



**The University of Zurich and the University Children's Hospital Zurich are preparing for a gene therapy multinational trial for patients with chronic granulomatous disease (CGD) caused by p47phox deficiency.**

**Previous experience:**

The University Children's Hospital Zurich has over 30 years of experience in hematopoietic stem cell transplantation and over 18 years of experience in developing and clinical use of gene therapies for CGD. Our team participated in two international clinical trials of gene therapy for X-CGD (NCT00927134 and NCT01855685). These studies have clearly demonstrated the potential of gene therapy to improve the outcome of CGD patients suffering from severe infections.

**New gene therapy vector:**

Gene therapies that were used in early clinical trials for the treatment of CGD and other immunodeficiencies were in some cases associated with oncogenic potential linked to the use of first generation gammaretroviral vectors with strong enhancers/promoters. Also, the corrective transgenes of those vectors were often prone to silencing, resulting in a loss of transgene expression over time.

We have developed a novel lentiviral self-inactivating vector with a myelospesific promoter to minimize the risk of oncogenesis and transgene silencing. This vector provides targeted transgene expression in myeloid cells already at low vector copy numbers. It is resistant to silencing and has demonstrated the absence of insertional mutagenesis, even when used at high doses, in the *in-vitro* immortalization (IVIM) assay. This new vector will be used to produce the gene therapy investigational medicinal product (GTIMP) for the clinical trial.

**Inclusion criteria:**

- Confirmed diagnosis of CGD due to the p47phox deficiency (confirmed mutation in *NCF1* gene)
- Male or female of at least 6 months of age
- Absent or >95%-reduced biochemical activity of the NADPH oxidase in a dihydrorhodamine test
- One or more ongoing or recurrent severe infectious and/or inflammatory complications
- Lack of an available 10/10 HLA-matched (A, B, C, DR, DQ) sibling donor
- Properly completed and signed informed consent (participant and/or parent / legal guardian)
- Ability to return to the study site for follow-up during the 1-year on-study, and during the off-protocol monitoring period

**Exclusion criteria:**

- Availability of a willing 10/10 HLA-matched (A, B, C, DR, DQ) sibling donor unless there is an unacceptable risk associated with an allogeneic HSCT procedure
- Previous allogeneic HSCT
- Contraindications to CD34+ cell mobilization, apheresis procedure, or conditioning regimen
- Contraindication for administration of filgrastim, or lenograstim, or plerixafor, or busulfan
- Concomitant HIV1 or HIV2, or HBV, or HCV, or adenovirus, or parvovirus B19, or HTLV1-5, or toxoplasmosis infection
- Major organ dysfunction/co-morbidity considered to compromise the safety of the participant
- Participant or parent / legal guardian unable or unwilling to comply with the protocol requirements

**Study duration and follow-up:**

After GTIMP administration, participants will be followed-up for 12 months with monthly visits to the study site during the first 3 months, then at months 6, 9 and 12. After the on-trial period, a long-term follow-up of patients is required by regulators for monitoring of their clinical status, as well as long-term safety and efficacy of the treatment. The frequency of visits and total duration of the post-treatment follow-up are foreseen as once a year for 5 years, but they may be adapted based on the national health care regulations.

**Projected enrollment start date:**

Q2 2025

**Planned study centers:**

Switzerland: University Children's Hospital Zurich, University Hospital Zurich

Germany: University Children's Hospital Ulm, University Children's Hospital Freiburg

Spain: Vall d'Hebron University Hospital Barcelona

**Additional information:**

For referrals and information about patients who may participate in the study, please contact Prof. Dr. Pere Soler Palacín, Unitat de Patologia Infecciosa i Immunodeficiències de Pediatria, Hospital Infantil Vall d'Hebron (Tel. +34 93 489 3140, e-mail: pere.soler@vallhebron.cat) or Dr. Oleksandr Pastukhov, Wyss Zurich Translational Center, ETH Zurich/University of Zurich (Tel. +41 44 634 6171, e-mail: oleksandr.pastukhov@wysszurich.ch).