Clinical Pharmacology BLA Review

Division of Clinical Evaluation General Medicine (DCEGM),

Office of Clinical Evaluation (OCE)

Office of Therapeutic Products (OTP)

Submission Number: BLA 125738.00

Product Name: Omidubicel: Allogeneic Unrelated Umbilical Cord Blood Cells (b) (4) Selected with (b) (4) Expanded Ex Vivo in the presence of Nicotinamide along with (b) (4) Negative Fraction (Omisurge, formerly NiCord); and Allogenic Unrelated Umbilical Cord Blood

Proposed Indication: (b) (4)

Applicant: Gamida Cell Ltd.

Date Submitted: Clinical Module Received: 03/ 03/ 2022 & Amended: 11/ 29/2022

RPM: Cara Pardon

Reviewer: Million Tegenge, PhD

Clinical Pharmacology Reviewer, DCEGM, OCE, OTP

Through: Tejashri Purohit-Sheth, MD

Director, DCEGM, OCE, OTP

Table of Contents

1. Executive Summary

Omidubicel (Omisurge) is a nicotinamide modified allogeneic cord blood hematopoietic progenitor cell therapy indicated to reduce the time to neutrophil recovery and the incidence of infection in adult and pediatric patients 12 years and older with hematologic malignancies undergoing myeloablative conditioning regimen followed by umbilical cord blood transplantation.

The data supporting the clinical pharmacology of Omisurge is based on two clinical studies that included pharmacodynamic (i.e., immune reconstitution) and dose-response assessments. The initial study (#P0301) demonstrate an increasing trend for reconstitution of CD4+T cells, CD8+ T cells and CD19+ B cells. In the pivotal study (#P0501) a total of 37 subjects were included in the immune reconstitution sub-study of which 17 were transplanted with Omisurge and 20 with umbilical cord blood (UCB). The recovery of CD4+ and CD8+ T cells are significantly higher in the Omisurge treated group on Days 7 and 14 compared to UCB, which suggests early immune recovery. The CD4+ and CD8+ cell counts are similar in the two groups from Day 21 to 1 year. The recovery of NK cells (CD56+) and B-cells (CD19+) are generally comparable between the Omisurge and UCB treated groups. A positive correlation between the CD34+ cell dose, and the reconstitution of T-cells (CD3+, CD4+ and CD8+ cells) and Natural Killer (NK) cells was identified.

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

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

Overall, the clinical pharmacology analysis supports the proposed single dose administration of Omisurge with minimum of $12x10^8$ TNC (from both cultured and non-cultured fraction), and minimum of $9.2x10^7$ CD34+cells (from cultured fraction).

2. Recommendations

This BLA is acceptable for approval from the clinical pharmacology perspective. Labeling recommendations are provided in section 5.

3. Background

Hematopoietic Progenitor Cell (HPC), Cord Blood, has been evaluated as a source of hematopoietic progenitor cells for transplantation to treat a variety of diseases affecting the hematopoietic system, such as hematological malignancies, hematological non-malignant disorders, primary immunodeficiency, and inborn errors of metabolism. Delayed hematopoietic recovery and increased rates of graft rejection are among the risks of standard cord blood transplant. Stem and progenitor cells required for engraftment and recovery of hematopoiesis after blood stem cell transplantation express the CD34 cell surface antigen. Thus, an adequate dose of total nucleated cells (TNC) expressing CD34 +cells is expected to ensure early and sustained hematopoietic recovery. The TNC and CD34 +cell dose can be considered the limiting factor for the use of umbilical cord blood (UCB) 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 [1],[2].

In this BLA submission, the applicant developed Omidubicel (Omisurge) to address limitations associated with standard UCB. Omisurge is a cryopreserved allogeneic hematopoietic cellular therapy consisting of two cell fractions both derived from the same specific cord blood unit (CBU):

- Cultured Fraction (CF): consists of allogeneic, hematopoietic CD34+ progenitor cells. The cells are expanded and enhanced through a nicotinamide (NAM) rich environment that is proposed to inhibit differentiation of the hematopoietic progenitor cells CD34+ cells. The CF fraction also consists of other cell populations, including more differentiated myelomonocytic cells, dendritic cells, and granulocytes.

[1] Kindwall-Keller T.L and Ballen K.K (2020). Umbilical cord blood: The promise and the uncertainty. Stem Cells Transl Med. 9:1153-1162.

[2] Shpall E.J, Champlin R.and Glaspy J.A (1998). Effect of CD34 peripheral blood progenitor cell dose on hematopoietic recovery. Biology of Blood and Marrow Transplantation 4:84–92.

- Non-cultured Fraction (NF): consists of allogeneic, hematopoietic mature myeloid and lymphoid cells.

The data supporting clinical pharmacology of Omisurge (previously also known as NiCord) were based on two clinical studies:

- Study#1- Allogeneic Stem Cell Transplantation of NiCord, Umbilical Cord Blood-derived Ex Vivo Expanded Stem and Progenitor Cells, in Adolescent and Adult Patients with Hematological Malignancies (P#0301)
- Study#2- A Multicenter, Randomized, Phase III Registration Trial of Transplantation of Omisurge (NiCord), Ex Vivo Expanded, Umbilical Cord Blood-derived, Stem and Progenitor Cells, versus Unmanipulated Umbilical Cord Blood for Patients with Hematological Malignancies (#P0501)

The overall objective of the Phase 3 study was to compare the safety and efficacy of Omisurge to unmanipulated CBU transplantation in patients with hematological malignancies. The primary endpoint was the time to neutrophil engraftment following transplantation. Neutrophil engraftment was defined as achieving an absolute neutrophil count (ANC) of ≥0.5 x 10^9 /L for 3 consecutive measurements on different days with subsequent donor chimerism (≤ 10% host cells by peripheral blood chimerism or bone marrow chimerism if peripheral blood chimerism was not available). The other clinical pharmacology relevant secondary and exploratory endpoints included assessment of platelet engraftment and kinetics of immune reconstitution following transplantation.

4. Summary of Clinical Pharmacology Findings

Conventional clinical pharmacology studies such as absorption, distribution, metabolism, excretion, drug-drug interaction, renal and hepatic impairment studies were not performed due to the cellular nature of Omisurge. The clinical pharmacology review focused on pharmacodynamics (i.e., immune reconstitution) and dose-response assessments. The major clinical pharmacology findings from the two clinical studies (#P0301 and #P0501) are summarized in the following sections.

Study #P0301:

Dose-Response

- The median total nucleated cell dose (TNC per kg) was $4.9x10^7$cells/kg (range 2-13 $x10^7$cells/kg).
- The median CD34+ cell dose was 6.3 x 10^6cells/kg (range 1.4-14.9 x 10^6/kg).
- Thirty-four of 36 (94%) subjects treated with Omisurge 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.

Pharmacodynamics (PD)/Immune reconstitution (IR)

- PD/ IR results are highly variable but a trend in increasing number of CD3+, CD4 + T cells & CD8 + T cells from Day 70 to Day 180 was observed.

Study #P0501:

Dose-Response

- The median total nucleated cell dose was $4.7x10^7$ cells/kg (range 1.7-12.4 $x10^7$/kg) for Omisurge group and 3.4 $x10^7$/kg (range 1.3-8.0 $x10^7$/kg) for unmanipulated CBU group.
- The median CD34+ cell dose was 9 x 10^6cells/kg (range 2-48 x 10^6/kg) for Omisurge group and 0.2 (range 0-0.8 $x10^6$ cells/kg) for unmanipulated CBU group.
- The median time to neutrophil engraftment was 12 days for the Omisurge group, and 22 days for the unmanipulated CBU group.
- 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 with an increase in cell dose.
- The inclusion of age as a covariate did not improve the dose-efficacy model.
- Dose-safety relationship was evaluated based on cell characteristics and adverse events such as acute graft versus host disease(aGvHD), chronic GvHD(cGvHD), primary graft failure and disease relapse.
- The dose-safety relationship is essentially flat suggesting that an increase in dose did not result in an increase in adverse events of interest such as aGvHD and cGvHD.

Pharmacodynamics (PD)/Immune reconstitution (IR)

- The PD/IR sub-study included a total of 37 subjects of which 17 transplanted with Omisurge and 20 with UCB.
- The CD4+ and CD8+ T cells are higher in the Omisurge group on Days 7 and 14 than the UCB, which suggests early immune reconstitution. The CD4+ and CD8+ cells are similar in the two arms from Day 21 to 1 year.
- The results of NK cell (CD56+) analysis demonstrate that the Omisurge group showed more rapid recovery during the first three weeks after transplant. After one month, NK reconstitution was similar in the UCB and Omisurge groups.
- The B-cell (CD19+) results are comparable between the Omisurge and UCB groups.
- Overall, higher early immune reconstitution (CD4+ cells, CD8+ cells and NK cells at Day 7 and 14) for Omisurge vs. UCB group was observed. However, the Day 7 and 14 immune reconstitution results are generally a minute fraction of the overall immune recovery that was 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 Natural Killer (NK) cells was identified. These data provide supportive evidence that the CD34+ progenitor cell content in

the Omisurge facilitate rapid reconstitution of the lymphoid and myeloid lineages in transplanted patients.

