SYNOPSIS

<table>
<tr><td colspan="3">NAME OF IND SPONSOR:
Gamida Cell Ltd.</td></tr>
<tr><td colspan="3">NAME OF STUDY DRUG:
NiCord</td></tr>
<tr><td colspan="3">Title of Study: 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.</td></tr>
<tr><td>Study Chairs:</td><td>Mitchell E. Horwitz, MD
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Hospital Universitario y Politecnico La Fe</td></tr>
<tr><td colspan="2">Publication (ref.):</td><td>Horwitz, M., et al. (2018). Phase I/II Study of Stem-Cell Transplantation Using a Single Cord Blood Unit Expanded Ex Vivo With Nicotinamide. Journal of Clinical Oncology. 37. JCO.18.00053. 10.1200/JCO.18.00053.</td></tr>
<tr><td colspan="2">Study Period:
(date of first enrollment): August 21, 2013
(date of last completed): June 29, 2018</td><td>Phase of Development:
Phase I/II</td></tr>
<tr><td colspan="3">Primary Objective(s):
• Assess the cumulative incidence of NiCord-derived neutrophil engraftment at 42 days following transplantation.
• Assess the incidence of secondary graft failure at 180 days following transplantation of NiCord</td></tr>
<tr><td colspan="3">Methodology: Multicenter, global, single arm study</td></tr>
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Number of Patients (planned and analyzed):

Planned: The original planned sample size estimated that 10 patients would be necessary to adequately assess graft function and safety of NiCord as a stand-alone graft source, and to confirm previous clinical experience. The sample size was increased twice: first to 20 patients (Amendment I) and then to 40 evaluable patients (Amendment IV), in order to broaden the clinical experience with NiCord and characterize safety and efficacy at multiple transplant centers.

Analyzed: All patients (N=38) who received NiCord as either a stand-alone graft or in combination with a second unmanipulated cord blood unit (UCBU) were analyzed. The majority of analyses in this report focus on the 36 patients who received NiCord as a stand-alone graft. A separate description of some of the safety endpoints is included for two patients who were transplanted with a NiCord product that failed to meet the release specifications, together with a UCBU.

Diagnosis and Main Criteria for Inclusion:

Patients were 12-65 years of age with high risk hematologic malignancies including acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML) chronic myelogenous leukemia (CML), myelodysplastic Syndrome (MDS), or lymphoma. with history of International Prognostic Scoring System (IPSS) risk category of INT-1 or greater.

Patients were to have a partially HLA-matched cord blood unit (CBU) meeting the cell count criteria for production of NiCord: total $CD34^+$ cell count of $\geq 8x10^6$ pre-cryopreserved total nucleated cell count of $\geq 1.8x10^9$, and total nucleated cell dose $\geq 1.8x10^7$ TNC/kg. Patients were required to meet medical requirements for hematopoietic stem cell transplantation, including appropriate cardiac, pulmonary, renal, and hepatic function. Key exclusion criteria included diagnosis of some lymphomas, CLL, CMMoL, or fibrotic bone marrow; previous allogeneic transplant, active infections or other comorbidities, or the availability of an 8/8 matched donor.

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Test Product, Dose and Mode of Administration:

The first five patients transplanted on this protocol received a NiCord product produced at Lonza in Walkersville, Maryland according to the manufacturer's SOPs. For these patients, the NiCord Cultured Fraction (CF) was shipped to the clinical site fresh (not cryopreserved) on the day of transplantation. The NiCord Non-cultured Fraction (NF) was shipped to the clinical site in a calibrated cryoshipper 2-4 days prior to transplant and kept frozen until immediately prior to transplant. An infusion solution, used to thaw and dilute the NF was shipped along with the CF.

Subsequent to the first five patients, NiCord was produced at Gamida Cell in Jerusalem, Israel according to the manufacturer's SOPs. Prior to transplantation, NiCord CF and NF (both cryopreserved) were shipped together under quarantine status with all available CBU segments and necessary documentation to the clinical site in a cryoshipper equipped with a calibrated data logger. The infusion solutions for NiCord CF and NF were delivered to the clinical site, in parallel with the cryopreserved products, in a 2-8°C shipper.

Thawing and dilution of the CF (where applicable) and NF was performed by the clinical site's personnel according to the Sponsor's SOP immediately prior to its infusion. The final volume of NiCord CF after thawing and reconstitution was 100 ml. The final volume of NiCord NF after thawing and reconstitution was 50 ml.

