Developing Advanced therapies for rare diseases in EU: opportunities and challenges in the experience of a Charity

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FONDAZIONE Telethon

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FONDAZIONE BENZI - XI FORESIGHT TRAINING COURSE

DISCLOSURE

The San Raffaele Telethon Institute for Gene Therapy (**SR-TIGET**) is a joint venture between Fondazione Telethon and Ospedale San Raffaele (OSR).

ADA-SCID gene therapy (Strimvelis) was licensed to GlaxoSmithKline (GSK) in 2010 and received European marketing authorization in 2016.

Wiskott-Aldrich Syndrome (WAS) and **Metachromatic Leukodystrophy (MLD)** gene therapies were licensed to GlaxoSmithKline (GSK) in 2014.

B-thalassemia (BTHAL) gene therapy was licensed to GlaxoSmithKline (GSK) in 2017.

Gene therapies for MLD, WAS and BTHAL are still in development, they are not approved for use in patients outside of clinical trial or pre-approved compassionate use.

Strimvelis, WAS, MLD and BTHAL were licensed to Orchard Therapeutics (OTL) in April 2018.


EVERY MINUTE OF EVERY DAY,
TEN CHILDREN AROUND THE WORLD
ARE BORN WITH A RARE GENETIC DISEASE.
TOMMASO IS ONE OF THEM.
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Fondazione Telethon: Mission & Vision

- **Fondazione Telethon** is one of the **major Italian biomedical charity** focused on **genetic diseases**
- **Founded in 1990** at the behest of a group of **patients**
- Supported by donations from the general public through **fund raising**

OUR MISSION

- *Advance biomedical research towards the cure of genetic diseases*

OUR VISION

- *Convert the results of excellent, selected and sustained research into available therapies*

Excellence-driven grant allocation

KEY FIGURES 1990-2017

- 498 M€ research investment
- 2,629 research grants and activities
- 1,611 PIs awarded
- 571 genetic diseases studied

- Three intramural institutes
- Extramural funding programs in Italy

R&D up to available therapies

- **19** orphan drug designations
- **92** patients treated with gene therapy
- **1** therapy on the market