- For subjects treated with Omisurge, but not with UCB, correlation was identified between CD3+ cells and CD4+ T cells and faster neutrophil engraftment (Day 7). Similar relationship was also observed for CD3+, CD8+ T cells and CD19+ B cells and faster platelet engraftment. For patients transplanted with UCB, such correlations were observed after 14-28 days.

Dose-Response Analysis (Combined for Studies #P0301 and /#P0501):

- The linear regression models showed association between cell dose (TNC/kg and CD34/kg) and the days to neutrophil engraftment.
- The dose-response model estimated a shorter timeframe to neutrophil engraftment with a higher dose of Omisurge (TNC/kg or CD34/kg).
- The median (min, max) CD34 dose was $7.25x10^6$ cells/kg ($1.5x10^6$, $47.6x10^6$ cells/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 minimum of $12x10^8$ TNC (from both cultured and non-cultured fraction), and minimum of $9.2x10^7$ CD34+cells (from cultured fraction).

5. Clinical Pharmacology Labeling Comments

The following is a summary of the clinical pharmacology labeling comments that were communicated to the Applicant.

Section 2.1: Dose:

- Requested to include clarifying statement to distinguish manufacturing and dose administered to patients

Section 12.1. Mechanism of Action

- Requested to include data supported statement to describe the mechanism of action and avoid speculative claims of untested mechanism of action

Section 12.2. Pharmacodynamics

- Requested to summarize the immune reconstitution results from the pivotal study including dose-pharmacodynamic relationship
- Recommended moving the immune reconstitution of T-cells & B-cells described in Section 14 to section 12.2

6. Comprehensive Clinical Pharmacology Review

6.1. General Pharmacology

Omisurge (omidubicel) is processed allogeneic cord blood hematopoietic progenitor cell (HPC) therapy consisting of two cell fractions; a Cultured Fraction (CF) and a Non-cultured Fraction (NF) which are both derived from the same patient-specific cord blood unit (CBU).

1) The CF consists of allogeneic hematopoietic CD34+ progenitor cells. The cells are expanded and enhanced through a proprietary process in the presence of nicotinamide (NAM) that is proposed to inhibit differentiation of the hematopoietic progenitor cells (HPCs) CD34+ cells. In addition to the CD34+ HPCs, the CF consists of other cell populations, including more differentiated myelomonocytic cells, dendritic cells and granulocytes.
2) The NF consists of allogeneic hematopoietic mature myeloid and lymphoid cells that are washed, formulated into a suspension, and cryopreserved in a patient-specific bag. In addition to the mature myeloid and lymphoid cells, the NF consists of other cell populations, including more lineage committed hematopoietic stem cells.

The precise mechanism of action of action of Omisurge is unknown. Like transplantation with unmanipulated cord blood (UCB), following single dose administration of Omisurge

the hematopoietic progenitor cells migrate to the bone marrow where they divide and mature. The mature cells are released into the blood, where some circulate and others migrate to tissue sites, partially or fully restoring blood counts and function including immune function.

6.2. Pharmacodynamics

Immune Cell Reconstitution (IR) Assessment

Immune cell reconstitution (IR) after a hematopoietic stem cell transplantation (HSCT) is a dynamic process which includes the recovery of the lymphoid cell subsets and maturation of T-cells in the thymus including the induction and generation of a diverse, de-novo lymphocyte repertoire. Thus, the IR analysis serves as a pharmacodynamic (PD) endpoint and provide supportive clinical evidence for Omisurge effectiveness.

The IR of Omisurge treated subjects was initially evaluated in Study #P0301 using cryopreserved blood samples collected at Days 7, 14, 28, 70, 100, 180 and 365 (Table 1). Although highly variable, an increasing trend for reconstitution of CD4+T cells, CD8+ T cells, CD19+ B cells and CD56+ NK cells were observed (Table 1).

A total of 125 patients were randomized in Study P0501 of which 67 subjects consented to participation in the IR sub-study. Of the 67 subjects who consented, 37 subjects from 14 global sites were included in the IR sub-study of which 17 were transplanted with Omisurge and 20 with UCB. Most patients who consented but were not included in the sub-study did not have a sufficient sample collected for IR analysis. The demographics and baseline characteristics of subjects who participated in the IR sub-study were generally similar to those of the overall study population of P0501. The two arms were generally well-balanced, except for median age. The median age was 30 years (13-62) for Omisurge versus 43 years (19-55) for the control (UCB) group. Age may influence outcomes, as younger patients have been shown to recover lymphoid cell lineages more rapidly resulting in better IR outcomes. Additionally, although all subjects underwent myeloablative conditioning, the Omisurge group had 47% subjects with total body

irradiation (TBI)-containing regimens versus 70% for the UCB patients. The impact of TBI on immune reconstitution is not well established.

The Omisurge manufacturing process led to a difference in the T cell dose administered to the Omisurge and UCB groups. The cord blood unit used to manufacture Omisurge undergoes (b) (4) which are cultured. The flow-through or NF which contains lymphocytes, including T (CD3+) cells, is re-cryopreserved and administered with the CF at the time of transplant. The cryopreservation step decreases the number of T cells compared to the original cord blood unit. For the IR sub-study (n=37), the Omisurge group received a median CD3+ dose of 1.8 x 10^6 cells/ kg (range,1.2 – 7.6 x 10^6) and the UCB group received a median of 6.0 x 10^6 cells/ kg (range, 1.7– 10.2).

Overall, Omisurge-treated subjects were transplanted with a T cell dose that was approximately 70% less than that of subjects transplanted with UCB. Despite infusion of a lower T cell dose, the recovery of CD4+ and CD8+ T cells was significantly higher in the Omisurge group on Days 7 and 14 compared to the UCB group, which suggests early immune recovery. The CD4+ and CD8+ cells were similar in the two arms from Day 21 to 1 year for both groups (Table 3). The results of the NK cell (CD56+) analysis demonstrate that the Omisurge group showed more rapid recovery during the first three weeks after transplant. After one month, NK reconstitution is similar in the UCB and Omisurge groups. The B-cell (CD19+) results seem to be similar between the Omisurge and UCB groups in the first month with slightly higher levels for Omisurge treated subjects from Day 28 through Day 365.

The IR-efficacy relationship was explored to understand if rapid lymphocyte immune reconstitution correlates with faster neutrophil engraftment in patients transplanted with Omisurge vs UCB. In the case of Omisurge, but not of UCB, statistically significant correlations were identified between CD3+ and CD4+ T cells and faster neutrophil engraftment. However, the Day 7 and 14 immune reconstitution results are generally a minute fraction of the overall immune recovery that was observed over the 1 year period. Also, several confounding factors (e.g., age range, myeloablative conditioning regimen,

etc.) make the comparison of immune reconstitution between Omisurge and UCB groups challenging.

Quantitative Assessment of Thymopoiesis

Thymopoiesis, the process of thymocyte maturation into mature T cells in the thymus, involves the rearrangement of T-cell receptors (TCRs). During TCR rearrangement, excised DNA fragments create circular DNA byproducts known as TCR excision circles (TRECs). TREC detection in the peripheral blood stream is an indication that a rearrangement process has occurred and serves as a surrogate marker for thymopoiesis. (b) (4) were used to detect total recent thymic emigrants (RTEs) and quantify TREC, respectively. Subjects treated with Omisurge and UCB have similar RTE (CD8+ and CD4+) and TREC results at 3, 6 and 12 months (Figure 3 & 4), which demonstrates T cell recovery, and a gradual progressive buildup of the RTE and TREC for both graft sources.

6.3. Dose-Response

Dose-efficacy assessment was conducted using a linear regression model evaluating cell characteristics and days to neutrophil engraftment (Study#P0501 and combined Studies #0301 & #P0501). Cell characteristics analyzed were TNC, TNC dose (TNC per kilogram), CD34+ cell count, and CD34+ cell dose (CD34+ cells per kg). In addition to a model including only the cell characteristics, an additional model containing age was also evaluated.

The linear regression models showed a significant association between each cell characteristics tested (TNC, TNC/kg, CD34, and CD34/kg) and the days to neutrophil engraftment/recovery. Days to neutrophil engraftment/recovery decrease with an increase in TNC and CD34+ cells. However, the results were not significant for the linear regression models based on days to platelet engraftment and cell characteristics.

