the minimization algorithm for the enrolled subjects in the same order in which they entered the trial, until the number of allocated subjects for a given arm reached the number of subjects randomized to that arm. When that limit was met, the remaining subjects were assigned to the other arm so that the total number of subjects allocated to each arm remained the same as observed in the trial.

Key secondary endpoint: Incidence of grade 2/3 bacterial or invasive fungal infections by 100 days following transplantation

The incidence of bacterial or fungal infections was estimated from the cumulative incidence curve at Day 100 for each treatment group. The estimation procedure used time to first such infection, with death as a competing event and loss to follow-up as a censoring event. The origin of the time axis was the day of transplant, but infections that occurred between randomization and transplant was counted as infections at time 0. For subjects who did not receive a transplant on or before Day 90 post-randomization, the origin of the time axis was 30 days following randomization. For these subjects, infections occurring in the first 30 days on or after randomization was counted as occurring at time 0. The comparison test-statistic (u) was the difference in the incidence of infections between the two groups.

Key secondary endpoint: Days alive and out of hospital in the first 100 days following transplantation

The number of days that a subject was alive and out of hospital in the first 100 days post-transplant, was counted. Partial days alive and out of hospital, the day of transplant, and the most recent visit day did not count as a day alive and out of hospital. The comparison test-statistic was the Mann-Whitney test statistic for the probability that there are more days alive and out of hospital in the omidubicel group than in the UCBC group. The difference in median number of days alive and out of hospital was also estimated.

Key secondary endpoint: Platelet engraftment by 42 days following transplantation

The proportion of subjects with platelet engraftment by Day 42 post-transplant in each group was estimated for each treatment group from the cumulative

incidence curve, with competing risks as follows: (i) failure to receive a transplant on or prior to Day 90 post randomization (counted as a competing risk event at Day 0), (ii) relapse, (iii) subsequent stem cell transplant and (iv) death. The difference in these proportions formed the test statistic.

Other endpoint: Time to neutrophil recovery by 42 days following transplantation

Statistical methods were the same as the prespecified primary efficacy endpoint of neutrophil engraftment by 42 days.

Confidence intervals based on re-randomization tests

In general, suppose the parameter of interest is μ and the sample test statistic is u. Assume that u is a consistent estimator of μ with asymptotic standard error s. Let $\hat{u}$ be the point estimate of μ in the trial data and $\hat{s}$ the estimated asymptotic standard error. From each re-randomized sample, the point estimate and standard error are denoted $\tilde{u}$ and $\tilde{s}$, respectively. Let $\tilde{z} = (\tilde{u} - \mu_0)/\tilde{s}$, where μ_0 denotes the value of μ under the null hypothesis. The proposed confidence interval is calculated as follows:

(b) (4)

where $\tilde{z}_\alpha$ is the α-quantile of the empirical distribution of $\tilde{z}$ among the set of re-randomized samples and the quantiles of $\tilde{z}$ are estimated from the same 8000 re-randomized samples used to perform the re-randomization test.

- *Application to the primary efficacy endpoint: test statistic* $\boldsymbol{P}$

(b) (4)

Source: Original BLA 125738/1; Module 5.3.5.1, Statistical Analysis Plan V5.0, p.28-29.

The confidence interval for P was obtained by using the following statistics as described below. Let C denote the control group (e.g., UCBU) and N denote the treatment group (e.g., omidubicel). Let Y_N and Y_C be the time to neutrophil engraftment after omidubicel and UCBU treatment, respectively. Let R_{Cj} and R_{Nj} denote the ranks of Y_{Cj} and

Y_{Nj} $(j = 1, 2, \ldots, n_C \; or \; n_N)$, respectively, among all observations. Let $R_{Cj}^{(C)}$ and $R_{Nj}^{(N)}$ denote the ranks of Y_{Cj} and Y_{Nj} among the $n_C \; or \; n_N$ observations in groups C and N, respectively. In practice, the sample test statistic u is replaced by its logit transformed value to improve the symmetry of its statistical distribution.

- *Application to the primary efficacy endpoint: difference in median times to neutrophil engraftment*
  The confidence interval was obtained by using the following statistics:

  (b) (4)

  where $\widehat{m}_N$ and $\widehat{m}_C$ are the estimated medians time to engraftment in the UCBU and omidubicel samples, respectively, and $\widehat{SE}(\widehat{m})$ is the estimated standard error of $\widehat{m}$, defined as:

  (b) (4)

  The estimate of cumulative incidence of neutrophil engraftment is denoted by $\widehat{CI}$, and the estimated median time to engraftment is defined as the minimal time t such that $\widehat{CI}(t) \geq 0.5$. The overall survival function of any event is denoted by S, which can be estimated by the Kaplan-Meier estimator. The Cause Specific Hazard (CSH) of the event of interest is estimated by smoothing the empirical hazard function, which can be obtained using the 'lifetest' procedure in SAS.