Enabling factors for competitive/ transformative research

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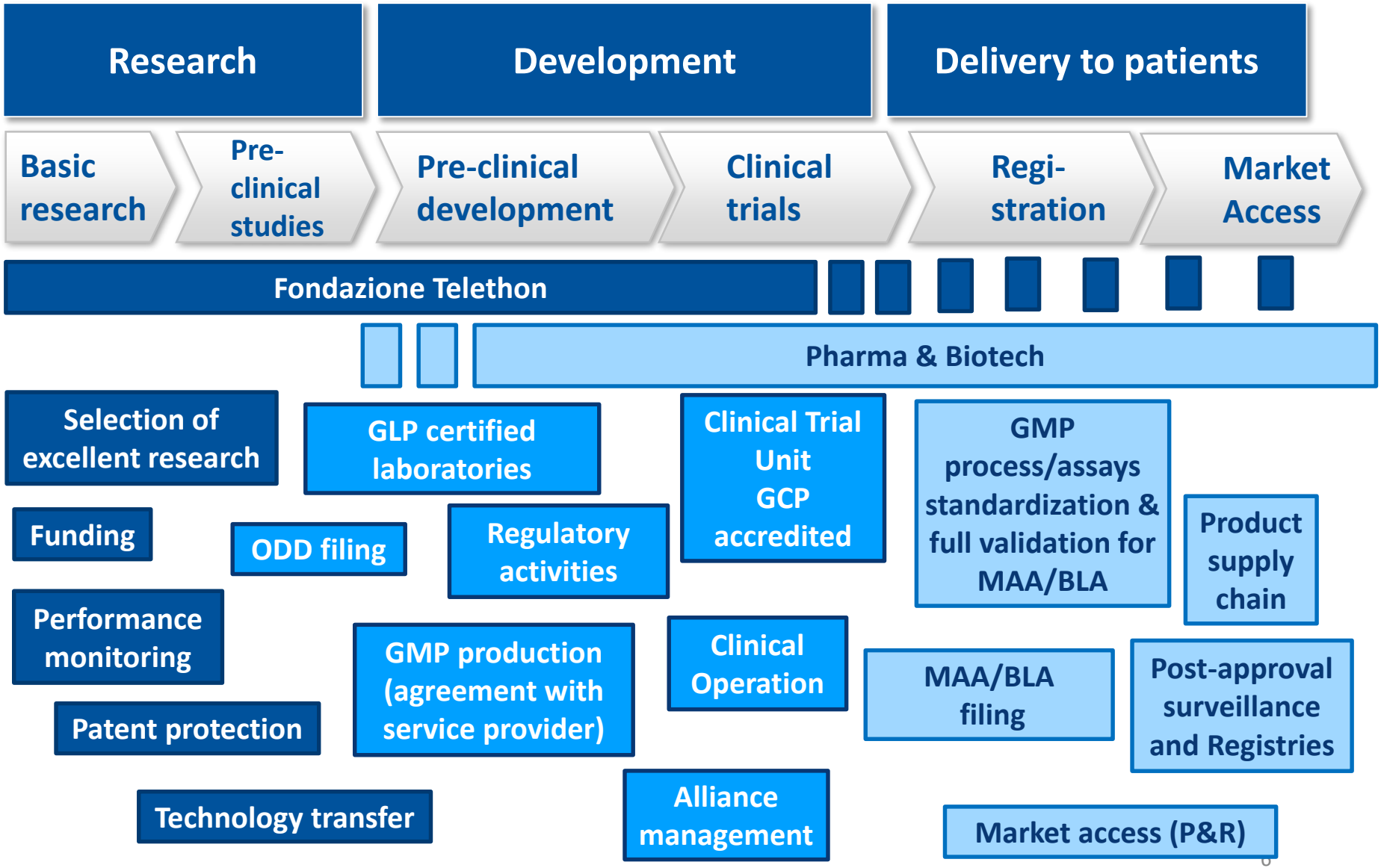
- **Excellent fundamental and pre-clinical research**
  - Stringent selection system (funding to max. top 20% proposals)
  - Adequate funding
  - Monitoring research progression and results

