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| **Proposal No.: *1016*** | | **Study Identifier: BIOR-025-IMD** |
| **Investigational product** | | BioR flex BBS (CE marked system for leucodepletion of red cell concentrates)  CompoFlex 4F RCC pediatric bags (CE marked phtalate-free bags for the storage of units destined to pediatric transfusion). |
| **Indication** | | -- |
| **Tentative title** | | **BORN Study**  **Umbilical or adult donor RBC to transfuse extremely low gestational age neonates. A randomized trial to assess the effect on ROP severity.** |
| **Marketing authorization for product in affected country(ies) of trial conduct:** | | **YES  NA  No** |
| **Trial proposer / Department or Region** | | Serena Borghi R&D filter IT / Fabio Remondi EMEA |
| **Study type** | | Clinical trial phase 2/3 (Blinded, prospective, interventional randomized, controlled) |
| **Sponsorship** | | IIT |
| **Study hypothesis**  In extremely low gestational age neonates (ELGANs) transfusion of cord blood red blood cell concentrates (CB-RBC) effectively prevents or restrains the fetal hemoglobin (HbF) loss consequent to adult donor standard transfusions (A-RBC).  The study hypothesis is: transfusing CB-RBCs instead of A-RBC may lower the incidence of severe retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD), in ELGANs needing transfusions. | | |
| **Scientific rationale**  Extremely low gestational age neonates (ELGAN, i.e., born before 28 gestation weeks) are among the most heavily transfused pediatric patients. In this clinical setting, repeated RBC transfusions independently predict a poor outcome, with a higher risk for mortality and morbidity.  Recent studies highlighted a close association between low levels of fetal hemoglobin (HbF) and severity of retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD), two disabilities that frequently complicate preterm birth.  In preterm neonates, the switch of the synthesis from HbF to adult hemoglobin (HbA) occurs around their due date, i.e., several weeks after the premature birth.  In normal prenatal life, developing organ and tissues are exposed exclusively to HbF until last weeks of gestation. When preterm neonates receive transfusions, their tissues are abruptly exposed to high levels of HbA.  Moreover preterm neonates have a highly immature antioxidant reserve and both ROP and BPD rely on the oxidative damage as underlying mechanism. In comparison with HbA, HbF is endowed with higher oxygen affinity, greater redox potential, higher tetrameric stability, and higher ability to generate unbound nitric oxide, all functions potentially protective in presence of an oxidative challenge.  Lee, E. Y., Kim, S. S., Park, G. Y. & Lee, S. H. Effect of red blood cell transfusion on short-term outcomes in very low birth weight infants. Clin. Exp. Pediatr.63, 56–62 (2020).  Crawford, T. M., Andersen, C. C., Hodyl, N. A., Robertson, S. A. & Stark, M. J. The contribution of red blood cell transfusion to neonatal morbidity and mortality. Journal of Paediatrics and Child Healthvol.55 387–392 (2019).  Ghirardello, S. et al. Effects of Red Blood Cell Transfusions on the Risk of Developing Complications or Death: An Observational Study of a Cohort of Very Low Birth Weight Infants. Am. J. Perinatol.34, 88–95 (2017).  Wang, Y. C.et al. Red Blood Cell Transfusion and Clinical Outcomes in Extremely Low Birth Weight Preterm Infants. Pediatr. Neonatol.58, 216–222 (2017).  Keir, A. et al. Adverse effects of red blood cell transfusions in neonates: a systematic review and meta-analysis. Transfusion56, 2773–2780 (2016).  dos Santos, A. M. N. et al. Red blood cell transfusions are independently associated with intra-hospital mortality in very low birth weight preterm infants. J. Pediatr.159, 371-376.e1–3 (2011). | | |
| **Cost estimation**  75.000€ | | |
| **Additional information** | | |
| **Ethical/business risk** | **Low  Medium  High** | |
| **Rationale**  *I indicated the ethical risk as medium because of :*  *- the highly critical patients, whose mortality is high*  *- the use OFF LABEL of BioR flex BBS*  *a.* ***BioR flex BBS*** *is a safe and of well established efficacy product intended for removal of leucocytes from red blood cells.*  *The product will be used OFF LABEL because it will be applied on CORD BLOOD instead of adult blood, for the same purpose: removal of leucocytes.*  *b.* ***CompoFlex 4F RCC*** *non DEHP paediatric minibags are applied within their intended use.*  *Minibags have been tested for storage up to 14 days of SAGM-LD-RBC (from adult blood)*  *Risks for OFF LABEL use have been extensively reviewed and have been find all acceptable:*  *1. filtration of CORD BLOOD is less critical than filtration of RCC because of the lower processing volume (70-100ml instead of 300ml), the lower HCT (35% instead of 65%)*  *2. collection, filtration and RCC preparation procedures have been set by the SPONSOR. Leucodepleted (LD)-RBC in SAGM stored in non DEHP minibags have been investigated by the main quality indicators. All indicators were positively evaluated. Data have been published at ISBT2021.*  *3. Residual WBC, hematocrit, and red cell mass recovery of Cord Blood (CB)-RBC units after filtration and hemolysis rate in CB-RBC units will be determined before distribution.*  *The subjects are extremely fragile. They will be treated according to the standard of care, in terms of need and frequency of transfusions.*  *The study is a no- profit investigator-initiated trial supported by Fresenius Kabi. Support from Fresenius Kabi consists of providing to participating centers transfusion devices (including filters, bags, Compomat G5 blood separator and assistance for CB-RBC fractionation) and financial contribution to cover the costs of the insurance policy of enrolled patients and of study management.*  *Fresenius Kabi has no responsibility in any pre-clinical or clinical decision or action.*  *The responsibility rests solely to the Sponsor and Investigator for any clinical aspect.*  *The study is a Blinded, prospective, interventional randomized, controlled trial. Sample size has been established based on primary outcome (development of ROP). It is described in §4.1 of the protocol.*  *The products in use (BioR flex BBS and CompoFlex 4F RCC) are not compared with similar or equivalent products.* | | |
| **Assessment completed by:** | *Serena Borghi, PhD*  *R&D Sr Director Filter, Mirandola* | |