For consistency with the clinical primary efficacy evaluation, we also preformed additional dose-response analysis of the Phase 3 study (P#0501) using updated data for days to

neutrophil recovery (i.e., without considering chimerism). The following is a summary of the dose-efficacy analysis using days to neutrophil recovery:

- A significant negative correlation ($p<0.05$) was observed between cell dose parameters (TNC, TNC/kg, CD34 cells, CD34 cells/kg) and neutrophil recovery.
- The dose-response model estimated a shorter timeframe to neutrophil recovery with a higher dose of Omisurge (TNC/kg or CD34/kg).
- The median (min, max) time to neutrophil recovery was 13 days (7, 35 days) and 8 days (6, 20) for subjects who received lower and higher than the median CD34 cells/kg, respectively.
- The median (min, max) time to neutrophil recovery was 12.5 days (6, 35 days) and 8 days (6, 20) for subjects who received lower and higher than the median TNC per kg, respectively.

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

- Primary graft failure occurred in two subjects who received lower than the median dose of CD34 cells/kg.
- The median (Min, Max) CD34 cells/kg ($x10^6$) in subjects with and without primary graft failure was 4.9 (4,5.8) and 10.3 $x10^6$ (2.1, 47.6), respectively.
- There was no statistically significant relationship between dose and disease relapse.

Dose-safety assessment was conducted between cell characteristics and adverse events such as acute graft versus host disease(aGvHD) and chronic GvHD(cGvHD). Acute GvHD usually presents around the time of engraftment and manifests as maculopapular rash, nausea, vomiting, abdominal pain, diarrhea, or increased serum bilirubin. Chronic GvHD is usually diagnosed later throughout the first year post-transplant. Clinical manifestations of cGvHD include a scleroderma-like or lichen planus- like skin involvement, gastrointestinal ulcerations, and sclerosis of the gastrointestinal (GI) tract, and increased bilirubin. For Omisurge treated subjects, no statistically significant relationship was identified for cell dose vs. aGvHD or cGvHD ($P> 0.1$). The TNC dose

and CD34 cell dose are essentially comparable between subjects with or without aGvHD/cGvHD (Table 6&7).

Overall, the dose-efficacy analysis using neutrophil recovery is consistent with the results of neutrophil engraftment and no dose-safety relationship was identified for adverse effects of interest such as aGvHD and cGvHD. Thus, the dose-response analysis supports the proposed single dose administration of a minimum of $12x10^8$ TNC (from both cultured and non-cultured fraction), and minimum of $9.2x10^7$ CD34+cells (from cultured fraction).

7. Appendix

7.1. Study#1- Allogeneic Stem Cell Transplantation of NiCord, Umbilical Cord Blood-derived Ex Vivo Expanded Stem and Progenitor Cells, in Adolescent and Adult Patients with Hematological Malignancies (P#0301)

The primary objective of the study was to evaluate the safety and efficacy of NiCord single ex vivo expanded cord blood unit transplantation in patients with hematological malignancies following myeloablative therapy. Two primary endpoints were evaluated:

- Cumulative incidence of NiCord-derived neutrophil engraftment at 42 days following transplantation. Neutrophil engraftment was defined as achieving an absolute neutrophil count (ANC) of ≥0.5 x 10^9 /L for 3 consecutive measurements on different days
- Incidence of secondary graft failure at 180 days following transplantation of NiCord

The clinical pharmacology relevant secondary and exploratory endpoints include:

- Time from infusion to neutrophil engraftment
- Time from infusion to platelet engraftment
- Incidence of platelet engraftment at 100 days
- Immune reconstitution at 70, 100, 180, and 365 days following treatment with NiCord

Overall Study Design: This was an open-label, non-randomized, interventional, single arm Phase 1/2 study, multicenter, global study of allogeneic stem cell transplantation of NiCord in patients with hematological malignancies. Once an optimally matched cord blood unit (CBU) was identified and the patient (or legal guardian) signed informed consent (IC), there were three phases of the study:

1. **Screening Phase:**

- Screening for available matched units in the public cord blood banking system

- The CBU was originally required to contain a pre-cryopreserved (post-processing), total CD34+ cell count of at least $10x10^6$, as well as a pre-cryopreserved (post-processing) total nucleated cell count of at least $1.8x10^9$, and a total nucleated cell dose of at least $1.8x10^7$ TNC/kg body weight. Beginning with protocol amendment (IV), the total CD34+ cell count requirement was lowered to $8x10^6$
- The selected CBU was then used to manufacture NiCord, which consisted of two fractions: a cultured fraction (CF) and non-cultured fraction (NF).
- The CF was comprised of CD133-selected cells that were cultured in the presence of nicotinamide and cytokines.
- The NF was comprised of the flow-through from the CD133 selection; it was cryopreserved after cell selection and reserved until the culture process was complete.

2. Conditioning Phase:

- The myeloablative conditioning regimen consisted of one of the following:
- Regimen A (Day -11 to -2): total body irradiation (TBI), Fludarabine (Flu) 160mg/m2.
- The TBI/Flu regimen was optionally supplemented with cyclophosphamide or Thiotepa
- Regimen B (Day -7 to -3): thiotepa 10 mg/kg, busulfan 9.6 mg/kg and fludarabine 150 mg/m2
- Regimen C (Day -5 to -2): clofarabine 120 mg/m2, fludarabine 40 mg/m2 and busulfan AUC 90 mg*h/L
- The GvHD prophylaxis regimen consisted of Mycophenolate Mofetil (MMF) and a calcineurin inhibitor (Tacrolimus or Cyclosporine).

3. Transplantation/ Follow-up:

- Beginning after the Screening Phase, the production site conducted ex vivo expansion and cryopreservation of NiCord CF + NF, which were shipped to the clinical site prior to transplantation on Day 0.

- NiCord CF was infused first, followed by NiCord NF.
- The first five patients transplanted under this protocol received fresh (non-cryopreserved) NiCord CF.
- The fresh NiCord CF was delivered to the transplant center on the day of transplant. Subsequent patients received cryopreserved NiCord CF.
- Post-transplant supportive care and follow-up were continued from Day +1 through Day +365.

Demographic and Other Baseline Characteristics

Most patients treated with NiCord were adults (18-63 years of age, n=34) and adolescents (12-17 years of age, n=2). The primary diagnoses were acute myelogenous leukemia (47%), acute lymphoblastic leukemia (25%), myelodysplastic syndrome (19%), chronic myelogenous leukemia (6%) and Hodgkin disease (3%).

Primary and secondary endpoints

Thirty-four of 36 NiCord recipients achieved neutrophil engraftment, defined as ANC by Day 42 post-transplant. The cumulative incidence of neutrophil engraftment at 42 days following transplantation was 94% for NiCord recipients. Among patients who engrafted, the median time to neutrophil recovery was 11.5 days (95% CI: 9-14 days) for NiCord recipients. For patients achieving platelet recovery, the median time to platelet recovery was 34 days (95% CI:32-42 days). The cumulative incidence of platelet engraftment at 100 days following transplantation was 81% for NiCord recipients.

Pharmacodynamics (Immune Reconstitution)

The results of immune reconstitution following treatment with NiCord are summarized in Table 1. The number of CD3+, CD4 + T cells and CD8 + T cells appear to increase from Day 70 to Day 180 and decrease at Day 365.

Table 1: Summary of Immune Reconstitution Results following Omidubicel Treatment (Median, inter-quartiles range, IQR: 25-75%) for P0301(Central Laboratory Testing)

Number of subjects (n)	Visit Days	CD3+ (cells / µL)	CD4+ (cells / µL)	CD8+ (cells / µL)	CD19+ (B cells) (cells / µL)	CD56+ (NK cells) (cells / µL)
n=4-9	14	ND	ND	ND	10.3 (8.1-29.0)	411.0 (153.0-752.0)
n=9-13	21	ND	ND	ND	47.7 (27.5-100.4)	1215.5 (580.3-3398.8)
n=10-18	42	94.0 (63.2-196.7)	45.2 (17.7-56.1)	8.8 (3.5-14.0)	112.2 (30.0-432.7)	1128.5 (478.0-2102.8)
(n=7-16)	70	117.8 (75.2-235.1)	63.9 (231.-98.7)	5.7 (3.7-39.0)	156.1 (39.3-541.9)	693.0 (466.5-831.0)
n=5-17	100	222.2 (122.8-278.5)	65.0 (53.3-197.2)	11.6 (4.7-84.0)	479.9 (51.7-660.9)	406.0 (238.0-773.0)
n=6-11	180	357.7 (222.1-660.8)	196.0 (148.4-257.6)	66.0 (41.6-123.7)	648.2 (273.5-979.1)	350.5 (270.3-526.8)
n=4-8	365	278.6 (79.7-675.8)	118.6 (23.6-231.9)	33.0 (2.3-191.1)	335.4 (154.3-925.5)	651.5 (442.8-1020.3)

ND = Not Determined

Source: summary-clin-pharm; Table 1.