- *Application to the secondary endpoint: probability of grade 2-3 bacterial/fungal infection by Day 100 post-transplant*

  For the confidence interval of the difference in probability of grade 2/3 bacterial/fungal infections by Day 100 post-transplant in the two treatment groups, the statistic of interest u is the difference between the two estimated cumulative incidences of infection. Each cumulative incidence and its estimated asymptotic standard error can be obtained from the procedure *cuminc* in the R software, or CIF or proc lifetest in SAS. The sample test statistic u is the difference between these two estimates. The statistics s is the square root of the sum of squares of the two asymptotic standard errors, and as before μ_0=0.

- *Application to other secondary endpoints*

The confidence intervals for these parameters were based primarily on the re-randomization method as described above and as a secondary alternative on the bootstrap percentile method.

Analyses on the AT population:
Analyses of the primary and the key secondary endpoints, time to neutrophil recovery were repeated on the AT population.

Handling of multiple testing:
Hommel's adjustment was applied to the key secondary efficacy endpoints to account for multiple testing.

Handling of intercurrent events:
Table 2 lists the types of intercurrent events for the primary efficacy endpoint and their assignment values for analysis as competing risks.

Table 2. Assignment of analysis values due to competing risks.

Primary Endpoint Outcome	Assigned analysis day
No neutrophil engraftment[1] by (and including) Day 42	43
Met definition for neutrophil engraftment after Day 42	43
Failure to receive a transplant within 90 days following randomization	43
Relapse on or prior to Day 42 without prior neutrophil engraftment[2]	43
Death on or prior to Day 42 without prior neutrophil engraftment[2]	43
Second transplant on or prior to Day 42 without prior neutrophil engraftment[2]	43
Loss to follow up on or prior to Day 42[3]	If this occurs, a different analysis method will be used.

[1]ANC recovery must occur on or before 42 days post-transplant and donor chimerism must occur any time on or after the day of engraftment up to the earlier of day 100 post-transplant, date of relapse, date of secondary graft failure, or date of death.
[2]Relapse, death, or second transplant must occur prior to ANC recovery by Day 42 post-transplant or on or before Day 42 in the absence of ANC recovery post-transplant.
[3]Loss to follow up must occur without prior neutrophil recovery. Loss to follow-up also includes the case of ANC recovery within 42 days but the occurrence of subsequent chimerism up to Day 100 is neither confirmed nor denied.

Source: BLA 125738/1; Module 5.3.5.1, Statistical Analysis Plan V5.0, p.33.

Handling of Missing Data

Time to neutrophil engraftment by Day 42:

If there was loss to follow-up prior to Day 42 following transplant, the Gehan-Wilcoxon test statistic would be used instead of the Mann Whitney statistic. The null hypothesis would be tested using the Gehan-Wilcoxon statistic under a competing risk model.

Reviewer's comment: There was no loss to follow-up in the first 42 days in Study P0501.

Key secondary endpoints:

For missing data regarding infections in the first 100 days post-transplant, either transplant or infection data may be missing. If the subject did not receive a transplant on or before Day 90 post randomization, time to the event was calculated from randomization day + 30. If data on infection were missing, the subject was censored at the time of last observation prior to 100 days.

For days alive and out of hospital, subjects who were lost to follow-up during the first 100 days, but had not relapsed or had graft failure, would have their value imputed as nM/m, where n was the number of days out of hospital following transplant until D, day of loss to follow-up; m was the mean number of days alive and out of hospital until D in the same treatment group among the TP with data until D; M was the mean number of days alive and out of hospital in first 100 days in the same treatment group among the TP population with data until 100 days. Subjects who were lost to follow-up during the first 100 days following transplant, and had relapsed or had graft failure, would be assigned the number of days out of hospital until the day that they were lost to follow-up. Subjects who did not receive a transplant on or prior to Day 90 post randomization was assigned a value of zero.

For platelet engraftment, if a subject was transplanted on or prior to Day 90 post randomization but lost to follow-up before Day 42 post-transplant, the subject was censored at the time of last observation.

Subgroup analyses:

Primary and secondary endpoints were analyzed for the following subgroups:

1. Disease risk groups (low, moderate, and high/very high risk).
2. Age groups (12-17, 18-39 and 40-65 years old).
3. Intention to perform single versus double CB transplant
4. Disease (ALL, AML, CML, MDS, Lymphoma, and other)
5. HCT-specific co-morbidity index (0, 1-2, 3+)
6. Sex (male, female)
7. Race/Ethnicity (e.g., White/Hispanic or Latino, White/Not Hispanic or Latino, Black/Hispanic or Latino, Black/Not Hispanic or Latino, Asian/Hispanic or Latino, Asian/Not Hispanic or Latino, etc.)
8. Geographical region (e.g., Europe, US, Other)

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The ITT population consisted of 125 subjects, of which 62 were randomized to omidubicel and 63 were randomized to UCBU. The Per Protocol (PP) or AT population consisted of 108 subjects, of which 52 received omidubicel and 56 received UCBU.

6.1.10.1.1 Demographics

Table 3. Demographics characteristics (ITT Population).