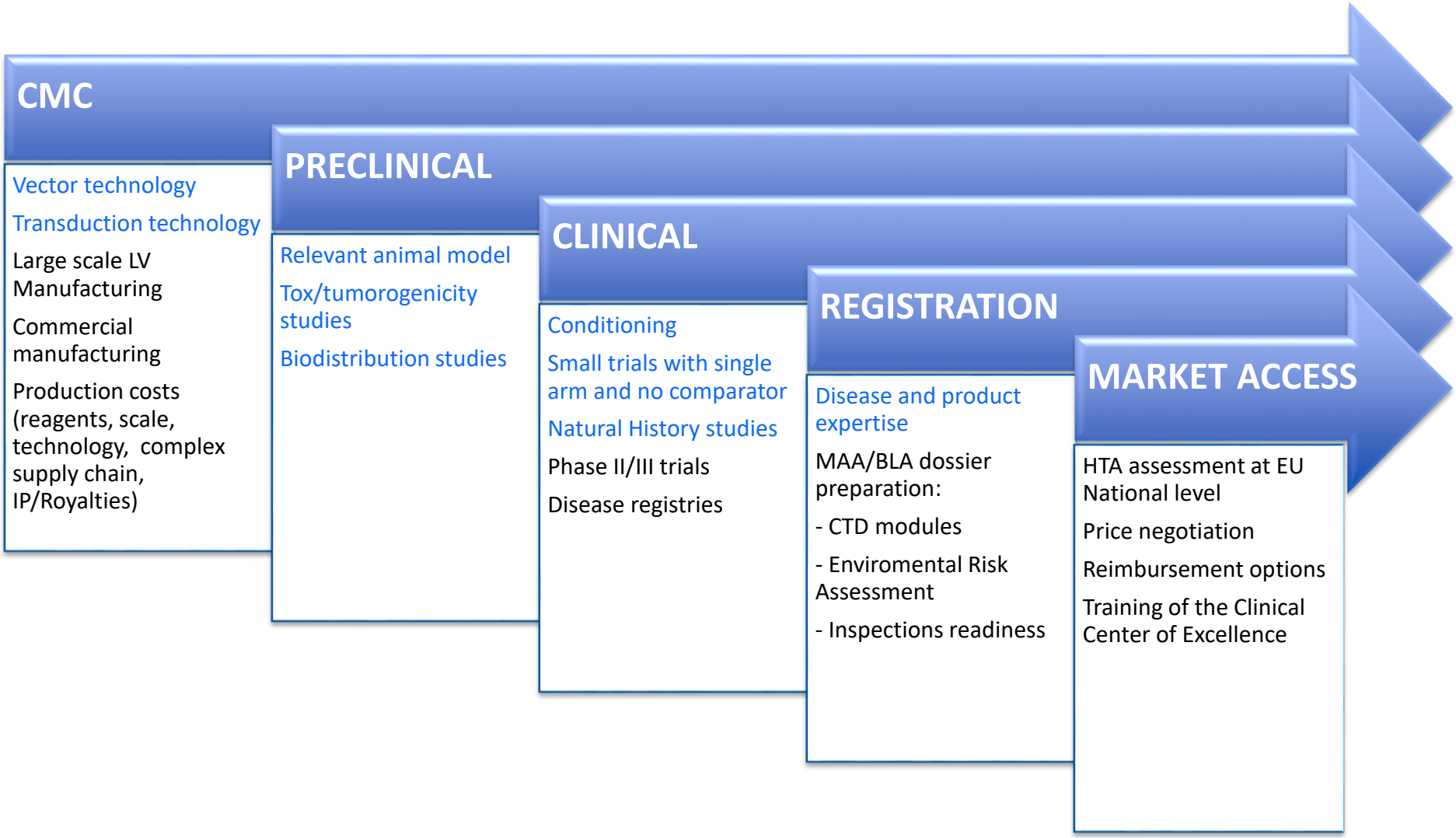
- **Identifying projects with translational potential**

- **Effective translational research**
  - Intellectual property protection and technology transfer
  - Management of strategic partnership/alliances
  - Management of clinical trials
  - Management of regulatory affairs
  - Competences in drug development

The research development pipeline: a collaborative model



Challenges faced from Product Basic Research up to Patient Availability



Blue: Telethon expertise
Black: Pharma expertise

We team with industrial partners: Our Major Alliances

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	Start year	Institute	Scope	Deal Structure
Orchard therapeutics	2018	TIGET	Retroviral-based ex vivo gene therapy for **ADA-SCID,** and lentivirus based for **WAS, MLD, beta thalassemia** and 3 other diseases.	Upfront:10M€ MS & Royalties
BIOMARIN	2011	TIGEM	Small molecule drug candidates for **Lysosomal Storage dis**	R&D MS
Shire	2012	TIGEM	Gene therap treatmen	
SANOFI	2018	TIGET	Lentivirus-b	
editas MEDICINE	2016	TIGET	Genome editing of **hematopoietic stem cell (HSC)** and **T cell therapies**	**Undisclosed**
BIOMARIN	2016	TIGEM	**Undisclosed**	**Undisclosed**

