Rare Diseases 360°
Collaborative Strategies to leave no-one behind
9th European Conference on Rare Diseases & Orphan Products
10-12 May 2018 Vienna

POSTER NUMBER: 251

POSTER THEME: 9

Gene therapy for ADA-SCID patients: Strimvelis™ as a successful model for the development of accessible advanced therapies for ultra rare diseases

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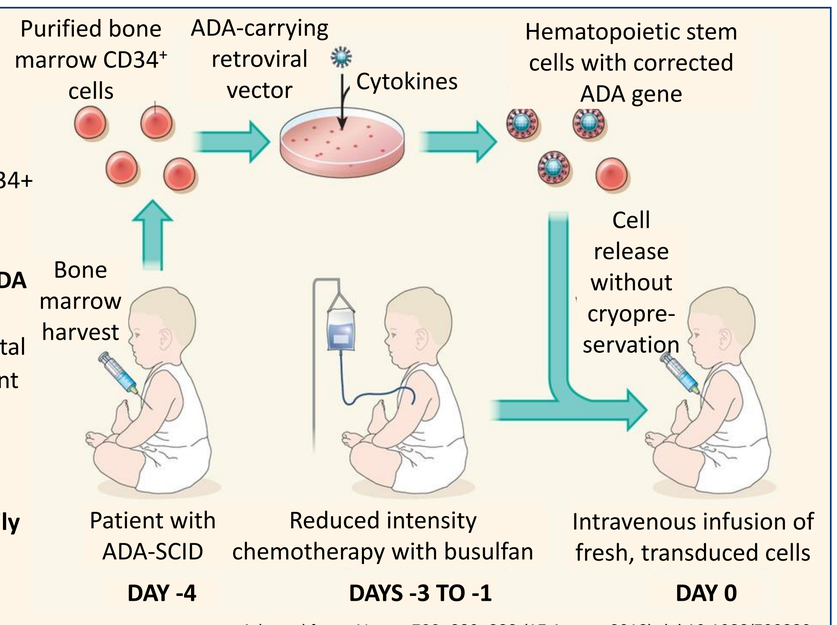
ADA-SCID EX VIVO GENE THERAPY

The therapy entails **transduction** of CD34+ cells purified from the patient's bone marrow engineered with a **gamma-retroviral vector** carrying the **correct ADA gene**. Cells are transduced in a clinical manufacturing facility nearby the hospital and then **reinfused fresh** into the patient following **low-dose chemotherapy**.

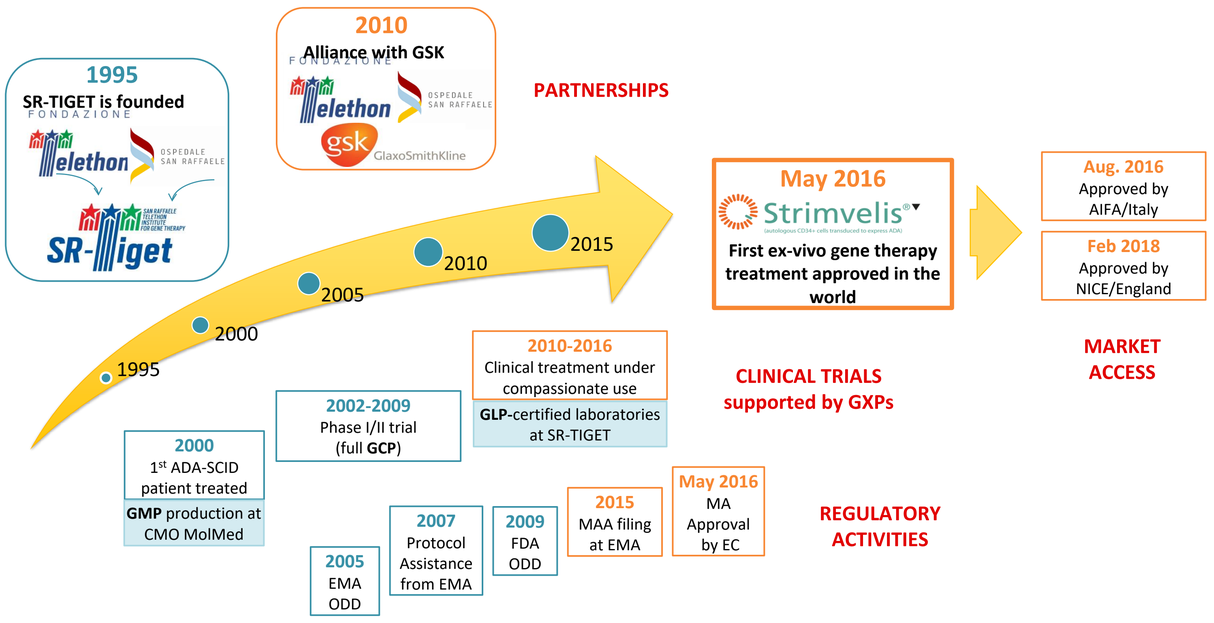
Overall, the treatment requires **hospitalization for approximately six weeks** and entails the **presence of family members** (parents and often siblings), given the patient's very young age.