	Randomized Treatment Group	
	Omidubicel (N=62) (n, %)	UCBU (N=63) (n, %)
Sex		-
Female	30 (48.4%)	23 (36.5%)
Male	32 (51.6%)	40 (63.5%)
Age (years)	-	-
12-39	31 (50.0%)	29 (46.0%)
40-59	27 (43.5%)	31 (49.2%)
60-65	4 (6.5%)	3 (4.8%)
Race	-	-
White	35 (56.5%)	37 (58.7%)
Black	11 (17.7%)	9 (14.3%)
Asian	7 (11.3%)	10 (15.9%)
Unknown/Other/ Missing or more than one race	9 (14.5%)	7 (11.1%)
Ethnicity	-	-
Hispanic or Latino	10 (16.1%)	6 (9.5%)

Abbreviations: ITT: Intent-to-treat; UCBU: Unmanipulated cord blood unit

Source: Adapted from BLA 125738/1; Module 5.3.5.1, Clinical Study Report, p.98.

Demographic characteristics are summarized in Table 3. The median age was 40 years old in the omidubicel group and 43 years old in the UCBU group. In the omidubicel group, 31 subjects (50.0%) were between 12 and 39 years old, 27 (43.5%) between 40 and 59 years old, and 4 (6.5%) between 60 and 65 years old. Similar age distributions were in the UCBU group with 29 subjects (46.0%) between 12 and 39 years old, 31 (49.2%) between 40 and 59 years old, and 3 (4.8%) between 60 and 65 years old. The omidubicel group consisted of approximately 52% males and the UCBU group consisted of 64% males. The study population was ethnically diverse. In the omidubicel group, 35 subjects (56.5%) were White, 11 (17.7%) Black, 7 (11.3%) Asian, and 9 (14.5%) others, mixed or unknown. Similar racial composition was seen in the UCBU group, with

37 (58.7%) White, 9 (14.3%) Black, 10 (15.9%) Asian, and 7 (11.1%) others, mixed or unknown. Approximately 16% of subjects in the omidubicel group were of Hispanic or Latino ethnicity, while the UCBU group consisted of 10% such subjects. The demographic characteristics were well balanced between the two treatment groups.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 4. Disease and medical characteristics (ITT Population).

	Randomized Treatment Group	
	Omidubicel (N=62) (n, %)	UCBU (N=63) (n, %)
HCT-specific Comorbidity Index	-	-
0	12 (19.4%)	14 (22.2%)
1-2	19 (30.6%)	16 (25.4%)
3+	31 (50.0%)	33 (52.4%)
Primary diagnosis	-	-
AML	27 (43.5%)	33 (52.4%)
ALL	20 (32.3%)	21 (33.3%)
MDS	6 (9.7%)	3 (4.8%)
CML	4 (6.5%)	2 (3.2%)
Lymphoma	3 (4.8%)	2 (3.2%)
Other rare disease	2 (3.2%)	2 (3.2%)
Disease risk group	-	-
Low	15 (24.2%)	15 (23.8%)
Moderate	27 (43.5%)	25 (39.7%)
High/Very High	20 (32.3%)	23 (36.5%)
Intended cord blood transplant	-	-
Single	20 (32.3%)	21 (33.3%)
Double	42 (67.7%)	42 (66.7%)
Antigen-level HLA match score (Intended Treatment CBU #1)	-	-
4/6	46 (74.2%)	46 (73.0%)
5/6	15 (24.2%)	16 (25.4%)
6/6	1 (1.6%)	1 (1.6%)

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

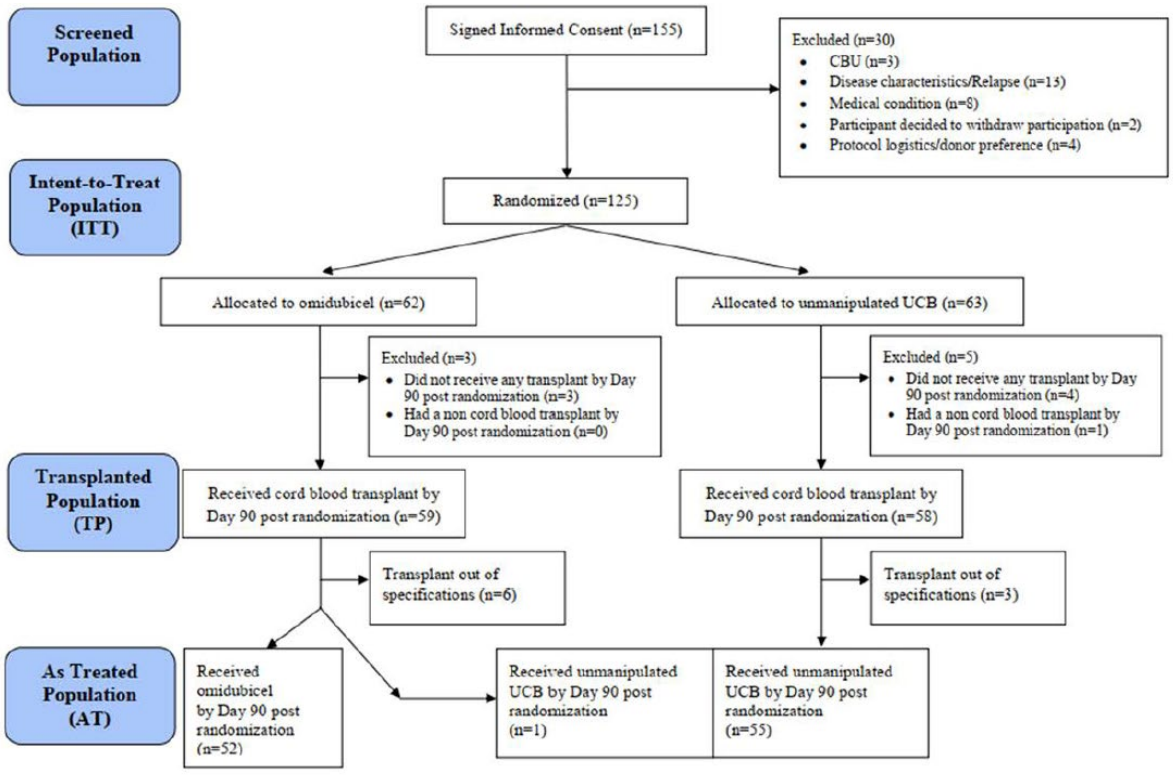
Source: Adapted from BLA 125738/1; Module 5.3.5.1, Clinical Study Report, p.98.