Reviewer comments: The immune reconstitution (IR) results are highly variable but a trend in increasing number of CD3+, CD4 + T cells & CD8 + T cells from Day 70 to Day 180 was observed.

Dose-Efficacy Assessments

The dose of NiCord administered to the patients is summarized in Table 2. The median total CD34+ cell content of the cord blood unit prior to cryopreservation and NiCord expansion was 13.3 x 10^6 (range 8.1 -25.2 x 10^6). Following NiCord expansion, the CD34 content of the graft increased by 33-fold to a median 446.1 x 10^6 (range 159.1-1311.4 x 10^6) CD34+ cells. This resulted in a median CD34+ cell dose of 6.3 x 10^6/kg (range 1.4-14.9 x 10^6/kg).

The CD3+ T-cells in the NiCord graft were contained solely in the unexpanded, CD133 negative fraction. CD3+ T-cell content of the negative fraction was a median of 196.9x10^6 (range 67.9- 1404.5x10^6) resulting in a median CD3+ content of 2.4x10^6/kg (range 0.7-24.0 x10^6/kg).

For the 36 patients transplanted with NiCord, proportional sub-distribution hazard models were used to explore the relationship between cell characteristics and rate of ANC and platelet engraftment. There was no evidence of a relationship between total cell dose, cell dose/kg, CD34, or CD34/kg and neutrophil engraftment.

Table 2: Characteristics of NiCord Dose (median, range) Administered to Patients

	CBU selected for NiCord (pre-cryopreservation), N=36	**NiCord product (pre-cryopreservation), CF and NF; N=36**
Total viable nucleated cell count (x10^9)*	2.4 (1.8-3.6)	3.7 (2.3-7.8)
Total viable nucleated cell dose (x10^7/kg)*	2.9 (1.8-7.1)	4.9 (2-13.3)
$CD34^+$ count (x10^6)	13.3 (8.1-25.2)	446 (159-1311)
$CD34^+$ dose (x10^6/kg)	0.2 (0.1-0.4)	6.3 (1.4-14.9)
$CD34^+$ fold increase (CF)	-	33.0 (10-105)
$CD3^+$ count (x10^6) (NF)	-	197 (68-1405)
$CD3^+$ dose (x10^6/kg) (NF)	-	2.4 (0.7-24)

*Values are reported by the CBB and based on the total viable nucleated cell count and FACS analysis of CD34+ cells before cryopreservation.

Source: CSR Table 11-2; Listing 16.4.1

Reviewer comments: There was no obvious dose-response relationship explored by linear regression and hazard models, which may be due to the limited sample size. For more detail on dose-response analysis refer to the “Integrated dose-response analysis using combined data from P#0301/P#0501”.

7.2. Study#2- A Multicenter, Randomized, Phase III Registration Trial of Transplantation of Omidubicel (NiCord®), *Ex Vivo* Expanded, Umbilical Cord Blood-derived, Stem and Progenitor Cells, versus Unmanipulated Umbilical Cord Blood for Patients with Hematological Malignancies (#P0501)

The overall study objective of this study was to compare the safety and efficacy of Omisurge single *ex vivo* expanded CBU transplantation to unmanipulated CBU transplantation in patients with hematological malignancies following conditioning therapy. The primary objective was to assess the time to neutrophil engraftment following transplantation. The clinical pharmacology relevant secondary and exploratory endpoints include:

- Platelet engraftment by 42 Days following transplantation
- Time from transplantation to platelet engraftment
- Neutrophil engraftment by 16 and 42 Days following transplantation
- Immune reconstitution at 7,14, 28, 70, 100, 180, and 365 Days following transplantation

Overall Study Design: This study was designed as an open-label, controlled, multicenter, Phase 3 randomized study of transplantation of Omisurge versus unmanipulated cord blood unit (UCB) in patients (12 to 65 years of age) with hematological malignancies. The study was planned to randomize 120 patients to transplantation of Omisurge or unmanipulated CBU in a 1:1 ratio. The conditioning regimens used includes total body irradiation (TBI)//Flu/Thiotepa, TBI/Flu/±Cy and Thiotepa/Bu/Flu. Centers were required to commit to using the same conditioning regimen for all patients at the transplant center or according to primary diagnosis/age group. GvHD prophylaxis comprised tacrolimus or cyclosporine, and mycophenolate mofetil, with centers being required to commit to using the same calcineurin inhibitor for all patients at the transplant center starting three days before transplantation. Mycophenolate Mofetil and tacrolimus/cyclosporine were continued for a minimum of 60 days and 100 days following transplantation, respectively. All patients received

premedication prior to infusion which included diphenhydramine (or dexchlorpheniramine), hydrocortisone, and acetaminophen/paracetamol. All patients who were transplanted within 90 days post-randomization were followed weekly through Day 42 post-transplant and then at the designated study visits through Day 365 with final contact at 15 Months post-randomization for survival and relapse status.

Demographic and Other Baseline Characteristics

Demographics and baseline disease characteristics were well-balanced in the two arms. The median age of patients in the study was 40 years (range,13 - 62 years) for the Omisurge arm and 43 years (range, 13 - 65 years) for the UCB arm. The median bodyweight of patients in the study was 80 kg (range,43 – 134 kg) for the Omisurge arm and 77 kg (range, 46 – 133 kg) for the UCB arm. The study population was ethnically diverse, with over 40% identified as non-Caucasian. Acute leukemias (AML and ALL) were the most common indications for transplant, and most patients had moderate to high risk disease.

Neutrophil Engraftment

Neutrophil engraftment was evaluated as part of:

- Primary endpoint: time to neutrophil engraftment following transplantation
- Exploratory endpoints: neutrophil engraftment by 16 days and 42 days following transplantation

The median time to neutrophil engraftment was 12 days for the Omisurge group, and 22 days for the unmanipulated CBU group, which is shorter in the Omisurge group by 10 days ($p<0.001$). A secondary analysis of the primary endpoint stratified by disease indicated that the difference in time to neutrophil engraftment was still statistically significant ($p<0.001$) when stratified by disease.

For exploratory endpoints, 81% of the patients treated with Omisurge achieved neutrophil engraftment by Day 16 compared to 23% treated with unmanipulated CBU ($p<0.001$). Also, 96% of patients who received Omisurge achieved successful neutrophil engraftment

by 42 days post-transplant, compared to 89% of patients who received unmanipulated CBU.

Platelet Engraftment

Platelet engraftment was defined as the first day of three consecutive measurements on different days with platelet count > 20 $\times 10^9$/L in the absence of platelet transfusions in the preceding seven days. Platelet engraftment was evaluated as part of:

- Secondary endpoint: platelet engraftment by 42 days following transplantation
- Exploratory endpoint: time from transplantation to platelet engraftment

The percentage of patients achieving platelet engraftment by Day 42 was 55% (n=34) in those randomized to receive Omisurge compared to 35% (n=22) in those randomized to receive unmanipulated CBU. Among the patients achieving engraftment, the median time to platelet engraftment in patients treated with Omisurge was 34 days (range, 21-180 days), compared to 42 days (range, 21-120 days) in patients treated with unmanipulated CBU.

Immune Reconstitution (IR)

For the IR sub-study (n=37), the Omisurge group received a median CD3+ dose of 1.8 x 10^6 cells/ kg (range,1.2 – 7.6) and the UCB group received a median of 6.0 x 10^6 cells/ kg (range, 1.7– 10.2). Overall, Omisurge-treated patients were transplanted with a T cell dose that was approximately 70% less than that of patients transplanted with UCB. The results of IR analysis (central lab. data) for CD3+, CD4+ and CD8+ T cells are summarized in Table 3. The CD4+ and CD8+ T cells are significantly higher in the Omisurge group on Days 7 and 14 than the UCB, which suggests early immune recovery. The CD4+ and CD8+ cells are similar in the two arms from Day 21 to 1 year for both groups (Table 3). The results of NK cell (CD56+) analysis demonstrated that the Omisurge group showed more rapid recovery during the first three weeks after transplant. After one month, NK reconstitution is similar in the UCB and Omisurge groups. B-cell (CD19+) results seem to be similar between the Omisurge and UCB groups in the first month with slightly higher levels of B-cells for Omisurge treated subjects from Day 28 through Day 365.