For all patients, NiCord CF was infused first, followed immediately (up to 1 hour) by the NF. The CF and NF were infused via the patient's central venous catheter as per site practice. Infusion of NiCord CF and NiCord NF targeted a rate of 5 cc/kg/h with a maximal rate of 10 cc/kg/hr. NiCord CF and NiCord NF were infused as soon as possible after thaw.

For the fresh NiCord CF, original release specifications required that the CF contain $\geq 0.12 \times 10^9$ total viable nucleated cells and at least 7% $CD34^+$ cells. For the cryopreserved NiCord CF, beginning with protocol amendment II, release specifications required that the CF contain $\geq 1.2 \times 10^9$ total viable nucleated cells and at least 7% $CD34^+$ cells and NiCord NF was required to contain $\geq 0.5 \times 10^9$ total viable nucleated cells. Beginning with protocol amendment IV, release specifications for the NiCord CF were lowered to $\geq 0.8 \times 10^9$ total viable nucleated cells and NiCord NF was required to contain $\geq 0.4 \times 10^9$ total viable nucleated cells.

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Duration of Treatment: A single infusion of NiCord CF and NF were administered. For the fresh NiCord CF, total duration of infusion would not exceed a maximum of 4 hours from end of thaw to end of infusion, while considering the minimal infusion time specified in the product's Certificate of Analysis (CoA). For the cryopreserved NiCord CF, total duration of infusion targeted a maximum of 2 hours from end of thaw to end of infusion, while considering the minimal infusion time specified in the product's CoA. Total duration of NiCord NF infusion would not exceed 1 hour from end of thaw to end of infusion, while considering the minimal infusion time specified in the product's CoA. The minimal infusion time was calculated based on the actual endotoxin test result and the endotoxin limit of 5 EU/Kg weight/60 minutes.
Reference Therapy, Dose and Mode of Administration, Batch Number: Not Applicable

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CRITERIA FOR EVALUATION:

The Primary Efficacy Endpoint was the cumulative incidence of neutrophil engraftment, defined as the proportion of patients achieving engraftment at 42 days following transplantation.

Secondary efficacy endpoints included:

- Time from infusion to neutrophil engraftment
- Time from infusion to platelet engraftment
- Cumulative incidence of platelet
- Overall Survival (OS)
- Non-Relapse Mortality (NRM)

The exploratory efficacy endpoint described in the original protocol was immune reconstitution assessed on days 70, 100 and 180 days by lymphocyte subset analysis.

- Additional exploratory efficacy endpoints not included in the original protocol and assessed in comparison with the CIBMTR registry included:
- Disease free survival (DFS), defined as the proportion of patients alive, not lost to follow up, and not relapsed, as assessed at 180 days, 1 year, and 2 years post-transplant.
- Relapse, defined as above in Secondary endpoints
- Primary Hospitalization, defined as the number of days in the hospital from the day of transplant.
- Days alive and out of hospital in the first 100 days

The primary safety endpoint is the incidence of secondary graft failure at 180s.

Secondary safety endpoints are:

- Incidence of acute GvHD grade II-IV and III-IV at 100 days
- Chronic GvHD
- Safety and tolerability of NiCord transplantation

Statistical Methods:

Population Analyzed: The primary population used for efficacy and safety analyses in this report is the NiCord Population (NP), defined as all patients who received NiCord as a stand-alone transplant. The NP was also used for comparison to the CIBMTR cohort.

Safety listings and some safety analyses in this report include both the NP and the NiCord Plus Unmanipulated cord (NPU) population, the latter of which consists of patients who received a NiCord unit that did not meet specifications along with an unmanipulated CBU.

The original protocol designated the intent to treat (ITT) population, defined as all patients who entered the study and were transplanted with either NiCord, an unmanipulated CBU, or both, as the principal cohort for primary and secondary efficacy analyses.

The original protocol also defined a per protocol (PP) population, which included all patients who met eligibility criteria, received NiCord and no other stem cells through day 28, did not die prior to day 21, received protocol-specified myeloablative conditioning, and did not receive NiCord that did not meet the final process quality controls (FPQC)

The NP was considered the most clinically relevant population for the assessment of the utility of NiCord in transplantation, and therefore the analysis of this population superseded those of the original populations defined in the protocol.

Data reporting cutoffs: The efficacy analyses in this report are based on data obtained through a cutoff date of November 16, 2017. At that time, all 36 NP patients had been enrolled and had completed at least 6 months of follow-up. All 36 were evaluable for the endpoints of neutrophil and platelet engraftment, and 32 (89%) had been followed for least one year or until death. These analyses represent the final analyses for efficacy in this study.