The disease or medical characteristics are summarized in Table 4. Acute leukemias (AML and ALL) were the most common indications for transplant. Forty-seven subjects (75.8%) were diagnosed with AML or ALL in the omidubicel

group, while 54 subjects (85.7%) in the UCBU group. Most subjects had moderate to high disease. Forty-seven subjects (75.8%) in the omidubicel group had moderate to high/very high disease risk, compared to 48 subjects (76.2%) in the UCBU group. Fifty subjects (80.6%) in the omidubicel group had HCT-specific comorbidity index of 1 or higher, compared to 49 subjects (77.8%) in the UCBU group. Most subjects received CBUs that were HLA-mismatched at two loci. Forty-six subjects (74.2%) in the omidubicel group had HLA match score of 4/6 and 73.0% had the same match score in the UCBU group. The disease and medical characteristics were well balanced between the two treatment groups.

6.1.10.1.3 Subject Disposition
The subject disposition is illustrated in Figure 1. Overall, 155 subjects were screened, of which 125 subjects were eligible and randomized. Of the 125 subjects, 62 were randomized to the omidubicel group and 63 to the UCBU group. Within the omidubicel group, 52 subjects received omidubicel and 1 subject received unmanipulated cord blood (UCB) by Day 90 post-transplantation. Fifty-five subjects received UCB by Day 90-post-transplantation in the UCBU group.

Figure 1. Study Flow Diagram for Study P0501.



Data Source: Figure 14.1.1
n= Number of patients in each defined group
Abbreviations: CBU: Cord blood unit; UCB: umbilical cord blood

Source: BLA 125738/1; Module 5.3.5.1, Clinical Study Report, p.86.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Pre-specified primary efficacy endpoint: neutrophil engraftment by Day 42
A total of 20 subjects were imputed with Day 43 for analyses:

- 1 subject achieved neutrophil recovery by Day 42 without subsequent donor chimerism
- 1 subject died on or prior to Day 42 without prior neutrophil recovery
- 3 subjects relapsed on or prior to Day 42 without prior neutrophil recovery
- 3 subjects received second transplant on or prior to Day 42 without prior neutrophil recovery
- 5 subjects did not achieve neutrophil recovery by Day 42
- 7 subjects failed to receive a transplant within 90 days following randomization

Table 5. Neutrophil engraftment by Day 42.

Analysis Population	Parameters	Omidubicel	UCBU	Absolute Difference
ITT	N	62	63	-
	# Neutrophil Engraftment by Day 42 (%)	53 (85.5)	52 (82.5)	-
	Median Days to Neutrophil Engraftment by Day 42 (95% CI)	12 (10, 16)	22 (19, 25)	Bootstrap: 10 (5, 14) Re-randomized: 10 (6.6, 12.7)*
AT	N	52	56	-
	# Neutrophil Engraftment by Day 42 (%)	48 (92.3)	50 (89.3)	-
	Median Days to Neutrophil Engraftment by Day 42 (95% CI)	10 (8, 13)	20 (18, 24)	Bootstrap: 10 (7, 14) **

Abbreviations: CI: confidence interval; ITT: Intent-to-treat; AT: As-treated; N: number of subjects; UCBU: Unmanipulated cord blood unit
*CI calculated by the re-randomization method; $p < 0.001$
**Re-randomized CIs for AT analysis not reliable

Table 5 summarizes the results on neutrophil engraftment by Day 42. The proportion of subjects in the ITT population achieving neutrophil engraftment by Day 42 was 85.5% in the omidubicel group and 82.5% in the UCBU group. The median time to neutrophil engraftment was 12 days (95% CI: 10 to 16) in the omidubicel group and 22 days (95% CI: 19 to 25) in the UCBU group, being shorter in the omidubicel group by 10 days (95% CI: 6.6 to 12.7). The estimated

probability that a subject treated with omidubicel had a shorter engraftment time than a subject treated with UCBU was 0.75 (95% CI: 0.66, 0.84). The study met its primary efficacy endpoint that the time to engraftment was shortened by omidubicel transplantation, compared to UCBU transplantation ($p < 0.001$).