**This page will be completed by the Global Trial Committee**

**(Date of GTC meeting/assessment:      /     /     )**

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| **Comments:**  General   * Does the A-RBC group also use or filters and bags? That was not completely clear from the protocol. I think, the procedures and used material should be as similar as possible in both groups (TdV) * Confusing use of the terms “phase 2” and “phase 3”: The study is defined as “phase2/3”in *Study Design*-section of the synopsis. This suggest that the term is used in the sense of phase of clinical development program. Later in the *Outcome*-section it seems that different phases in the sense of periods of the study conduct (primary outcomes belong to phase 2 and 3 while secondary outcomes belong to phase 3) are meant. And in the *Statistical Aspect*’s section (4.4) the term phase is used to describe the periods of something like a *group-sequential* or *adaptive* design with an interim analysis. Please clarify the use of the term “phase”! (CGl)   Study outcomes   * Imprecise secondary outcomes (2.4.2):   “*Median HbF threshold predicting severe ROP and BPD at 32 and 36 weeks of PMA.*” A median value that predicts something other (ROP etc.) could (maybe) be the result of statistical analysis but would not be a *study outcome*. Actually, “median” is a parameter that belongs rather to descriptive statistics. (CGl)   * Median number of days without transfusion between either CB-RBC or A-RBC transfusions. Is this an outcome or a predictor? I.e. does the number of days without transfusion depend on the treatment group (CB-RBC vs. A-RBC). Or do other outcomes depend on the number of day with or without transfusions of CB-RBC vs. A-RBC? Please make sure, that treatment and outcome (i.e. cause and effect) are not mixed-up. (CGl)   Inclusion/exclusion criteria   * Should patients with a generally low life expectancy be excluded? (TdV)   Formal   * “*…which occurs before…*” The phrase “*…which occurs before…*” is used frequently during the CSP if the occurrence of two events is analyzed. I suggest that “*…which occurs first…*” would be more appropriate. (CGl)   Statistics   * Restrictions of randomization:   + “*In case of unavailability of an ABO/Rh matched CB-RBC unit, patients in arm B receive A-RBC.*” (2.6 INTERVENTION DESCRIPTION)     - This sentence is used twice in the paragraph.     - This is a deviation from the randomization schedule, which very important in clinical trials! Can be excluded that no bias is introduced by this “work-around”?  Maybe, it is better to exclude patients if no matching CB-RBC-treatment is available… Maybe, such exclusion introduce more bias than the current rule… Reconsider this approach. (CGl)   + “*Twins will be assigned to the same arm.*” (3.1. TREATMENT ALLOCATION AND RANDOMIZATION) Are there any ethical or medical reason for providing uniform treatment to twins that justify a deviation from the randomization schedule? From a statistical point of view it would be better if twins are divided to both treatment groups because this would improve the comparability of treatment groups. (But I would not recommend a violation of the randomization schedule for this reason.) I recommend avoiding any modification of randomization. (CGl) * 4.1. SAMPLE SIZE: (all CGl)   + Please consider revise wording: “…Incidence (Severe ROP | *~~Untreated~~* *A-RBC*) > Incidence (Severe ROP | *~~Treated~~* *CB-RBC*)…” The control group is not *untreated* but treated with an active treatment (*A-RBC*).   + There is a blurred description of several stages of testing: First assessment of safety and then – if safety is okay – efficacy… If something like adaption of study design or sample size is intended this mandatorily requires clear and comprehensive a-priori planning in the study protocol.   + Sample size estimation for the assessment of safety: The combination of a higher α-level of 0.01 with an unusually low Power of 70% does not make sense. (I cannot verify the sample size result itself because I did not find a table with h-values for Power=70%.)   + Sample size estimation for the assessment of efficacy:     - My recalculation (with the h-value table of my very old teaching book) of sample size results in 2\*49 patients instead of 2\*31.3 for α=5% and Power=80%.     - I disagree with the “mortality correction” of sample size. Drop-out due to death is currently considered only for one treatment group but mortality is likely to occur in both groups.     - “…sample size of 146 subjects (73 per arm)…” 72 subjects in total had been derived in the previous sentences of this sections. Hence, doubling of sample size is not appropriate. * 4.2. STATISTICAL ANALYSIS   + A clear definition and description of the primary analysis / hypothesis is needed.   + The primary (and secondary) efficacy analyses should consider *gestational age*! This baseline characteristic had been descripted as having a strong impact on ROP-rates in the sample size section. Hence, its impact on study results should be controlled. This could be done by using categories of gestational age as a stratification factor of the Cochran-Mantel-Haenzel-test. (CAVE! According to the sample size section *center* is already used as a stratification factor.)   + Confusing text about “phase II and phase III”…   + “The association between median HbF and incidence of prematurity-associated diseases or infections is investigated by logistic regression analysis and expressed as an odds ratio with a relative 95% confidence interval (95% CI). The AUC method is used to identify which is the best predictive value.” I do not understand the meaning of “median HbF” within this statistical approach. The median is a statistical parameter to summarize a set of values (e.g. from a sample of patients). If you want to do use HbF as a predictor for the incidence of diseases or infections than you need individual HbF-data for each patient but no summarized data. Hence, median HbF conflicts with the idea of prediction. (Nevertheless, there are reasonable and appropriate possibilities to use medians in this situation. But this should be described in a comprehensible way.)  What is intended with the AUC method? How shall a predictive value be defined by this method? Which (clinical) variable shall be used as a predictor? * 4.3. ANALYSIS SETS (CGl) Reconsider the usage of the *“treated” set*. This is likely to be similar to the *“intention to treat” set*, hence such analyses might not be fruitful. Usually a *Per-Protocol set* (excluding all patients with major protocol deviations) is used to contrast the analyses of the *“intention to treat” set*. * 4.4. ANALYSIS PLAN (CGl) An interim analysis should be planned more carefully. Otherwise the integrity of the study could be compromised.   + Statistical tests must be adapted to the interim analysis, i.e. α-levels at interim and final analyses must be adapted.   + Procedures to maintain the blind of treatment allocation must be defined (e.g. the interim analysis should be conducted by an *independent data monitoring committee*) | | | | |
| **Approval:** | **Rejected** | **Pending** | | **Approved** |
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| **Further actions required:** | | | | |
| Copy to  CEO Fresenius Kabi  President of Fresenius Kabi division  Resp. president of Fresenius Kabi region  Resp. BU head  CSO  Resp. heads of submitting department  Resp. regional medical and/or scientific head  Resp. BU medical and/or scientific head  Trial proposer  Global Sourcing Manager (if applicable)  Global Vigilance (EU-QPPV) | | | Date (dd/mmm/yyyy)  \_\_\_\_\_/\_\_\_\_\_\_\_\_\_/\_\_\_\_\_  \_\_\_\_\_/\_\_\_\_\_\_\_\_\_/\_\_\_\_\_  \_\_\_\_\_/\_\_\_\_\_\_\_\_\_/\_\_\_\_\_  \_\_\_\_\_/\_\_\_\_\_\_\_\_\_/\_\_\_\_\_  \_\_\_\_\_/\_\_\_\_\_\_\_\_\_/\_\_\_\_\_  \_\_\_\_\_/\_\_\_\_\_\_\_\_\_/\_\_\_\_\_  \_\_\_\_\_/\_\_\_\_\_\_\_\_\_/\_\_\_\_\_  \_\_\_\_\_/\_\_\_\_\_\_\_\_\_/\_\_\_\_\_  \_\_\_\_\_/\_\_\_\_\_\_\_\_\_/\_\_\_\_\_  \_\_\_\_\_/\_\_\_\_\_\_\_\_\_/\_\_\_\_\_  \_\_\_\_\_/\_\_\_\_\_\_\_\_\_/\_\_\_\_\_ | |

**Study proposal reviewed and assessed by the GTC:**

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<Name/function> Signature Date