SYNOPSIS

Title of Trial: A multi-center, multi-national, historical cohort-controlled study to evaluate efficacy and safety of transplantation of StemEx®, umbilical cord blood stem and progenitor cells expanded *ex vivo*, in subjects with hematologic malignancies following myeloablative therapy

Trial Number: GC P#02.01.001

Trial Period (years): 1 October 2007 to 20 February 2012 (day 180 / visit 22; follow-up of subjects up to 2 years is ongoing)

Number of Patients: 126 patients screened, 101 patients enrolled and 101 patients treated

Number of Centers: 36 participating centers 25 enrolling centers (US 14, Israel 3, Italy 1, Hungary 1, Spain 6)

Phase of Development: II/III

Trial Objectives and Endpoints:

The primary and secondary endpoints of the study were established in the original study design and were not subsequently modified.

Primary Efficacy Objective and Endpoint: The primary objective was to assess the effect of StemEx single expanded umbilical cord blood (UCB) transplantation in comparison with the double umbilical cord blood transplant (DUCBT) 2006-2010 historical control group on overall 100-day mortality, with the endpoint defined as the proportion of overall mortality at 100 days.

Secondary Efficacy Objectives and Endpoints: Secondary efficacy objectives were to assess the effect of StemEx transplantation in comparison with the contemporaneous DUCBT 2006-2010 control group on the following endpoints:

- Time from infusion of UCB cells to overall mortality at 100 days.
- Proportion of overall mortality at 180 days.
- Time from infusion of UCB cells to overall mortality at 180 days.
- Proportion of subjects who developed acute GvHD (aGvHD) grades III-IV.
- Proportion of subjects with neutrophil engraftment failure.

Supportive Efficacy Endpoints: The following endpoints and analyses were added in the last protocol amendment, prior to data lock and analysis, in parallel to the introduction of

the 2006-2010 historical control group, to complete the picture of the effect of StemEx on early engraftment and its relation to mortality:

- Proportion of subjects with delayed (>60 days) or failed platelet engraftment.
- Combined early graft function: proportion of subjects with early neutrophil engraftment (≤20 days) and early platelet engraftment (≤60 days).
- Relationship of early engraftment to mortality.

Exploratory Efficacy Endpoints: The exploratory efficacy endpoints include time to neutrophil and platelet engraftment, as well as additional explorations of the relationships of graft characteristics to clinical outcomes. The efficacy comparison of the effect of StemEx transplantation to the original historical control group (1995-2005) was originally designed as the primary analysis for the study, and was moved to exploratory in the last protocol amendment, in parallel to the introduction of the 2006-2010 historical control group as the main comparator for the study, see Section 1.

Safety and Tolerability Objectives: To assess the incidence and frequency of adverse events and acute toxicity, laboratory data and vital signs during treatment follow-up.

Trial Design and Population: This multi-center, multi-national, historical cohort-controlled study was designed to evaluate the efficacy and safety of transplantation of StemEx, umbilical cord blood stem and progenitor cells expanded *ex vivo* from a fraction of the UCB unit (UCBU) and transplanted with the remaining unmanipulated fraction, i.e., administered in a single UCBU configuration, in subjects with hematologic malignancies following myeloablative therapy. Because of the duration of the study recruitment (over 4 years) and developments in the approach to UCB transplantation and patient management, the original historical control group from the years 1995-2005 was updated to the more contemporaneous control group from the years 2006-2010, in order to ensure comparison of StemEx to the current standard of care.

The original 1995-2005 historical control group (n=514) and the 2006-2010 historical control group (n=295) comprise subjects who received cord blood transplantation following myeloablative therapy, registered with one of two international cord blood registries: CIBMTR, Milwaukee, Wisconsin; and Eurocord, Paris, France. The 1995-2005 historical control group contains also records from the New York registry (NCBP), the reporting from which was later done through CIBMTR. Subjects received single UCBT (1995-2005 control group) or double UCBT (2006-2010 control group) and were selected to meet eligibility criteria similar to those required of the StemEx-treated subjects.

Statistical and Analytical Methods: For the final efficacy analysis, a test for superiority of StemEx over control was performed. The test was one-sided at a significance level of 0.025. The primary analysis tested the log odds ratio of 100-day mortality for StemEx versus Control. The null and alternative hypotheses were: $H_0 : \beta=0$ versus $H_1 : \beta<0$. The overall one-tailed 2.5% level test is equivalent to a two-tailed 5% significance level,

except that there was no formal final test that StemEx compares unfavorably to Control for the primary endpoint (protection against this event is provided by the safety and futility analyses). In this document, the two-sided p-value will be quoted; both two-sided and one-sided p-values are quoted only for the primary analysis of the primary endpoint.

For further details, see Section 2.4.

Summary and Conclusions

Data analysis was performed according to the amended SAP. Based on this analysis, the primary endpoint was statistically significant demonstrating a 100-day mortality of 15.8% for the StemEx patients vs. 25.4% for the 2006-2010 historical control population (p=0.035).

The statistical significance and magnitude of the day 100 overall survival results supported by improved early graft function provide substantial evidence of effectiveness and clinical benefit. By improving the short term outcomes of UCBT, StemEx may extend the use of umbilical cord blood as a graft source and allow more patients to be treated with allogeneic hematopoietic stem cell transplantation.

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