ATTACHMENT NO. 3

Information for the patient

(*The terms used in this attachment are of a general nature and are not the same as those defined in paragraph 1 of the GTC)*

1. What are stem cells? What is their potential?

Stem cells are the primary and unspecialised cells of the human body. According to current medical knowledge, they are distinguished by their unlimited or almost unlimited dividing capacity within a given cell type and by their ability to reconstitute blood cells or potentially other tissues. There is a constant process of apoptosis in the body, which is the death of cells. What allows tissues to be rebuilt are stem cells. Initially universal, it is only during successive divisions that they specialise to form differentiated cell types. The extraordinary properties of stem cells account for their enormous potential. Even today, transplantation of stem cells from umbilical cord blood is already used to treat many diseases. Numerous and diverse clinical trials are underway for the use of these cells in so-called regenerative medicine - in children with autism, cerebral palsy, patients after strokes, trauma and burns. It is still unclear where their potential ends, which makes them undoubtedly a great hope for medicine.

2. **Why is it worth to obtain stem cells from umbilical cord blood?**

Unlike bone marrow, peripheral blood and adipose tissue stem cells, those derived from umbilical cord blood are obtained in a non-invasive manner after the cord separation. Contrary to popular belief, the umbilical cord blood is not taken from the child - if not collected, it would become medical waste. Umbilical cord blood collection is a quick, painless procedure that does not require anaesthesia. The properties of cord blood-derived haematopoietic stem cells most closely resemble those of bone marrow-derived haematopoietic stem cells. However, they have a greater proliferative potential, longer telomeres, and a greater capacity to produce certain cytokines.

The primary purpose of obtaining stem cells and the subsequent collection, processing, storage, release, distribution is to be able to be put to a targeted therapeutic use by an authorised medical practitioner in an authorised treatment facility, i.e. for transplantation into a recipient for autologous or allogeneic haematopoietic reconstitution in a therapy with proven efficacy based on EBM (evidence-based medicine) criteria).

In addition, the aim is also to use a specific type of advanced therapy product (ATMP) manufactured by a qualified pharmaceutical manufacturer as part of a therapeutic experiment in case of a hospital-exemption advanced therapy medicinal product (HE-ATMP) under the full responsibility of a physician and as an investigational ATMP in the context of a clinical trial from which an advanced therapy medicinal product (ATIMP) is prepared.

Cells from umbilical cord blood can be used in both autologous (donor is the recipient) and allogeneic (for another recipient) transplants. For allogeneic transplants, an appropriate donor and recipient match in terms of HLA (Human Leukocyte Antigen) compatibility is required. Tissue incompatibility between donor and recipient can result in either a rejection reaction of the transplanted cells or graft-versus-host disease (GvHD). The risk of such reactions is lower when umbilical cord blood-derived cells are used, as umbilical cord blood lymphocytes are less mature and less immunologically competent. Therefore, in allogeneic stem cell transplants from umbilical cord blood, lower HLA compatibility is accepted and therefore finding a donor is easier.

3. Why is it important to obtain placental blood as well?

The number of stem cells that are obtained from umbilical cord blood is limited. An opportunity to increase this number and at the same time make full use of the available material is to additionally obtain blood from the placenta, immediately after birth. This allows an additional portion of stem cells to be obtained. The collection of placental blood, like the collection of umbilical cord blood, is a safe and non-invasive procedure. The cells collected from the placenta are frozen separately from the cells collected from the umbilical cord blood and can be used without compromising the primary deposit. The composition and use of umbilical cord blood and placenta-derived blood are identical. The collection of cells from the placenta provides an opportunity to increase the use of stored cells and flexibility in the allocation of the frozen deposit.

4. What diseases can be treated with umbilical cord blood stem cells?

Transplantation of stem cells from umbilical cord blood has already been used since 1988 to treat a number of haematopoietic diseases, both malignant (e.g. leukaemias, lymphomas) and those associated with bone marrow failure (aplastic anaemia) or immune disorders. It should be emphasised that in case of cancer and diseases with a known genetic basis, allogeneic transplantation, where the recipient receives cells from another donor (e.g. the patient's sibling), is used far more frequently. Treatment using cells from umbilical cord blood is also used in diseases such as type 1 diabetes or ischaemic strokes. In recent years, there has been intensive research into the use of stem cells from umbilical cord blood in so-called regenerative medicine, using the patient's own (autologous) cells. Most research concerns diseases of the nervous system such as autism, cerebral palsy, brain and spinal cord injuries. The administration of stem cells from umbilical cord blood can lead to inhibition of the pathological inflammatory process, has immunomodulatory effects, inhibits apoptosis (a type of cell death), induces cell migration, proliferation and differentiation, and stimulates angiogenesis (formation of new blood vessels).