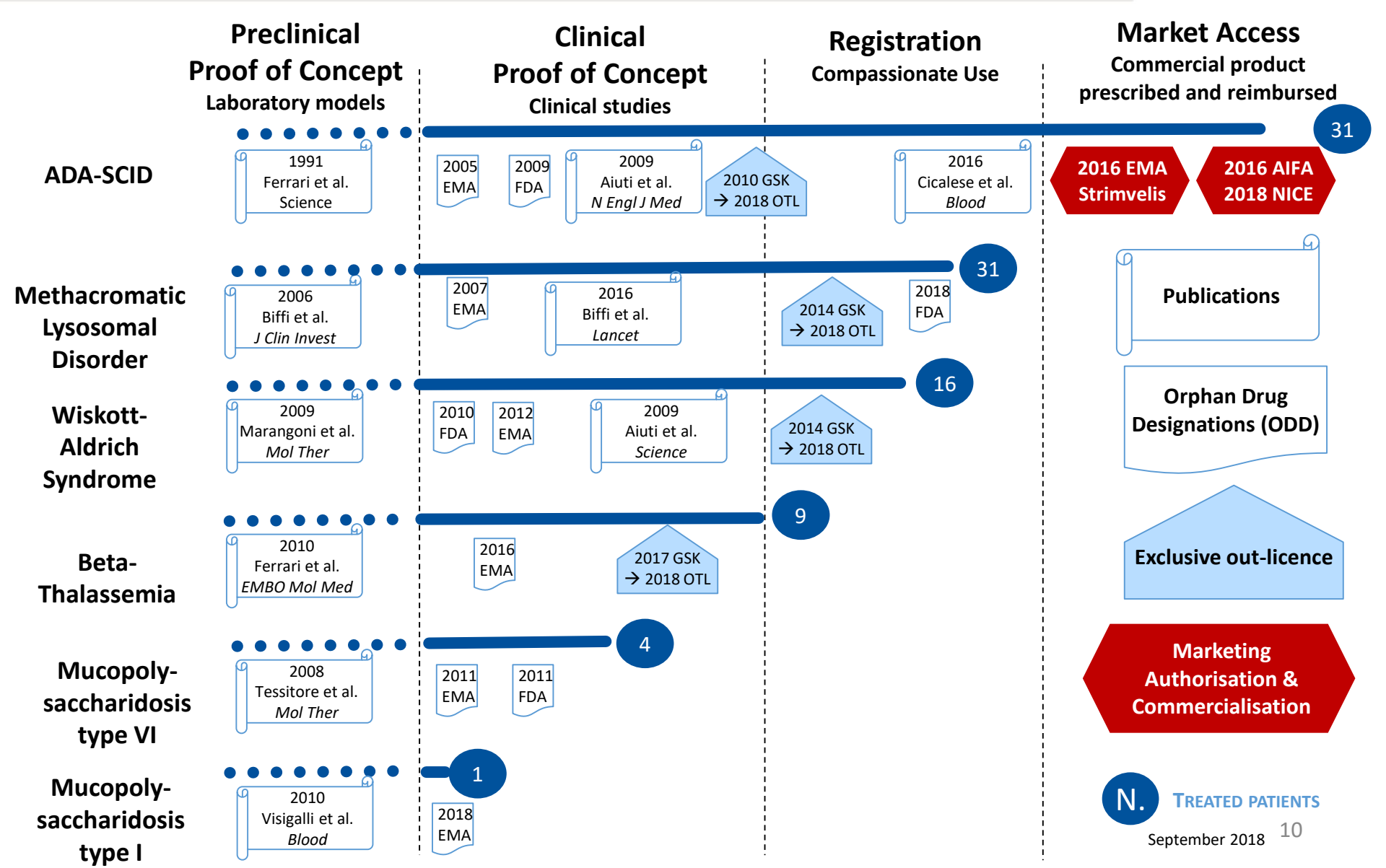
92 pts treated with gene therapy for:
- ✓ ADA-SCID
- ✓ Metachromatic Leukodistrophy
- ✓ Wiskott Aldrich
- ✓ Beta thalassemia
- ✓ MPS VI
- ✓ MPSI