Similar conclusion of shorter time to engraftment with omidubicel was observed in the AT population. As shown in Table 5, 92.3% in the omidubicel group achieved neutrophil engraftment by Day 42, compared to 89.3% in the UCBU group. The median time to neutrophil engraftment was 10 days (95% CI: 8 to 13) in the omidubicel group and 20 days (95% CI: 18 to 24) in the UCBU group, being shorter in the omidubicel group by 10 days (95% CI: 7 to 14). The estimated probability that a subject treated with omidubicel had a shorter engraftment time than a subject treated with UCBU was 0.83 (95% CI: 0.74, 0.91).

Neutrophil recovery by Day 42

Tables 6. Neutrophil recovery by Day 42.

Analysis Population	Parameters	Omidubicel	UCBU	Absolute Difference
ITT	N	62	63	-
	# Neutrophil Recovery by Day 42 (%)	54 (87.1)	52 (82.5)	-
	Median Days to Neutrophil Recovery by Day 42 (95% CI)	12 (10, 15)	22 (19, 25)	Bootstrap: 10 (6, 14) Re-randomized: 10 (6.6, 12.7)*
AT	N	52	56	-
	# Neutrophil Recovery by Day 42 (%)	49 (94.2)	50 (89.3)	-
	Median Days to Neutrophil Recovery by Day 42 (95% CI)	10 (8, 12)	20 (18, 24)	Bootstrap: 10 (7, 14) **

Abbreviations: CI: confidence interval; ITT: Intent-to-treat; AT: As-treated; N: number of subjects; UCBU: Unmanipulated cord blood unit
*CI calculated by the re-randomization method; $p < 0.001$
**Re-randomized CIs for AT analysis not reliable

The FDA review team determined that the primary evidence of efficacy should be demonstrated by neutrophil recovery by Day 42, without subjects' subsequent donor chimerism status. Thus, one subject, who achieved neutrophil recovery by Day 42 but did not have subsequent donor chimerism in the omidubicel group, was determined to have achieved neutrophil recovery but not engraftment.

Discrepancy between manually and automated calculated ANC was partially updated by the applicant (see amendment 36). The applicant only updated the days to neutrophil recovery for 2 subjects randomized to the UCBU arm. Re-adjudication for the manually calculated ANC and time to neutrophil recovery was done internally by the FDA, and later agreed upon with the applicant. As a result, 13 additional subjects in the updated efficacy dataset were identified to have inconsistent neutrophil recovery days based on manual vs automated ANC calculations. Of these, 5 subjects were randomized to the omidubicel arm, and 8 subjects were randomized to the UCBU arm. In total, 12% (n=15) of the subjects were impacted. The median days to neutrophil recovery differed by at most 1 or 2 days, so the impact on the efficacy results due to the discrepancy was minimal.

Post-hoc analyses of neutrophil recovery by Day 42 followed the same statistical methodology as the primary efficacy analysis for neutrophil engraftment and used the same handling of intercurrent events as described in Table 2. Since the post-hoc analyses were not pre-specified, hypothesis testing was not performed, and p-values were not presented. Confidence intervals were constructed as described in Section 6.1.9. Direction and magnitude of treatment effect were comparable to those of the pre-specified primary efficacy analysis. The results of the post-hoc analyses did not impact the approval decision for the product.

6.1.11.2 Analyses of Secondary Endpoints

Analyses of key secondary endpoints included incidence of platelet engraftment by Day 42, incidence of grade 2/3 bacterial or invasive fungal infections by Day 100, and median days alive and out of the hospital within 100 days are summarized in Table 7. The proportion of subjects achieving platelet engraftment by Day 42 was 54.8% in the omidubicel group, compared to 34.9% in the UCBU group. The absolute difference in incidence was 19.9% (95% CI: 2.3%, 37.4%; p=0.0275). The proportion of subjects having a Grade 2-3 bacterial infection or invasive fungal infection within 100 Days following transplant was 38.7% in the omidubicel group, compared to 60.3% of in the UCBU group, demonstrating a difference of 21.6% (95 CI 4.1%-39.2%; p=0.0275) in favor of omidubicel. Compared to UCBU, transplantation with omidubicel was associated with a higher probability of more time alive and out of hospital in the first 100 days following transplantation (p=0.014). However, the difference in median days alive and out of the hospital was 12.5 days (95% CI: -2, 32.5), which was not statistically significant. Similar conclusions in favor of omidubicel were observed in the AT population.

Table 7. Key secondary endpoints.