Table 3: Summary of CD3+, CD4+ and CD8+ T cells (central lab. data study#0P051)

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

Reviewer comments: The IR analysis using central laboratory were based on a small sample size and the data demonstrated higher variability. It should be noted that although significantly higher early IR (Day 7 and 14) was observed for the Omisurge group vs the UCB group, the IR results at Day 7 &14 are generally a minute amount of the overall immune recovery that was observed over the 1 year period. These IR values are also lower than the normal reference ranges for lymphocyte subsets[3]. The overall trend of delayed IR is consistent with previous observation in the setting of UCB[4]. Per an FDA information request the applicant discussed potential sources of variability and conducted

[3] ABIM (2022). American Board of Internal Medicine, Laboratory Test Reference Ranges, January 2022.
[4] Danby and Rocha (2014). Improving engraftment and immune reconstitution in umbilical cord blood transplantation. Front. Immunol., 24 February 2014

additional comparability analysis between central and local laboratory IR data. The correlation coefficient between central vs local lab. was ≥0.7. The following is a summary of potential sources of IR variability discussed by the applicant:

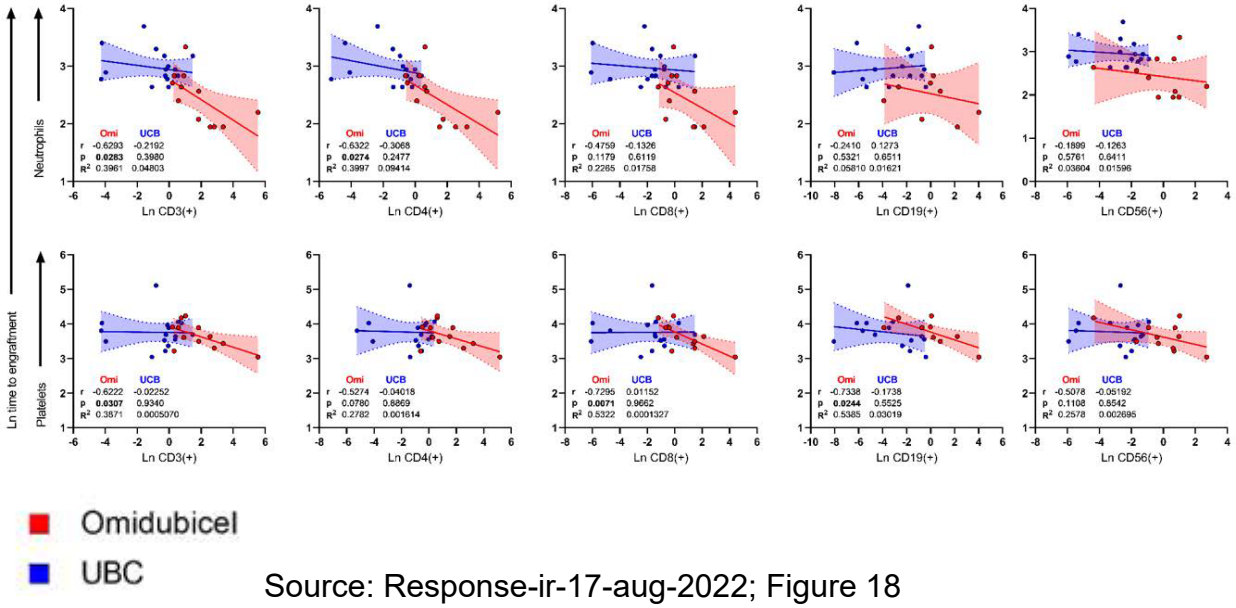
- Variability in infused total nucleated cells and CD34+ cells
- Patient demographics (e.g., age range from 13 to 65 years and bodyweight range from 43 to 134 kg)
- Disease characteristics and variability in conditioning regimens
- Assay related variability

Also, the applicant performed an IR analysis using combined data obtained from #P0301 and #P0305 studies using central and local lab. data. IR analysis of the combined data showed similar results with the #P0501 study with a small reduction in variability.

Immune Reconstitution-Efficacy Assessment:

The IR-efficacy relationship was evaluated to see if rapid lymphocyte immune reconstitution correlates with faster neutrophil and platelet engraftment in patients transplanted with Omisurge vs patients transplanted with UCB. In the case of Omisurge, but not of UCB, statistically significant correlations were identified between CD3+ and CD4+ T cells and faster neutrophil engraftment times (Figure 2, upper panel). Similar data were also observed for CD3+, CD8+ T cells and CD19+ B cells and faster platelet engraftment times (Figure 2, lower panel).

Figure 2: Early Lymphocyte Subsets Reconstitution Patterns (Day 7) Correlate with Faster Neutrophil and Platelet Engraftment for Patients Transplanted with Omisurge



Source: Response-ir-17-aug-2022; Figure 18

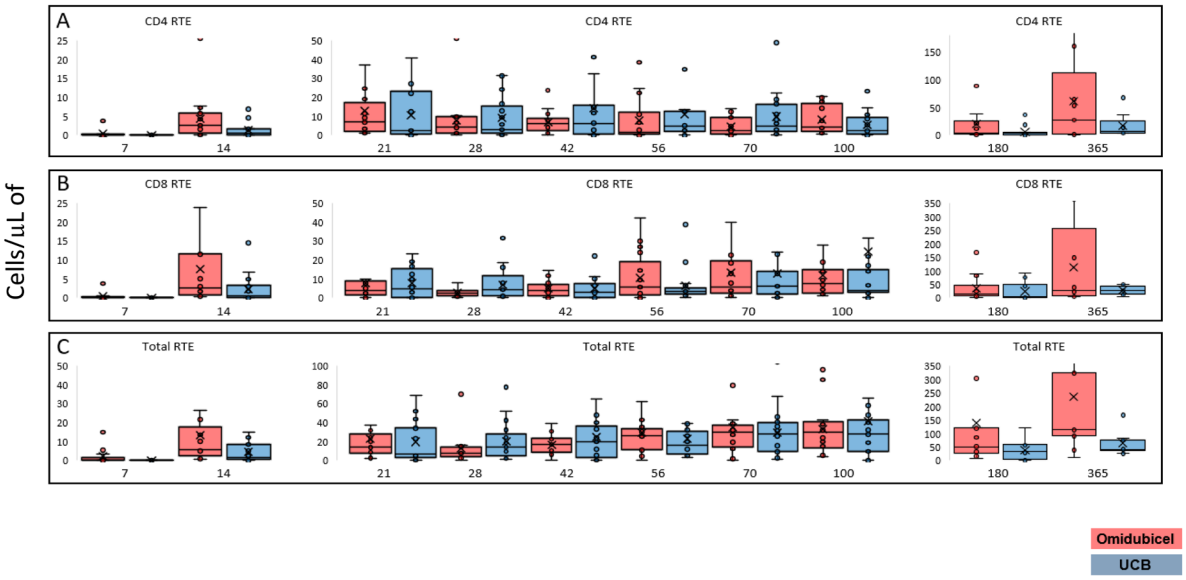
Quantitative Assessment of Thymopoiesis

Thymopoiesis, the process of thymocyte maturation into mature T cells in the thymus, involves the rearrangement of T-cell receptors (TCRs). During TCR rearrangement, excised DNA fragments create circular DNA byproducts known as TCR excision circles (TRECs). TREC detection in the peripheral blood stream is an indication that a rearrangement process has occurred and serves as a surrogate marker for thymopoiesis. (b) (4) were used to detect RTEs and quantify TREC, respectively.

(b) (4) (Figure 3) for the detection of RTEs and (b) (4) (Figure 4) for quantification of TREC, demonstrated the long-term kinetics of T cell reconstitution following transplantation with omidubicel. Patients treated with omidubicel and UCB have similar RTE (CD8+ and CD4+) and TREC results at 3, 6 and 12 months (Figure 3& 4) that demonstrates T cells recovery, peripheral expansion of the infused CD3 cells after

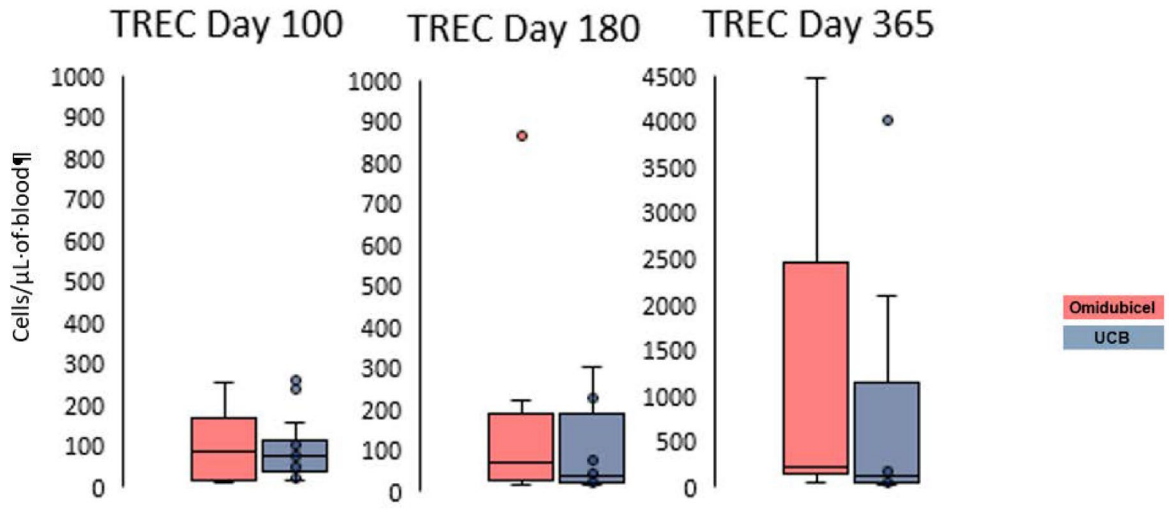
transplantation and a gradual progressive buildup of the de novo T cells (RTE and TREC), for both graft sources.