The pillars of Fondazione Telethon's industrial agreements

The agreements between Fondazione Telethon and industrial Partners

- Safeguard **research independence** of Telethon investigators
- Retain **intellectual property rights**
- Mandate **commitment in developing therapies**
- Imply **return of any IP** and **results co-developed**, in case the Partner does not pursue therapy development up to patient access
- Provide **funding** in support of the research in the collaboration programs
- Supply **additional funding** through milestones/royalties, in support of further/other research activities

Fondazione Telethon Gene Therapy Pipeline




“TELETHON SHALL EXIST UNTIL WE WRITE THE WORD ‘CURABLE’ NEXT TO THE NAMES OF ALL GENETIC DISEASES.”
Susanna Agnelli
Founder of Telethon
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Telethon

Strimvelis®

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•Strimvelis is an autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence from human haematopoietic stem/progenitor (CD34+) cells

•Strimvelis is indicated for the **treatment** of **patients** with severe combined immunodeficiency due to adenosine deaminase deficiency (**ADA-SCID**), **for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available**

FIRST EX-VIVO STEM CELL GENE THERAPY APPROVED WW

•Strimvelis can provide **long-term clinical benefits** with a **single therapeutic intervention**, and avoids the risk of graft rejection and GvHD

•A **long-term registry** has been set up to monitor the long-term safety and efficacy of Strimvelis for at least 15 years on 50 patients

SR-Tiget San Raffaele Telethon Institute for Gene Therapy

PUBLIC-PRIVATE PARTNERSHIP: Strimvelis® path

1995
SR-TIGET is founded

2010
Alliance with GSK

2018
GSK transferred to OTL

Aug. 2016
G.U. by AIFA

May 2016
First ex-vivo gene therapy treatment approved in the world
Strimvelis®
(autologous CD34+ cells transduced to express ADA)

Feb 2018
NICE appraisal

2000
2005
2010
2015
2016

2000
1st ADA-SCID patient treated

2005
EMA ODD

2009
FDA ODD

2002-2009
Phase I/II PIVOTAL trial

2007-2008
Protocol Assistance from EMA

GMP production at CMO MolMed

2010-2016
Clinical treatment under compassionate use

2014 GLP-certified laboratories at SR-TIGET

2015
MAA filing at EMA

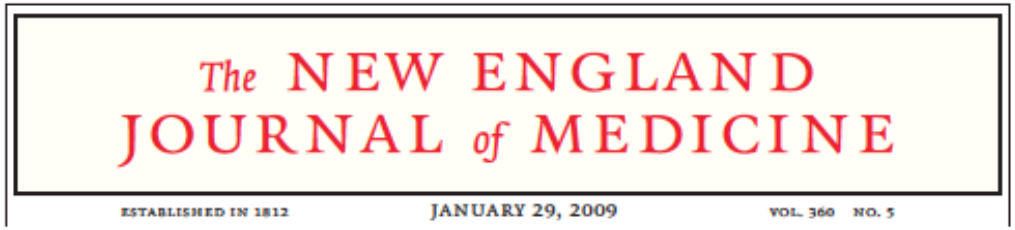
May 2016
MAA by EMA

CLINICAL TRIALS
supported by GCP

REGULATORY ACTIVITIES

MARKET ACCESS

Gene therapy with Strimvelis®



Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Defici

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GENE THERAPY

Update on the safety and efficacy of retroviral gene therapy for immunodeficiency due to adenosine deaminase deficiency

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- Data on first **18 patients** for **EMA filing**
- Most adverse reactions considered to be potentially related to busulfan conditioning or to immune reconstitution
- To date **no leukemic** transformation observed
- Overall **24 patients treated with investigational product** in trials/compassionate use/hospital exemption)
- **7 patients treated with commercial Strimvelis**
- **All alive, longest follow up 18 years**