Adapted from: *Nature* **500**, 280–282 (15 August 2013) doi:10.1038/500280a

THE PATH TO STRIMVELIS™

- **First ex-vivo, autologous, stem cell gene therapy** for adenosine deaminase severe combined immunodeficiency (ADA-SCID)
- Available upon request to **children for whom no suitable HLA-matched related donor is available**
- Result of a 20 years' research and development enterprise by the San Raffaele Telethon Institute for Gene Therapy (**SR-TIGET**) in Milan
- Developed thanks to the **partnership with GlaxoSmithKline** in 2010 leading to **marketing authorization** in Europe in May 2016



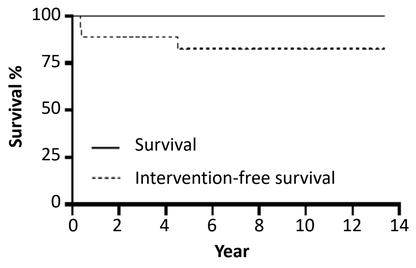
Countries of origin of the 27 ADA SCID patients treated with GT at OSR

PARADIGM CHANGE
To ensure excellence of care, the patient travels, not the drug

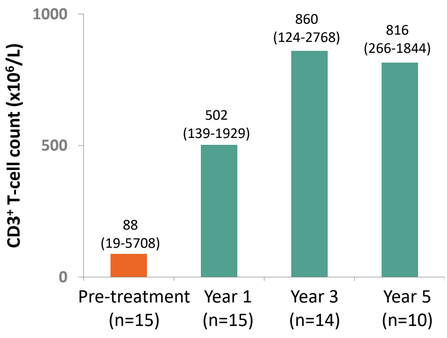
27 PATIENTS FROM 15 COUNTRIES TREATED WITH ADA-SCID GENE THERAPY

- **Eighteen** children treated in the **development phase** supporting the approval by the European Medicines Agency
  - **All alive** at three or more years post-treatment – longest follow-up 17 years
  - **No serious adverse events** related to the medicinal product
    - Most adverse events considered to be potentially related to busulfan conditioning or to immune reconstitution
  - To date **no leukemia event** observed
  - **Immune competence acquired** by most children without additional treatments
- **Four** patients treated under **expanded access**
- **Five** children treated **after the marketing authorization**
  - All showing outcomes in line with the previous observations.

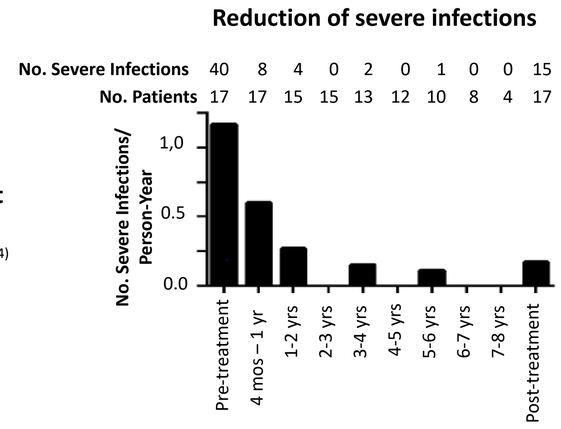
Survival after gene therapy



Correction of immune and metabolic defect



Reduction of severe infections



Adapted from: Cicalese et al., Blood 2016

ACCESS TO STRIMVELIS™

Today, **Strimvelis™ is delivered exclusively at the** Pediatric Immunohematology and Bone Marrow Transplantation Unit of the **San Raffaele Hospital in Milan** (OSR).

Several factors contribute to this setting:

- Treatment entailing a **complex process**
- Infusion of a "fresh" drug" **6 hours shelf-life**
- **Production at MolMed**, the only authorized production site, close to the hospital
- **OSR accredited** as a clinical center for blood and marrow transplantation and for cellular therapy **by JACIE** (Joint Accreditation Committee-ISCT & EBMT)
- **Experienced medical equipe** in ADA-SCID patient management and treatment with ex-vivo gene therapy
- A **charitable program** ("**Just like home**") in support of the patients' families during the whole duration of the treatment

The Italian national competent authority set a price for the treatment that is the basis for agreements with national health systems and insurance bodies for cost coverage.

A multi-faceted team to make ADA-SCID children and families feel their stay at OSR "Just like home"

THE PATH FORWARD

Overall, Strimvelis™ serves as a **successful example** of an **innovative therapy** for an **extremely rare disease** that has completed the path from the clinical phase to patients' access; the design and set-up of the treatment take advantage of the **most advanced knowledge and tools** and apply the **best practices** available at the time of its development.

Therefore, therapy with Strimvelis™ may be taken as the **starting model** for the implementation of innovative medicinal products in the gene therapy field and of **new production processes** in future gene therapy clinical trials for other rare genetic diseases.

These could include, for example, the **introduction of a freezing step** in the preparation of the transduced cells, which could allow separation of the manufacturing facility from the clinical center and the **activation of more clinical centers**.

In all cases, only a few, specialized centers will be able to accrue all the competences and facilities needed to offer complex, advanced therapies such as Strimvelis™ to patients in an efficient and safe way.

While this and other solutions may contribute to enriching the portfolio of available gene therapies, **Strimvelis™ will stay as an effective treatment** benefitting children with ADA-SCID today and in the future.

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- Ferrua F and Aiuti A. Twenty-Five Years of Gene Therapy for ADA-SCID: From Bubble Babies to an Approved Drug. Hum Gene Ther. 2017;28:972-981

FONDAZIONE Telethon — SR-Tiget San Raffaele Telethon Institute for Gene Therapy — Ospedale San Raffaele