A list of diseases for which stem cells can be used can be found at the website of nOvum: www.novumbank.com

See below for a list of particularly interesting and recent scientific publications:

Autism:

- Simhal AK, Carpenter KLH, Kurtzberg J, Song A, Tannenbaum A, Zhang L, Sapiro G, Dawson G. *Changes in the geometry and robustness of diffusion tensor imaging networks: Secondary analysis from a randomized controlled trial of young autistic children receiving an umbilical cord blood infusion*. Front Psychiatry. 2022 Oct 20;13:1026279. doi: 10.3389/fpsyt.2022.1026279. eCollection **2022**.
- *White Matter Tract Changes Associated with Clinical Improvement in an Open-Label Trial Assessing Autologous Umbilical Cord Blood for Treatment of Young Children with Autism*. Carpenter KLH, Major S, Tallman C, Chen LW, Franz L, Sun J, Kurtzberg J, Song A, Dawson G. Stem Cells Transl Med. 2019 Feb;8(2):138-147. doi: 10.1002/sctm.18-0251. Epub **2019** Jan 8.
- *Safety and Observations from a Placebo-Controlled, Crossover Study to Assess Use of Autologous Umbilical Cord Blood Stem Cells to Improve Symptoms in Children with Autism*; Michael Chez, Christopher Lepage, Carol Parise, Ashley Dang-Chu, Andrea Hankins, Michael Carroll; Stem Cells Translational Medicine, Volume 7, Issue 4, April **2018**, Pages 333–341, https://doi.org/10.1002/sctm.17-0042.
- Dawson G, Sun JM, Davlantis KS et al. *Autologous cord blood infusions are safe and feasible in young children with autism spectrum disorder: Results of a single-center phase I open-label trial*. STEM CELLS TRANSLATIONAL MEDICINE **2017**;6:1332–1339.

Safe administration:

- *Intrabone infusion for allogeneic umbilical cord blood transplantation in children*. Stephanie Vairy, Isabelle Louis, Marie-France Vachon, Johanne Richer, Pierre Teira, Sonia Cellot, Edith Villeneuve, Elie Haddad, Michel Duval & Henrique Bittencourt; Bone Marrow Transplantation volume 56, pages 1937–1943 (**2021**).

Hodgkin's lymphoma:

- Double umbilical cord blood transplant is effective therapy for relapsed or refractory Hodgkin lymphoma. Philip A Thompson, Travis Perera, David Marin, Betul Oran, Uday Popat, Muzaffar Qazilbash, Nina Shah, Simrit Parmar, Katayoun Rezvani, Amanda Olson, Partow Kebriaei, Paolo Anderlini, Gabriela Rondon, Amin Alousi, Stefan Ciurea, Richard E Champlin, Ashish Bajel, Jeffrey Szer, Elizabeth J Shpall, David Ritchie, Chitra M Hosing; Leuk Lymphoma; 2016 Jul;57(7):1607-15. doi: 10.3109/10428194.2015.1105370. Epub **2015** Dec 23.

Diabetes:

- *Transplantation of stem cells from umbilical cord blood as therapy for type I diabetes*. Rachel Stiner, Michael Alexander , Guangyang Liu, Wenbin Liao, Yongjun Liu, Jingxia Yu, Egest J Pone, Weian Zhao, Jonathan R T Lakey; Cell Tissue Res. 2019 Nov;378(2):155-162. doi: 10.1007/s00441-019-03046-2. Epub **2019** Jun 17.
- *The efficacy of platelet gel derived from umbilical cord blood on diabetic foot ulcers: A double-blind randomized clinical trial.* Seyedeh Esmat Hosseini, Behnam Molavi, Alireza Goodarzi, Ahad Alizadeh, Alireza Yousefzadeh, Niloofar Sodeifi, Leila Arab, Nasser Aghdami; Wound Medicine, Volume 28, March **2020**, 100178.

HIV:

- Hsu J., Van Besien K., Glesby M., et al. CROI; **2022**. *HIV-1 Remission with CCR5Δ32Δ32 Haplo-Cord Transplant in a US Woman*: IMPAACT P1107, CROI, Boston.