In order to provide a longer follow-up for assessment of toxicity after transplantation with NiCord, the safety analyses in this report are based on data obtained through August 2, 2018, at which time all surviving patients had completed at least one year of follow-up.

Statistical Methodology: Endpoints are described using counts, proportions, and percentages for categorical endpoints and using medians and ranges for numeric endpoints. Incidence and time to engraftment are estimated along with 95% confidence intervals using cumulative incidence curves. An age-adjustment was used for cumulative incidence for neutrophil engraftment (recovery) and platelet engraftment when compared with CIBMTR data, due to the differences in the age distributions between the two sources. The Van Elteren test was used to test for differences among time to engraftment. Survival and disease-free survival were estimated using the Kaplan-Meier method. Differences between treatment groups were tested using the log-rank test. Relapse differences with the CIBMTR data were tested using a Cox model and Fine-Gray model. Differences in days alive and out of hospital in the first 100 days were tested using the Van Elteren test. Fine-Gray models and Cox models were used to explore the relationship between recovery/engraftment and cell characteristics.

Results:

Efficacy:

This single arm study explored the efficacy and safety of NiCord as a standalone graft for allogeneic transplantation in 36 patients with hematologic malignancies.

Neutrophil engraftment was achieved in 94% of patients in a median of 11.5 days in patients transplanted with NiCord, comparing favorably to published data with standard cord blood and to a cohort of patients selected from the CIBMTR. In the CIBMTR comparison cohort of 146 standard cord blood recipients, neutrophil engraftment was achieved in 85% of patients in a median of 21 days.

Neutrophil engraftment was more rapid in NiCord recipients. Among patients who engrafted, the median time to neutrophil recovery was 11.5 days (95% CI: 9-14 days) for NiCord recipients and 21 days (95% CI: 20-23 days) for the CIBMTR comparator cohort ($p<0.001$ by van Elteren test).

Platelet engraftment was also more rapid among NiCord recipients. For patients achieving platelet recovery, the median time to platelet recovery was 34 days (95% CI:32-42 days) and 46 days (95% CI:42-50 days) for NiCord and the CIBMTR comparator cohort, respectively ($p<0.001$ by van Elteren test).

The age-adjusted cumulative incidence of platelet engraftment at 100 days following transplantation was 81% for NiCord recipients, and 63% for the CIBMTR comparator cohort.

Overall survival for NiCord recipients was 80% (95%CI, 63%-90%) at 6 months and 51% (95% CI, 33%-67%) at 1 year post transplant.

The unadjusted 2-year probability of overall survival for NiCord recipients was 51% (95% CI, 33%-67%) and 48% (95% CI, 40%-56%) for the CIBMTR comparator cohort ($p=0.72$).

Median CD4 recovery for the NiCord population was 159 cells/uL (range 50-442) and 287 cells/uL (range 40-847) at 100 and 180 days respectively.

The 2-year probability of disease-free survival for NiCord recipients was 43% (95% CI, 24%-61%) and 45% (95% CI, 37%-53%) for the CIBMTR cohort ($P=0.77$). With adjustment for both age and disease-risk index, there was no difference in disease-free and overall survival between the two cohorts.

The unadjusted 2-year cumulative incidence of relapse for NiCord recipients was 33%. Relapse for NiCord recipients was not statistically different from the CIBMTR cohort when compared using a Cox model ($p=0.11$), but higher when compared using a Fine-Gray model ($p=0.04$).

NiCord recipients spent a median of 73 days (range; 0-85 days), and CIBMTR standard cord blood recipients spent a median of 57 days (range; 0-92 days) alive and out of hospital during the first 100 days post transplant. This difference was statistically significant ($p<0.001$) using the Stratified Wilcoxon (Van Elteren) test.

Overall, neutrophil engraftment was rapid and robust in patients transplanted with NiCord, associated with lower treatment-related mortality and reflecting improved recovery following transplantation.

Safety:

The cumulative incidence of secondary graft failure in the 36 NiCord recipients was 2.8% (95% CI: 0.2-12.6%) at 6 months and was 5.6% (95%CI: 1.0-16.6%) at 1 year post transplant.

Two patients had secondary graft failure in the year following NiCord transplant, both in the setting of viral infection.

The incidence of acute GvHD grade II-IV at 100 days post NiCord transplant was 44.4% (95% CI: 27.7-59.9). This was numerically lower than that observed in CIBMTR controls (56% [95% CI, 47% to 64%]), although the Fine-Gray model HR was nonsignificant (HR, 0.7; P = .20).