Figure 3: CD4+, CD8+ and Total Recent Thymic Emigrants (RTEs) Reconstitution over First-Year Post-Transplantation



Box plots (median, box: IQR,whiskers: full range excluding outliers - 1.5 times the IQR limits)
A: CD4+ RTE reconstitution days 7 through 365 post-transplantation
B: CD8+ RTE reconstitution days 7 through 365 post-transplantation
C: Total RTE (CD4+ and CD8+ combined) reconstitution days 7 through 365 post transplantation. Source:
Source: Response-ir-17-aug-2022; Figure 9

Figure 4: T-Cell Receptor Circles (TREC) Outcomes at 100 - 365 days Post-Transplantation



Source: Source: Response-ir-17-aug-2022; Figure 10

Dose-Response Assessment

I. **Cell Dose Range used for Transplantation**:

The cell doses administered to Omisurge and unmanipulated CBU recipients was evaluated by:

- Total nucleated cell counts (TNC) and TNC per kg
- CD34+ cells counts and CD34+ cells per kg
- CD3+ cell counts and CD3+ cell per kg

The decisions on the selection of CBUs are based on specific histocompatibility data, cell dose, availability, and in some cases the source of the CBU. Eligible CBUs for the study were required to meet HLA match and cellular requirements. The HLA match and cellularity parameters (TNC, TNC/kg, CD34, CD34/kg) were similarly distributed among the treatment groups in both the ITT population and the treated population.

As shown in Table 4, the total nucleated cell counts following expansion are only about 1.3-1.8-fold higher than the CBU TNC counts, either in comparison to the CBUs selected for Omisurge, or in comparison to the CBUs selected for unmanipulated CBU

transplantation. However, the total CD34 counts of Omisurge following expansion are over 40-fold higher than the CD34 counts of the CBU before expansion, or of the unmanipulated CBUs, demonstrating the stem and progenitor cell enrichment afforded by the expansion process.

Patients treated with Omisurge received a graft containing a median of 9.0 $\times 10^6$ CD34 cells/kg, compared to 0.3 x 10^6 CD34 cells/kg in the patients treated with unmanipulated CBU. Thus, although the total nucleated cell doses of Omisurge are like unmanipulated CBU, Omisurge recipients received a substantially higher dose of CD34+ cells than unmanipulated CBU. On the other hand, patients treated with Omisurge were infused with a lower number, and dose of CD3+ lymphocyte cells. The CD3+ lymphocytes in Omisurge are derived from the Omisurge NF. As a result of the manufacturing process manipulations and freeze-thaw cycles, the CD3+ dose of the Omisurge NF is lower than in a unmanipulated CBU transplantation. The median CD3+ cell dose in Omisurge was 3×10^6 cells/kg, compared to 4.6×10^6 cells/kg in the unmanipulated CBUs. The median CD3+ cell count in Omisurge was 210×10^6 cells, compared to 413×10^6 cells in the unmanipulated CBUs (Table 4).

Although a lower infused lymphocyte dose may have been associated with impaired immune system recovery, the study data did not raise any concerns. Immune reconstitution data from Omisurge transplantation demonstrated multilineage recovery of immune cells in the weeks following transplant, which was at least comparable to the unmanipulated CBU group (see results of IR and dose-IR relationship). These results indicate that the lower CD3+ dose in Omisurge did not increase the risk of impaired immune recovery following transplantation.

Table 4: Cell Dose Used for Transplantation for Omisurge and UCBU Treated Patients (#P0501)

	Omisurge				UCBU[b] (Total)
	Cord Blood Bank Results		Production Results[a]		
	N	Median (Range)	N	Median (Range)	Median (Range)
Weight for CBU selection (kg)	52	80 (43-132)	52	80 (43-132)	73 (49-135)
Total viable nucleated cell count ($\times 10^9$ cells)	48	2.2 (1.6-3.4)	52	3.9 (1.2-10.2)	2.9 (0.8-6.5)
Total viable nucleated cell dose ($\times 10^7$ cells/kg)	48	2.9 (1.8-6.9)	52	4.7 (1.7-12.4)	3.4 (1.3-8.0)
Total CD34+ cell count ($\times 10^6$ cells)	52	14.0 (8.6-39.6)	52	655 (280-3900)	15.8 (0.2-46.4)
Total CD34+ cell dose ($\times 10^6$ cells/kg)	52	0.2 (0.1-0.5)	52	9.0 (2.1-47.6)	0.2 (0.0-0.8)
Total CD3+ cell count ($\times 10^6$ cells)	NA	NA	52	210 (71–640)	413 (4.4-990)
Total CD3+ cell dose ($\times 10^6$ cells/kg)[e]	NA	NA	52	3.0 (1.1-12.4)	4.6 (0.0-14.8)

[a]Certificate of Analysis values; values are from the end of production prior to cryopreservation. Source: CSR; Table 26

II. Dose-Immune reconstitution Assessments

To address whether different cellular components measured in Omisurge during the production process correlate with early lymphocyte reconstitution, patterns in the raw data from the # P0501 immune reconstitution sub-study were examined, and Pearson's correlation analysis of the log transformed datasets was conducted. Computation of correlation assumes that variables are normally distributed. Since biological samples commonly distribute in a lognormal fashion, all datasets underwent log transformation based on the natural logarithm. Following calculation of Pearson's correlation coefficient

(r), linear regression models were fitted including determination of the threshold significance (α=0.05) and goodness of fit (R^2) parameters as accepted. For this analysis, the following Omisurge intrinsic cellular parameters were included:

- the total number of viable cells (TNVC) in both the Cultured Fraction (CF) and Non-cultured Fraction (NF),
- CD34+ progenitor cells (in the CF) and CD3+ lymphocytes (in the NF).

Since early immune reconstitution is relevant to the clinical context, these intrinsic cellular parameters were evaluated with respect to the five common lymphocyte subsets measured in the peripheral blood of transplanted patients seven days following transplantation, namely: CD3+, CD4+, CD8+, CD19+ and CD56+ cells. Statistically significant correlations between cellular elements from the CF, and specifically between the CD34(+) cell content, and the reconstitution of T-cells (CD3+, CD4+ and CD8+ cells) and Natural Killer (NK) cells were identified (Figure 5).