Immunotherapy:

- *Cord-Blood Natural Killer Cell-Based Immunotherapy for Cancer*. Xiaoyan Zhao, Li Cai, Yu Hu, Huafang Wang; Front Immunol; 2020 Oct 22;11:584099. doi: 10.3389/fimmu.2020.584099. eCollection **2020**.

Regenerative medicine:

- Cartilage Regeneration Using Human Umbilical Cord Blood Derived Mesenchymal Stem Cells: A Systematic Review and Meta-Analysis. Dong Hwan Lee, Seon Ae Kim, Jun-Seob Song, Asode Ananthram Shetty, Bo-Hyoung Kim and Seok Jung Kim; Medicina **2022**, 58(12), 1801; https://doi.org/10.3390/medicina58121801.
- Jeyaraman, M.; Muthu, S.; Ganie, P.A. *Does the source of mesenchymal stem cell have an effect in the management of osteoarthritis of the knee? Meta-analysis of randomized controlled trials*. Cartilage **2021**, 13, 1532S–1547S.
- Lim, H.C.; Park, Y.B.; Ha, C.W.; Cole, B.J.; Lee, B.K.; Jeong, H.J.; Kim, M.K.; Bin, S.I.; Choi, C.H.; Choi, C.H.; et al. *Allogeneic Umbilical Cord Blood-Derived Mesenchymal Stem Cell Implantation Versus Microfracture for Large, Full-Thickness Cartilage Defects in Older Patients: A Multicenter Randomized Clinical Trial and Extended 5-Year Clinical Follow-up*. Orthop. J. Sport. Med. **2021**, 9, 2325967120973052.
- Moon, S.W.; Park, S.; Oh, M.; Wang, J.H. *Outcomes of human umbilical cord blood-derived mesenchymal stem cells in enhancing tendon-graft healing in anterior cruciate ligament reconstruction: An exploratory study*. Knee Surg. Relat. Res. **2021**, 33, 32.
- Song, J.S.; Hong, K.T.; Kong, C.G.; Kim, N.M.; Jung, J.Y.; Park, H.S.; Kim, Y.J.; Chang, K.B.; Kim, S.J. *High tibial osteotomy with human umbilical cord blood-derived mesenchymal stem cells implantation for knee cartilage regeneration*. World J. Stem Cells **2020**, 12, 514–526.
- Yang, H.Y.; Song, E.K.; Kang, S.J.; Kwak, W.K.; Kang, J.K.; Seon, J.K. *Allogenic umbilical cord blood-derived mesenchymal stromal cell implantation was superior to bone marrow aspirate concentrate augmentation for cartilage regeneration despite similar clinical outcomes.* Knee Surg. Sport. Traumatol Arthrosc. **2022**, 30, 208–218.

Cerebral palsy:

- *Potentiation of cord blood cell therapy with erythropoietin for children with CP: a 2 × 2 factorial randomized placebo-controlled trial*. Kyunghoon Min, Mi Ri Suh, Kye Hee Cho, Wookyung Park, Myung Seo Kang, Su Jin Jang, Sang Heum Kim, Seonkyeong Rhie, Jee In Choi, Hyun-Jin Kim, Kwang Yul Cha, MinYoung Kim; Stem Cell Res Ther. **2020** Nov 27;11(1):509. doi: 10.1186/s13287-020-02020-y.

- A Randomized, Placebo-Controlled Trial of Human Umbilical Cord Blood Mesenchymal Stem Cell Infusion for Children With Cerebral Palsy. Li Huang, Che Zhang, Jiaowei Gu, Wei Wu, Zhujun Shen, Xihui Zhou, Haixia Lu; Cell Transplant. **2018** Feb;27(2):325-334. doi: 10.1177/0963689717729379.
- *Motor function and safety after allogeneic cord blood and cord tissue-derived mesenchymal stromal cells in cerebral palsy: An open-label, randomized trial*. Jessica M Sun, Laura E Case, Colleen McLaughlin, Alicia Burgess, Natalie Skergan, Sydney Crane, Joan M Jasien, Mohamad A Mikati, Jesse Troy, Joanne Kurtzberg; Dev Med. Child Neurol. 2022 Dec;64(12):1477-1486. doi: 10.1111/dmcn.15325. Epub **2022** Jul 10.
- *Umbilical cord blood CD34+ cells administration improved neurobehavioral status and alleviated brain injury in a mouse model of cerebral palsy*. Yanqun Chang, Shouheng Lin, Yongsheng Li, Song Liu, Tianbao Ma, Wei; Child Nerv Syst. 2021 Jul;37(7):2197-2205. doi: 10.1007/s00381-021-05068-0. Epub **2021** Feb 9.