Analysis Population	Endpoint	Omidubicel	UCBU	Absolute Difference (95% CI)*
ITT	N	62	63	-
	Incidence of platelet engraftment by Day 42 (%)	34 (54.8)	22 (34.9)	19.9 (2.3, 37.4)
	Incidence of grade 2/3 bacterial or fungal infections by Day 100 (%)	24 (38.7)	38 (60.3)	21.6 (4.1, 39.2)
	Median days alive and out of the hospital within 100 days	60.5	48	12.5 (-2, 32.5)
AT	N	52	56	-
	Incidence of platelet engraftment by Day 42 (%)	33 (63.5)	22 (39.3)	24.2 (5.6, 42.4)
	Incidence of grade 2/3 bacterial or fungal infections by Day 100 (%)	18 (34.6)	34 (60.7)	26.1 (7.7, 44.4)
	Median days alive and out of the hospital within 100 days	62.5	50.5	12 (-2.5, 27)

Abbreviations: CI: confidence interval; ITT: Intent-to-treat; AT: As-treated; N: number of subjects; UCBU: Unmanipulated cord blood unit
*CI calculated by bootstrap method

6.1.11.3 Subpopulation Analyses

Analyses were performed for the following subgroups: disease risk group, age group, sex, race/ethnicity, geographic regions, disease, intention to perform single versus double CB transplant, HCT-specific Co-morbidity index. Selected subgroup analyses results for the primary endpoint of neutrophil recovery are summarized in Table 8. The difference in median time to neutrophil recovery between treatment groups was 13 days (95% CI: 6, 17) among males and 6 days (95% CI: 1, 14) among females, 11 days (95% CI: 5, 18) among white non-Hispanic subjects, 14 days (95% CI: -10, 18) among subjects with high/very high disease risk, 12 days (95% CI: 2, 20) among subjects diagnosed with ALL, and 7 days (95% CI: 2, 14) among subjects diagnosed with AML.

Table 8. Selected subgroup analysis of neutrophil recovery by Day 42 (ITT Population).

Subgroup Category	Randomized Treatment Group	Number of Subjects in Subgroup	Neutrophil Recovery (%)	Median days to neutrophil recovery (95% CI)*	Difference in median days to neutrophil recovery UCBU-omidubicel (95% CI)*

Age (years)	-	-	-	-	-
12-17	Omidubicel	8	87.5	11 (7, 19)	14 (0, 22)
	UCBU	6	66.7	25 (16, 29)	-
18-39	Omidubicel	23	78.3	10 (8, 20)	11 (-1, 16)
	UCBU	23	87.0	21 (19, 26)	-
40-65	Omidubicel	31	93.6	12 (9, 16)	10 (3, 15)
	UCBU	34	82.4	22 (18, 27)	-
Sex	-	-	-	-	-
Male	Omidubicel	32	87.5	11 (10, 17)	13 (6, 17)
	UCBU	40	80.0	24 (20, 27)	-
Female	Omidubicel	30	86.7	12 (8, 16)	6 (1, 14)
	UCBU	23	87.0	18 (16, 24)	-
Race/Ethnicity	-	-	-	-	-
Asian/Any ethnicity	Omidubicel	7	85.7	8 (7, 19)	11 (-1, 24)
	UCBU	10	90.0	19 (16, 32)	-
Black/Any ethnicity	Omidubicel	11	90.9	10 (8, 14)	7 (2, 14)
	UCBU	9	100.0	17 (14, 24)	-
White/Hispanic	Omidubicel	5	100.0	11 (8, 20)	7 (-3, 16)
	UCBU	5	100.0	18 (14, 26)	-
White/Non-Hispanic or unknown	Omidubicel	30	90.0	13 (8, 18)	11 (5, 18)
	UCBU	32	75.0	24 (21, 31)	-
Other, including unknown	Omidubicel	9	66.7	13 (9, 20)	7 (-4, 10)
	UCBU	7	71.4	20 (16, 20)	-
Disease Risk	-	-	-	-	-
Low	Omidubicel	15	93.3	15 (10, 18)	6 (1, 25)
	UCBU	15	73.3	21 (17, 40)	-
Moderate	Omidubicel	27	88.9	12 (9, 16)	8 (4, 15)
	UCBU	25	88.0	20 (17, 27)	-
High/Very high	Omidubicel	20	80.0	10 (7, 35)	14 (-10, 18)
	UCBU	23	82.6	24 (20, 26)	-
Disease	-	-	-	-	-
ALL	Omidubicel	20	85.0	13 (8, 20)	12 (2, 20)
	UCBU	21	85.7	25 (19, 29)	-
AML	Omidubicel	27	88.9	12 (10, 17)	7 (2, 14)
	UCBU	33	78.8	19 (18, 24)	-

Abbreviations: ALL: Acute lymphoblastic leukemia; AML: Acute myelogenous leukemia; CI: confidence interval; ITT: Intent-to-treat; UCBU: Unmanipulated cord blood unit
*CI calculated by bootstrap method

Selected results of subgroup analyses for cumulative incidence of bacterial or fungal infections by 100 days are summarized in Table 9. The cumulative incidence of infection among males in the omidubicel group was 44% and 53% in the UCBU group, compared to 33% among females in the omidubicel group and 74% in the UCBU group; 33% among white/non-Hispanics in the omidubicel group and 50% in the UCBU group; 30% among the high/very high disease risk subjects in the omidubicel group and 57% in the UCBU group; 35% among subjects with ALL in the omidubicel group and 57% in the UCBU group; and 44% among subjects with AML in the omidubicel group and 67% in the UCBU group.