OSR as sole treatment center: criteria & implications

- **"Fresh" drug:** 6 hours shelf-life
- **Complex** process
- **MolMed** is the only AUTHORIZED and REGISTERED production site => close to the hospital
- Experienced **medical equipe:**

  in ADASCID patients management

  In ADASCID patients treatment with ex-vivo Gene Therapy
- **JACIE** accredited clinical centre (HSCT) and **CNT** (Italian Competent Authority per Tissue Directive)

- *The **Patient travels** to the Centre of Excellence*
- ***Trans-border European Legislation** applies for EU patients (**Form S2**), then OSR is reimbursed through Lombardia Region*

STRIMVELIS® TREATMENT: THE PATIENT'S JOURNEY

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5. Long-term follow-up

1. Clinical validation/ consent

2. Funding

3. Preparation and travel

4. In Milan – preparation, treatment

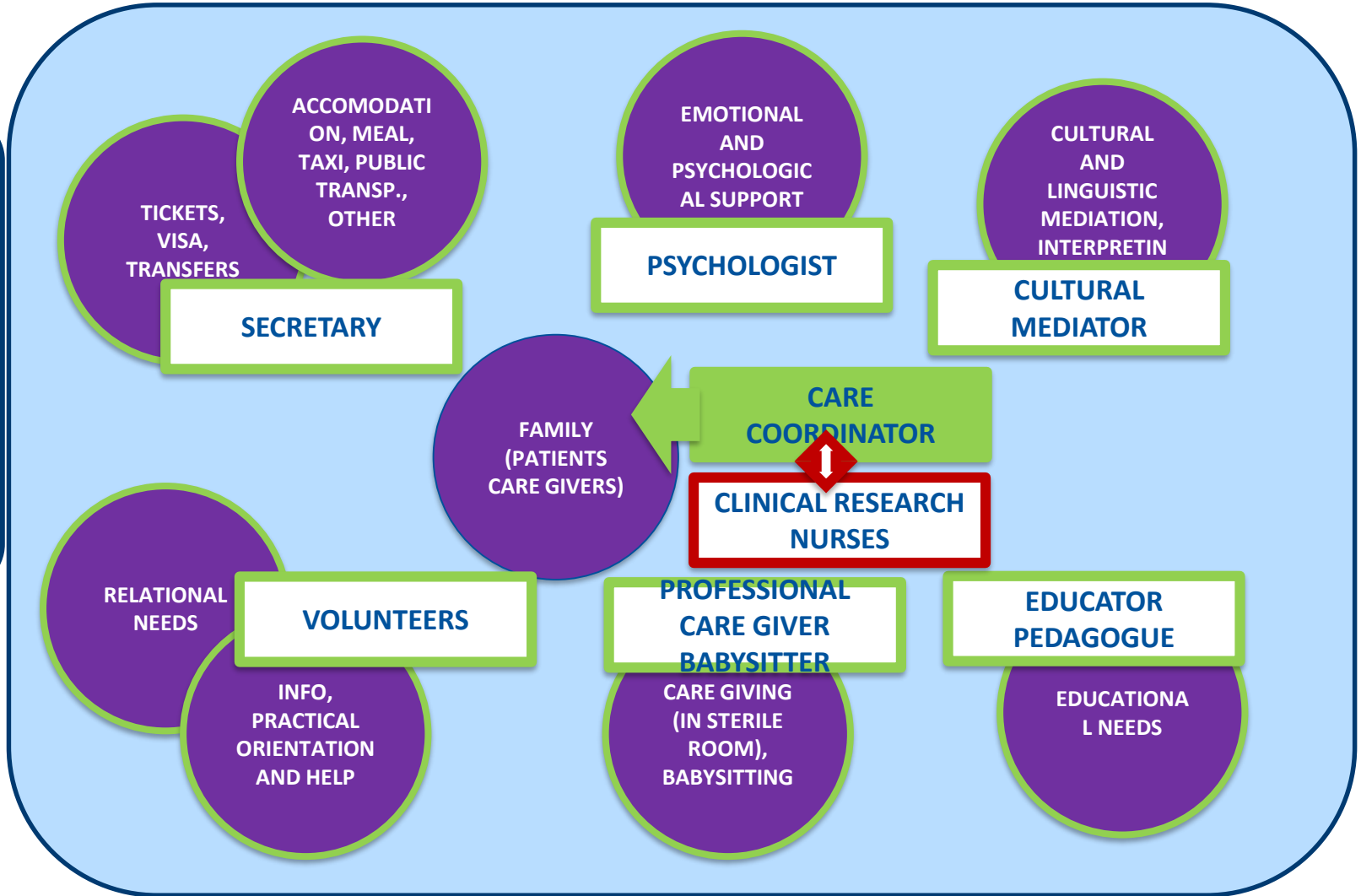
STRIMVELIS®: INNOVATIVE AND COMPLEX TREATMENT PATH

SR-Tiget San Raffaele Telethon Institute for Gene Therapy

"*Just like home*" program: mapped needs and people involved in the project

A **multidisciplinary team** works to facilitate the access to this therapy by **helping to remove**, where needed and possible, **any road-block leading to the gene therapy treatment**

Change of paradigm: The **PATIENT TRAVELS - NOT** the **DRUG**



PRESS RELEASE

SOFINNOVA
PARTNERS FOR LIFE

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Parte il Fondo Sofinnova Telethon primo fondo italiano dedicato al biotech

- **Raccolti più di 80 milioni di euro da investitori pubblici e privati. La piattaforma ITAtech – joint venture tra CDP e FEI – vi ha destinato 40 milioni di euro. A questi si aggiungono più di 40 milioni provenienti dal mercato. La raccolta continua.**

- **Il Fondo è frutto di una partnership fra Sofinnova Partners, società di venture capital leader a livello internazionale specializzata nelle bioscienze, e Fondazione Telethon, charity biomedica riconosciuta dal MIUR e punto di riferimento per la lotta contro le malattie genetiche rare, e si pone l'obiettivo di fondare e finanziare 15/20 aziende biotecnologiche Italiane**