Multiplication:

- *Cord blood expansion has arrived*. Elizabeth J Shpall, Katayoun Rezvani; Blood. **2021** Oct 21;138(16):1381-1382. doi: 10.1182/blood.2021012725.
- *Effects of glucose on the proliferation of human umbilical cord blood hematopoietic stem cells*. Mina Dadkhah, Mohammadreza Sharifi, Mohammad Jafar Sharifi, Rana Moradian Tehrani; Cell Tissue Bank. **2022** Nov 25. doi: 10.1007/s10561-022-10048-y. Online ahead of print.
- *The monoculture of cord-blood-derived CD34+ cells by an automated, membrane-based dynamic perfusion system with a novel cytokine cocktail.* Mark Jones, Annie Cunningham, Nathan Frank, Dalip Sethi. Stem Cell Reports. **2022** Dec 13;17(12):2585-2594. doi: 10.1016/j.stemcr.2022.10.006. Epub 2022 Nov 3.

Haematological tumours:

- *Decreased Mortality in 1-Year Survivors of Umbilical Cord Blood Transplant vs. Matched Related or Matched Unrelated Donor Transplant in Patients with Hematologic Malignancies*. Lauren Bohannon, Helen Tang, Kristin Page, Yi Ren, Sin-Ho Jung, Alexandra Artica, Anne Britt, Prioty Islam, Sharareh Siamakpour-Reihani, Vinay Giri, Meagan Lew, Matthew Kelly, Taewoong Choi, Cristina Gasparetto, Gwynn Long, Richard Lopez, David Rizzieri, Stefanie Sarantopoulos, Nelson Chao, Mitchell Horwitz, Anthony Sung; Transplant Cell Ther. 2021 Aug;27(8):669.e1-669.e8. doi: 10.1016/j.jtct.2021.05.002. Epub **2021** May 12.

Multiple sclerosis:

- *Optimizing the Production of a Human Umbilical Cord Blood-Derived Cell Therapy Product, DUOC-01*. Li Xu, Roberta Parrott, Madison French, Joanne Kurtzberg and Anthony Filiano; Stem Cells Transl Med. **2021** Sep; 10(Suppl 1): S4. Published online 2021 Sep 18. doi: 10.1002/sct3.13006.
- *DTI Tract-Based Quantitative Susceptibility Mapping: An Initial Feasibility Study to Investigate the Potential Role of Myelination in Brain Connectivity Change in Cerebral Palsy Patients During Autologous Cord Blood Cell Therapy Using a Rotationally-Invariant Quantitative Measure.* Lijia Zhang, BS, Susan Ellor, MD, PhD, Jessica M. Sun, MD, Chunlei Liu, PhD, Joanne Kurtzburg, MD, and Allen W. Song, PhD; J Magn Reson Imaging. **2021** Jan; 53(1): 251–258.
- *Gene products promoting remyelination are up-regulated in a cell therapy product manufactured from banked human cord blood.* Paula Scotland, Susan Buntz, Pamela Noeldner, Arjun Saha, Tracy Gentry, Joanne Kurtzberg, Andrew E Balber; Cytotherapy. 2017 Jun;19(6):771-782. doi: 10.1016/j.jcyt.2017.03.004. Epub **2017** Apr 5.

Stroke:

- *Allogeneic Umbilical Cord Blood Infusion for Adults with Ischemic Stroke: Clinical Outcomes from a Phase I Safety Study*. Daniel T Laskowitz, Ellen R Bennett, Rebecca J Durham, John J Volpi, Jonathan R Wiese, Michael Frankel, Elizabeth Shpall, Jeffry M Wilson, Jesse Troy, Joanne Kurtzberg; Stem Cells Transl. Med. **2018** Jul;7(7):521-529. doi: 10.1002/sctm.18-0008. Epub 2018 May 12.
- *Complete Restoration of Motor Function in Acute Cerebral Stroke Treated with Allogeneic Human Umbilical Cord Blood Monocytes: Preliminary Results of a phase I Clinical Trial*. Tian-Kuo Lee, Cheng-You Lu, Sheng-Tzung Tsai, Pao-Hui Tseng, Yu-Chen Lin, Shinn-Zong Lin, Jonas C Wang, Chih-Yang Huang, Tsung-Lang Chiu; Cell Transplant. **2021** Jan-Dec;30:9636897211067447. doi: 10.1177/09636897211067447.