Similarly, for grade 3-4 acute GvHD, the cumulative incidence of at 100 days post-transplant was 11% (95% CI:3-24) for the NiCord population and 27% (95% CI: 20-34) for CIBMTR controls, and the Fine-Gray HR was nonsignificant (HR, 0.4; P = .09).

Fifteen (42%) NP patients had chronic GvHD in the year following NiCord transplant. Five cases of chronic GvHD were extensive while the other ten were limited.

The cumulative incidence of chronic GvHD was 30.6% (95% CI: 16.3-46.1) at 6 months post-transplant and 41.7% (95% CI:25.1-57.4) at 1 year post transplant. The cumulative incidence of chronic GvHD at 1 year post transplant was 40% (95% CI: 24-57) for the NiCord population and 29% (95% CI: 22-36%) for the CIBMTR controls. When classified as mild, moderate, or severe according to the National Institute of Health consensus grading criteria, the cumulative incidence of moderate or severe chronic GvHD was 10% at one and two years post-transplant for both the NiCord population and the CIBMTR controls (95%CI: 2-24% and 6-16% respectively). None of the differences in chronic GvHD were statistically significant at the $p<0.05$ level.

At least one treatment-emergent adverse event was reported in all patients, and serious adverse events were reported in 92% of patients. Overall, 40% of patients had a treatment-emergent AE that was related to the study drug, and 42% had a treatment-emergent death.

28 (78%) of patients had an adverse event within 24 hours of NiCord infusion. Most events were grade 1 or 2. There were no grade 4 or 5 toxicities, and 3 patients had a maximum grade 3 toxicity, which included atrial fibrillation, hypertension, pain and mucositis. There were 15 patients with a maximum grade 2 toxicity, and 10 patients had a maximum grade 1 toxicity.

The most common adverse event within 24 hours was hypertension, reported in 10 patients. Other events included pain (7 patients), mucositis (6 patients), changes in cardiac rhythm (6 patients), hypoalbuminemia (6 patients), nausea (5 patients), anorexia (4 patients), hypokalemia (4 patients) and hypomagnesemia (4 patients).

Two infusion toxicities (grade 2 serious infusion-related hypersensitivity and grade 3 non-serious hypertension) were reported. Grade 3-5 adverse events were reported in 34 patients (94%). The most common system organ classes (SOCs) for grade 3-5 events were metabolism and nutrition disorders (44%), infections and infestations (44%), general disorders and administration site conditions (42%) and vascular disorders (39%). The most common events by preferred term (PT) were hypertension (36%), nausea (28%) and decreased appetite (25%). The most common adverse events attributed to NiCord were GvHD and transplant failure.

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Grade 3-5 treatment-emergent AEs related to NiCord were reported in 25% of NP patients; 19% had GvHD events, and 6% had transplant failure.

Ninety-five SAEs were reported in 34 NP patients (94%). The majority of the events were associated with initial or prolonged hospitalization (74%). After 24 hours post transplant, the only events determined by the Medical Monitor to be related to NiCord were GvHD and primary graft failure events. There were no serious unexpected suspected adverse reactions (SUSARs). The most common SAES were infections (47% of patients), GVHD (31% of patients) and relapse (22%).

Sixteen deaths were reported the 36 NiCord recipients (44%) were reported. The most common primary causes of death were disease recurrence/persistence (n=8), infection (n=4), GvHD (n=2), interstitial pneumonia (viral) (n=1) and cardiogenic shock (n=1).

Overall, the frequency and nature of adverse events and deaths reported in patients treated with NiCord were similar to those reported in patients undergoing allogeneic stem cell transplantation following myeloablative therapy and did not suggest toxicity attributable to NiCord.

The overall risks of cord blood administration following a cytotoxic conditioning regimen can be serious and fatal. The potential risks associated with any HSCT, and as defined for cord blood in particular, include death, infusion reactions, GvHD and graft failure. Adverse events experienced by NiCord recipients in this study were consistent with the expected toxicities of allogeneic stem cell transplantation following conditioning therapy.

Conclusions:

Prompt and robust engraftment of neutrophils is the first and critical step on the way to hematopoietic recovery following stem cell transplantation. This study is the first to show that an expanded umbilical cord blood unit can be infused as a stand-alone graft and is capable of providing robust, durable hematopoiesis. This study provides data demonstrating that transplantation of NiCord is safe and effective in reducing the time to hematopoietic recovery, thus decreasing transplant-related morbidity and time in the hospital.

Date of the Report: 20 June 2019