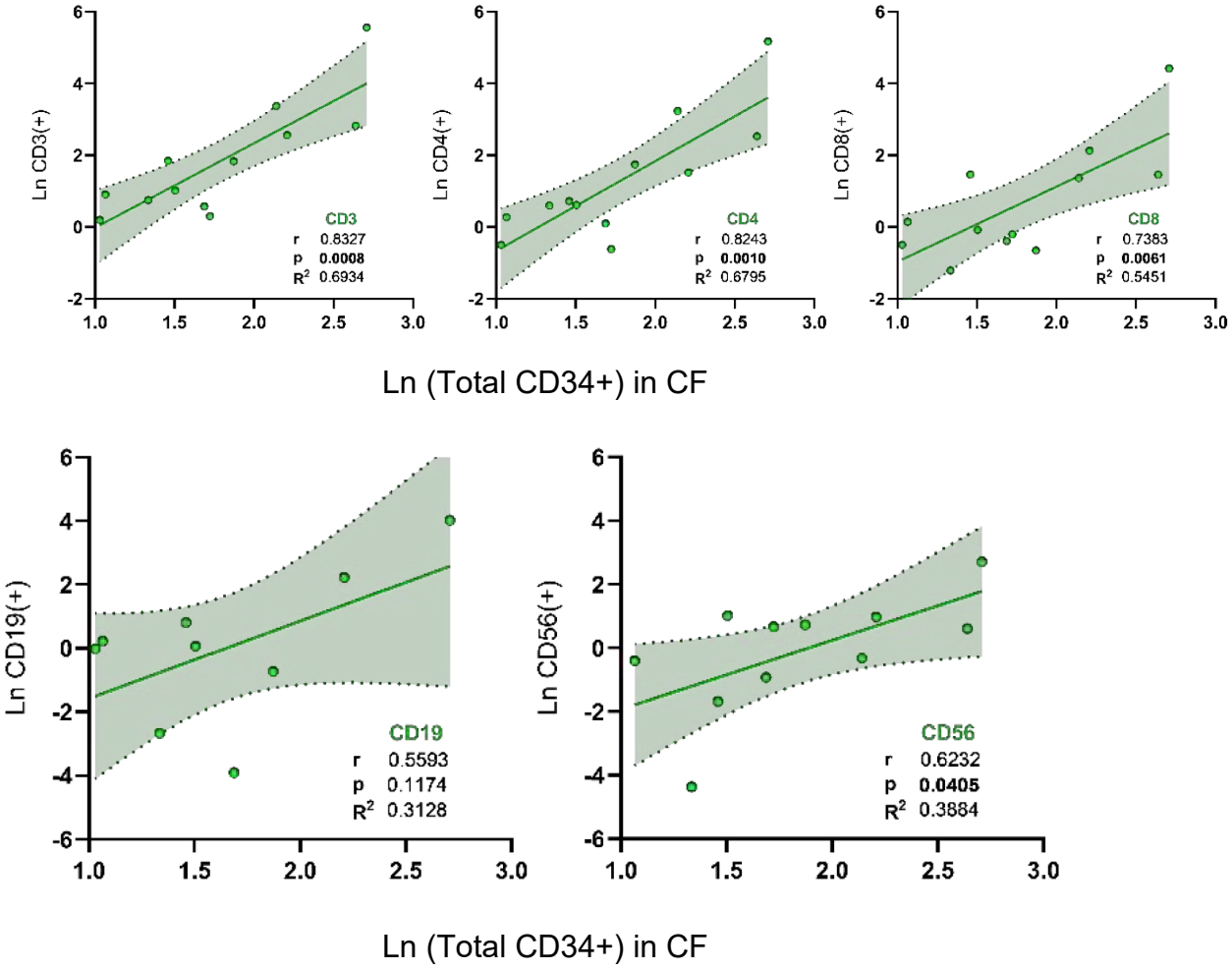
III. Dose-Efficacy Assessments:

Dose-efficacy assessment was conducted using the linear model between cell characteristics and days to neutrophil or platelet engraftment. Cell characteristics analyzed were TNC, TNC dose (TNC per kilogram), CD34+ cell count, and CD34+ cell dose (CD34+ cells per kg). In addition to a model including only the cell characteristic as a covariate, an additional model containing age was also analyzed. If the linear model had a significant association between engraftment and the cell characteristic, further models were used based on survival analysis methodology; these models included those participants who were censored or had competing risks. Both proportional subdistribution hazard models and cause-specific hazard models were utilized. A statistically significant association was defined as $p<0.05$ for the test of significance of the cell characteristic parameter estimate.

The linear regression models showed a significant association between each cell characteristics tested (TNC, TNC/kg, CD34, and CD34/kg) and the days to neutrophil engraftment. Days to neutrophil engraftment decreased with an increase in TNC and CD34+ cells (Figure 6). These results were consistent with the models based on survival

analysis. However, the results were not significant for the linear models based on days to platelet engraftment and cell characteristics (Table 5).

Figure 5: Dose-Dependent Correlations between the CD34+ Cell Content in the Omisurge CF and Early Reconstitution of T and NK cells in Omisurge Transplanted Patients



Dots represent actual day 7 data and lines represent the linear regression models. Dashed lines represent the 95% confidence interval of the linear regression models. Source: Response-ir-17-aug-2022; Figure 17

Reviewer comments: Per FDA request, the applicant conducted more detail dose-response analysis using combined data from P#0301 (n=31 subjects) and P#0501 (n= 53 subjects). The objective of the integrated dose-response analysis was to evaluate the relationship between cell dose and efficacy (e.g., day to neutrophil engraftment). The summary of the parameter estimates for the cell characteristic from the model with no additional covariates using the joint data are shown in Tables 5. The linear regression models showed a significant association between each cell characteristic tested (TNC, TNC/kg, CD34, and CD34/kg) and the days to neutrophil engraftment based the combined data from P0301/P0501. Days to neutrophil engraftment decreased with an increase in TNC and CD34+ cells.

The following are summary results of reviewer dose-response analysis of the combined data (P#0301 and P#0501).

- The median (min, max) CD34 dose was 7.25x10^6 cells/kg (1.5x10^6, 47.6x10^6 cells/kg)
- The median (min, max) neutrophil engraftment day was 13 days (7, 35 days) and 8 days (6, 20) for subjects who received lower and higher than the median CD34 dose, respectively (Figure 7).
- The median (min, max) TNC was 4.8x10^9 cells/kg (1.9x10^9, 10.2x10^9 cells/kg)
- The median (min, max) neutrophil engraftment day was 13 days (6, 35 days) and 9 days (6, 20) for subjects who received lower and higher than the median TNC dose, respectively (Figure 8).

Following discussion with the clinical team and for consistency with the clinical primary efficacy evaluation, we also preformed additional dose- efficacy analysis of the Phase 3 study (P#0501) using updated data for days to neutrophil recovery (i.e., without considering chimerism). The following is a summary of the dose-efficacy analysis using days to neutrophil recovery:

- A significant negative correlation ($p<0.05$) was observed between cell dose parameters (TNC, TNC/kg, CD34 cells, CD34 cells/kg) and neutrophil recovery.

- The median (min, max) time to neutrophil recovery was 13 days (7, 35 days) and 8 days (6, 20) for subjects who received lower and higher than the median CD34 cells/kg, respectively.
- The median (min, max) time to neutrophil recovery was 12.5 days (6, 35 days) and 8 days (6, 20) for subjects who received lower and higher than the median TNC per kg, respectively.
- Overall, the dose-efficacy analysis using neutrophil recovery is consistent with the results of neutrophil engraftment.

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

- Primary graft failure occurred in two subjects who received lower than the median dose of CD34 cells/kg.
- The median (Min, Max) CD34 cells/kg ($x10^6$) in subjects with and without primary graft failure was 4.9 (4,5.8) and 10.3 (2.1, 47.6), respectively.
- There was no statistically significant relationship between dose and disease relapse (Table 6&7).

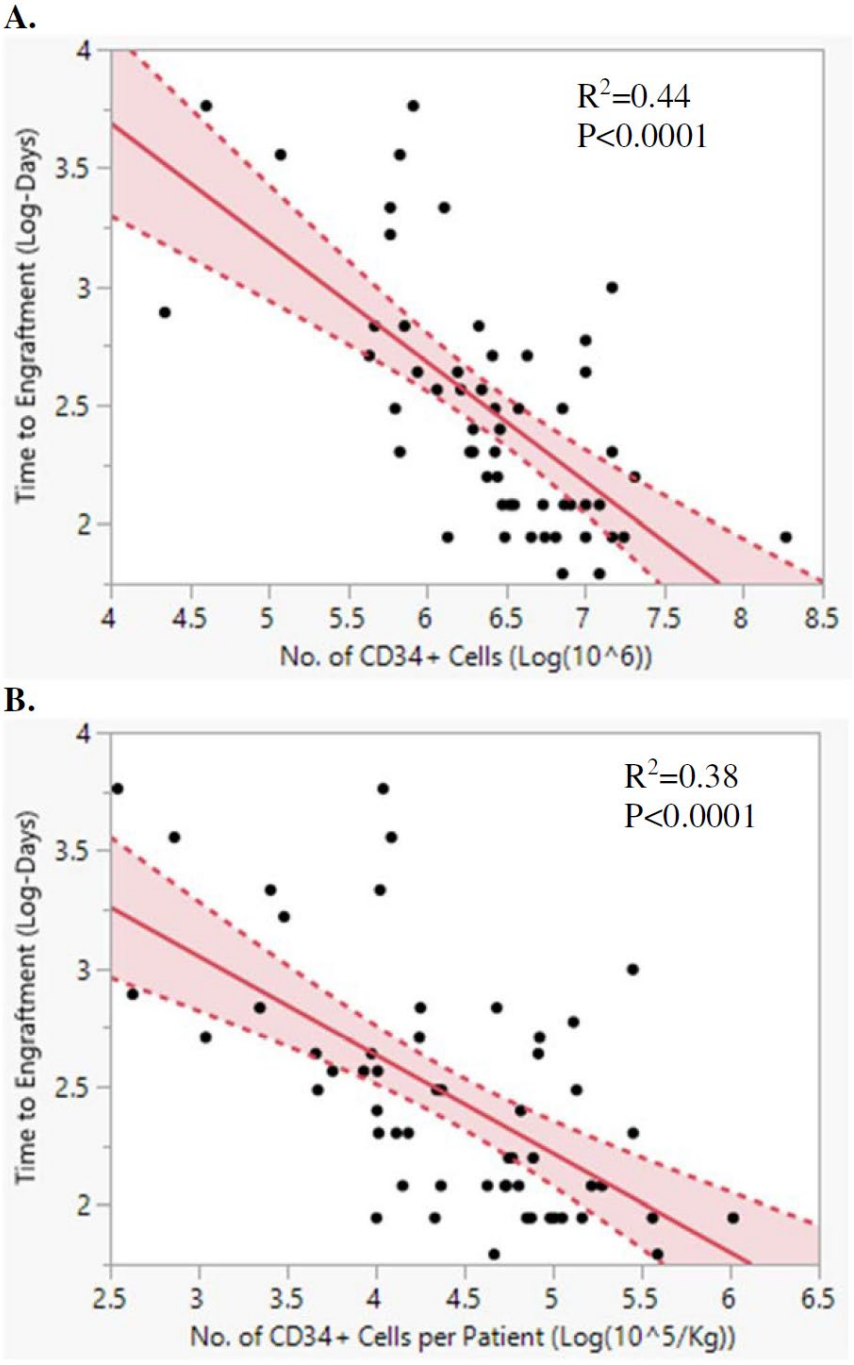
Dose-safety assessment was evaluated based on cell characteristics and adverse events such as acute graft versus host disease(aGvHD) and chronic GvHD(cGvHD). Acute GvHD usually presents around the time of engraftment and manifests as maculopapular rash, nausea, vomiting, abdominal pain, diarrhea, or increased serum bilirubin. Chronic GvHD is usually diagnosed later throughout the first year post-transplant. Clinical manifestations of cGvHD include a scleroderma-like or lichen planus- like skin involvement, gastrointestinal ulcerations, and sclerosis of the gastrointestinal (GI) tract, and increased bilirubin. For Omisurge treated subjects, no statistically significant relationship was identified for cell dose vs aGvHD or cGvHD ($P > 0.1$). The TNC dose and CD34 cell dose are essentially comparable between subjects with or without aGvHD/cGvHD (Table 6 & 7).