Table 9. Subgroup analyses of time to first bacterial infection Grades 2-3 or fungal infection by Day 100 following transplantation (ITT Population).

Subgroup Category	Randomized Treatment Group	Number in Subgroup	Number with a Qualifying Infection	Cumulative Incidence (95% CI)*
Age (years)	-	-	-	-
12-17	Omidubicel	8	2	0.25 (0.00, 0.63)
	UCBU	6	3	0.50 (0.17, 0.83)
18-39	Omidubicel	23	12	0.52 (0.30, 0.74)
	UCBU	23	18	0.78 (0.61, 0.96)
40-65	Omidubicel	31	10	0.32 (0.16, 0.48)
	UCBU	34	17	0.50 (0.32, 0.68)
Sex	-	-	-	-
Male	Omidubicel	32	14	0.44 (0.28, 0.59)
	UCBU	40	21	0.53 (0.38, 0.68)
Female	Omidubicel	30	10	0.33 (0.17, 0.50)
	UCBU	23	17	0.74 (0.57, 0.91)
Race/Ethnicity*	-	-	-	-
Asian/any ethnicity	Omidubicel	7	3	0.43 (0.00, 0.86)
	UCBU	10	8	0.80 (0.50, 1.00)
Black/any ethnicity	Omidubicel	11	6	0.55 (0.27, 0.82)
	UCBU	9	6	0.67 (0.33, 1.00)
White/Non-Hispanic or unknown ethnicity	Omidubicel	30	10	0.33 (0.17, 0.50)
	UCBU	32	16	0.50 (0.31, 0.66)
Anything else including unknown	Omidubicel	9	2	0.22 (0.00, 0.56)
	UCBU	7	5	0.71 (0.43, 1.00)
Disease Risk	-	-	-	
Low	Omidubicel	15	8	0.53 (0.27, 0.80)
	UCBU	15	9	0.60 (0.33, 0.87)
Moderate	Omidubicel	27	10	0.37(0.19, 0.56)
	UCBU	25	16	0.64 (0.44, 0.80)
High/Very High	Omidubicel	20	6	0.30 (0.10, 0.50)

	UCBU	23	13	0.57 (0.35, 0.74)
Disease*	-	-	-	-
ALL	Omidubicel	20	7	0.35 (0.15, 0.55)
	UCBU	21	12	0.57 (0.28, 0.76)
AML	Omidubicel	27	12	0.44 (0.26, 0.63)
	UCBU	33	22	0.67 (0.52, 0.82)

Abbreviations: ALL: Acute lymphoblastic leukemia; AML: Acute myelogenous leukemia; CB: Cord Blood; CI: confidence interval; HCT: Hematopoietic cell transplantation; ITT: Intent-to-treat; UCBU: Unmanipulated cord blood unit; US: United States
*Some subgroup analyses were not reliable due to limited sample sizes (n<7).
**CI calculated by bootstrap method

Source: Adapted from BLA 125738/1; Module 5.3.5.1, Tables, Figures, And Graphs Referred To But Not Included in the Text Clinical Study Report (CSR) P0501, p.154

Due to small sample sizes and multiple comparisons, formal statistical comparisons were not made for the subgroup analyses. However, the descriptive statistics show that efficacy results seemed to be consistent across the subgroups. The median day for neutrophil engraftment or neutrophil recovery was shorter for omidubicel across all the subgroups. Transplantation with omidubicel also had a lower incidence of bacterial or fungal infections in the first 100 days following transplantation.

6.1.11.4 Dropouts and/or Discontinuations

Section 6.1.9 describes the planned strategy for handling intercurrent events and missing data due to loss to follow up. There were no subjects lost to follow-up in Study P0501.

6.1.11.5 Exploratory and Post Hoc Analyses

Post-hoc analyses on time to neutrophil recovery were critical to characterizing the overall clinical performance of omidubicel. Results of these post-hoc analyses were included in the Package Insert (PI) and can be found in Section 6.1.11.1.

6.1.12 Safety Analyses

No formal statistical analysis of safety data was performed. Safety analyses were based on the Safety Population (SP), which comprised all subjects who received omidubicel on study and within specifications (n=52) and all UCBU subjects who received an UCBU that met protocol criteria (n=56).

6.1.12.3 Deaths

A total of 42 deaths were reported during the study. Seventeen deaths occurred in subjects randomized to omidubicel, and 25 deaths occurred in subjects randomized to UCBU. Of these, 2 subjects on the omidubicel arm and 3 subjects on 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, the common causes of death were infections, acute GvHD, and relapse. In subjects treated with UCBU, the most common causes of death were infection or septic shock, respiratory disorders, including hypoxic respiratory failure, ARDS, idiopathic pneumonia, and pulmonary organ failure, disease relapse, and GvHD.