KEY FUND TERMS

- **€75m to €100m** fund managed by Sofinnova Partners
- Dedicated to **Italy**, focused on **rare/genetic** diseases
- **Strategic partnership** with Fondazione Telethon
- Experienced **dedicated team** with complementary skills (TT & VC)
- **15-20** investments in a period of 5 years: 10-15 seeds, 4-5 series A
- Maximum investment size **€10m**

MAXIMIZING **COMPLEMENTARITY**

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THE 3 Is OF MODERN TECHNOLOGY TRANSFER

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SOFINNOVA PARTNERS FOR LIFE

IDENTIFY	INCUBATE	INVEST
▶ Capillary knowledge of the Italian research system ▶ Access to the best in class researchers nationwide ▶ Capability to guide institutes and researchers toward technology transfer	▶ Sharp focus on early stage research projects with the highest commercial potential ▶ Bring to Proof of Concept via dedicated seed investments	▶ Invest in the most promising and successful seed projects ▶ Structure broad international Series A ▶ Develop management teams with strong domain expertise

CONCLUSIONS

- 20 year of Telethon Research has delivered remarkable results.
- The Italian Collaborative model among Charity/Academia, Pharma, Regulators has been successful in delivering Innovation and Advance Therapies to all the EU and ex-EU eligible patients in medical need.
- The Model has been mapped, tested and validated: IT WORKS.
- STRIMVELIS® is available to all the patients in need through the current Cross-Boarder Legislation.
- Telethon is exploring a new model – VC.

TAKE HOME MESSAGES

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- Developing therapies for ultra-rare diseases remains a huge challenge.
- Profitability of therapies for ultra-rare diseases maybe significantly lower than “standard” drugs.
- New drug development to be focused on compelling unmet needs (particularly when orphan drug designation is pursued).

Acknowledgements

Referring Physicians worldwide

All the patients and their families


THANK YOU