Table 5: Summary of linear regression model parameter estimates for dose-response analysis using combined data from P0301 and P0501 studies

	Parameter Estimate	95% Lower Confidence Limit	95% Upper Confidence Limit	Pr > |t|
Neutrophil Engraftment				
Total viable nucleated cell count	-5.918	-9.44	-2.40	0.001
Total viable nucleated cell/kg	-3.728	-6.32	-1.13	0.005
CD34 cell count	-4.347	-6.33	-2.36	<.001
CD34 cell /kg	-3.448	-5.17	-1.73	<.001
Platelet Engraftment				
Total viable nucleated cell count	-12.162	-28.37	4.04	0.139
Total viable nucleated cell/kg	-7.773	-19.69	4.14	0.197
CD34 cell count	-7.717	-17.33	1.89	0.114
CD34 cell /kg	-6.366	-14.68	1.95	0.131

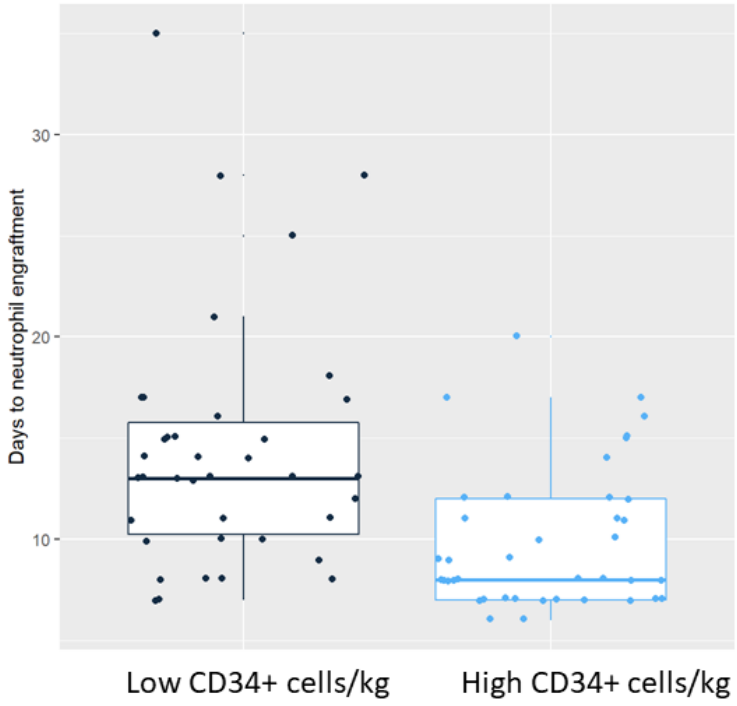
Source: Response-ir-17-aug-2022; Table 49,53,57,61,66,68,70 and 72.

Figure 6: Correlation of CD34+ Total Cell Count or Cell Dose per Kg with Time to Neutrophil Engraftment of Omisurge Treated Patients (combined data from P0301 and P0501)



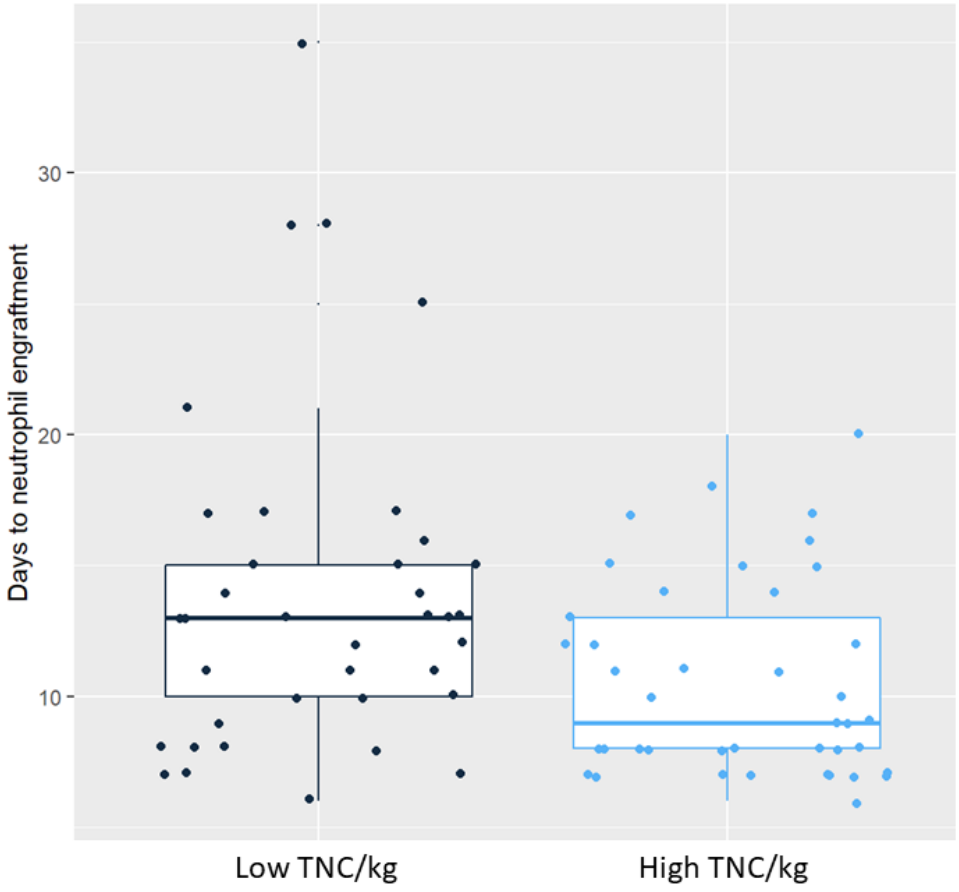
Source: CSR; Figure 23

Figure 7: Time to Neutrophil Engraftment of Omisurge Treated Patients with Lower and Higher than Median Dose of 7.25 x10^6 CD34+ cells/kg (combined data from #P0301 and #P0501)



Source: Reviewer analysis

Figure 8: Time to Neutrophil Engraftment of Omisurge Treated Patients with Lower and Higher than Median Dose of 4.8 x10^9 Total nucleated cells (TNC)/kg (combined data from P0301 and P0501)



Source: Reviewer analysis

Table 6: Summary of Median (Min, Max) CD34 dose per kg (x10^6) in subjects with or without adverse events

	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)	-

*Only two subjects with primary graft failure. Source: Reviewer analysis

Table 7: Summary of Median (Min, Max) TNC dose per kg (x10^7) in subjects with or without adverse events

	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)	-

*Only two subjects with primary graft failure. Source: Reviewer analysis