6.1.12.4 Nonfatal Serious Adverse Events

Within the SP, a total of 263 treatment-emergent SAEs were reported in 98 subjects; 128 events in 47 subjects treated with omidubicel and 135 events in 51 subjects treated with UCBU. The most common SAE was infection, experienced by 26 (50%) of omidubicel subjects and 28 (50%) of UCBU subjects. In total, 51 (98%) subjects who received omidubicel and 53 (95%) of subjects who received UCBU experienced a TEAE of Grade 3-5. The most common Grade 3-5 adverse events in subjects treated with omidubicel were pain in 17 (33%) subjects, mucosal inflammation in 16 (31%), hypertension in 13 (25%), and gastrointestinal toxicity in 10 (19%). The most common Grade 3-5 adverse events in subjects treated with UCBU were hypertension in 21 (38%) subjects, mucosal inflammation in 19 (34%), and gastrointestinal toxicity in 19 (34%).

6.1.12.5 Adverse Events of Special Interest

Within the SP, subjects who received omidubicel experienced primary graft failure in 4% of subjects, acute GvHD (Grade 3-4) in 15%, chronic GvHD in 35%, and disease relapse in 15%. Subjects who received UCBU experienced primary graft failure in 11% of subjects, acute GvHD in 20%, chronic GvHD in 25%, and disease relapse in 11%.

10. Conclusions

10.1 Statistical Issues and Collective Evidence

I verified the primary efficacy and key secondary efficacy results of the pivotal study P0501, as prespecified in the SAP. I also conducted post-hoc analyses for the median time to neutrophil recovery by Day 42 post-transplantation.

P0501 was an open-label, multicenter, randomized controlled study for evaluating the safety and efficacy of omidubicel transplantation in subjects with hematological malignancies. A total of 125 subjects were enrolled and randomized in a 1:1 ratio to either omidubicel or UCBU. Subjects were followed for up to 15 months post-randomization. Sixty-two subjects were randomized to receive omidubicel and 63 subjects to UCBU. The AT population consisted of 108 subjects, of which 52 received omidubicel and 56 received UCBU. The prespecified primary efficacy endpoint was time to neutrophil engraftment, defined as achieving neutrophil recovery with subsequent donor chimerism following transplantation. However, the efficacy of omidubicel was established

based on time to neutrophil recovery following transplantation and incidence of bacterial or fungal infections. Major discrepancies were found in the primary efficacy endpoint, which was adjudicated internally by the Food and Drug Administration (FDA) review team. All minor discrepancies were resolved via information requests (IR).

In the ITT population, 85.5% of subjects randomized to omidubicel and 82.5% of subjects randomized to UCBU achieved neutrophil engraftment within 42 days post-transplantation. The median time to neutrophil engraftment was 12 days (95% CI: 10, 16) for the omidubicel group, in contrast to 22 days (95% CI: 19, 25) for the UCBU group. The median time to neutrophil recovery was 12 days (95% CI: 10, 15) for the omidubicel group, in contrast to 22 days (95% CI: 19, 25) for the UCBU group. Transplantation with omidubicel shortened the median time to neutrophil engraftment by 10 days (95% CI: 6.6, 12.7; $p < 0.001$), and the same was observed for median time to neutrophil recovery. When adjusted for multiplicity, significant differences in favor of omidubicel were also observed for the key secondary endpoints of platelet engraftment by Day 42 post-transplantation ($p = 0.028$), incidence of grade 2/3 bacterial or invasive fungal infections by Day 100 post-transplantation ($p = 0.028$), and days alive and out of the hospital within 100 days ($p = 0.014$). The incidence of bacterial or fungal infections was about 39% in the omidubicel group and 60% in the UCBU group, with a reduced incidence of bacterial or fungal infections in the omidubicel group by 22% (95% CI: 4, 39). Analyses in the AT population and subgroup analyses were consistent with the results of the primary efficacy analysis.

A total of 42 deaths were reported, of which 17 occurred in the omidubicel group and 25 occurred in the UCBU group. Treatment emergent SAEs occurred in 47 subjects treated with omidubicel and 51 treated with UCBU. Among the subjects who received omidubicel, 4% experienced primary graft failure, 15% acute Grade 3-4 GvHD, 35% chronic GvHD, and 15% disease relapse. Among the subjects who received UCBU, 11% experienced primary graft failure, 20% acute Grade 3-4 GvHD, 25% chronic GvHD, and 11% disease relapse. Safety analysis did not show any substantial differences in deaths or non-fatal serious adverse events between omidubicel and UCBU. The overall frequency of deaths and serious adverse events were similar between omidubicel and UCBU groups.

10.2 Conclusions and Recommendations

Based on the efficacy results from the pivotal P0501 study, adequate statistical evidence supports approval for the proposed indication of omidubicel in reducing the time to neutrophil recovery and the incidence of infection in adult and pediatric subjects (12 years and older) with hematologic malignancies following transplantation.