Advanced Therapies for Hb Disorders: Challenges in Access & Lessons Learned – Patients' Rights

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Securing Equitable Patient Access to Advanced Therapies across Europe
24 October 2022 – Brussels, Belgium

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EPIDEMIOLOGY

Haemoglobin disorders are now present in all countries of the world, consequent to past and recent population movements.

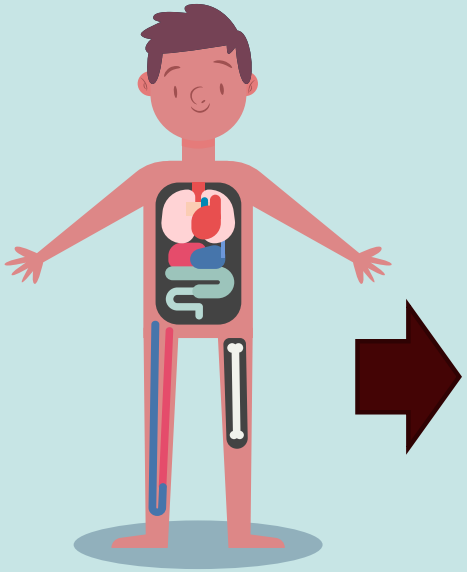
This very fact has caused the appearance of a number of inequalities within countries, between countries and between regions.

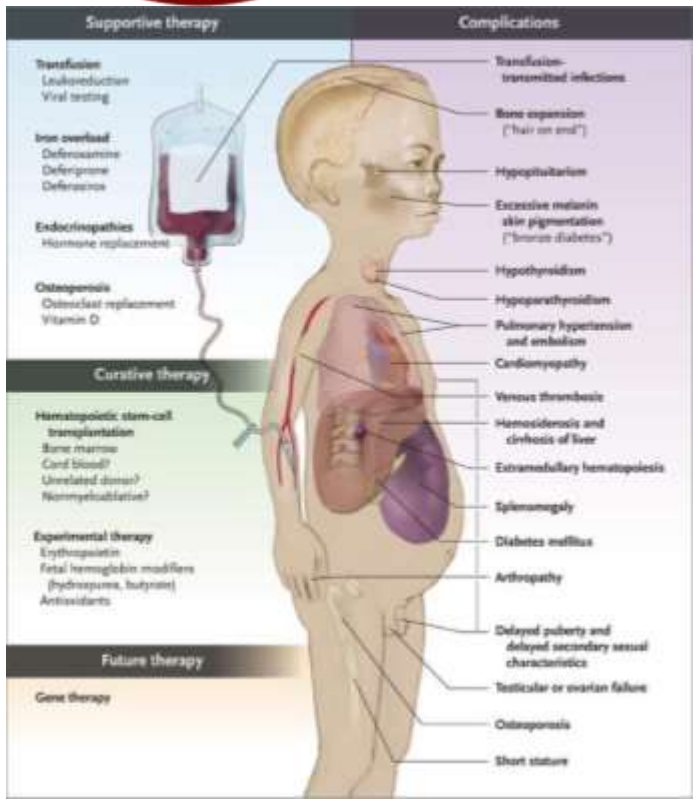
ABOUT BETA-THALASSAEMIA

Therapy & Complications

Beta-thalassaemia requires:

- **lifelong frequent blood transfusions,**
- **iron chelation therapy and**
- **multidisciplinary care for complications consequent to the disease pathology and treatment.**

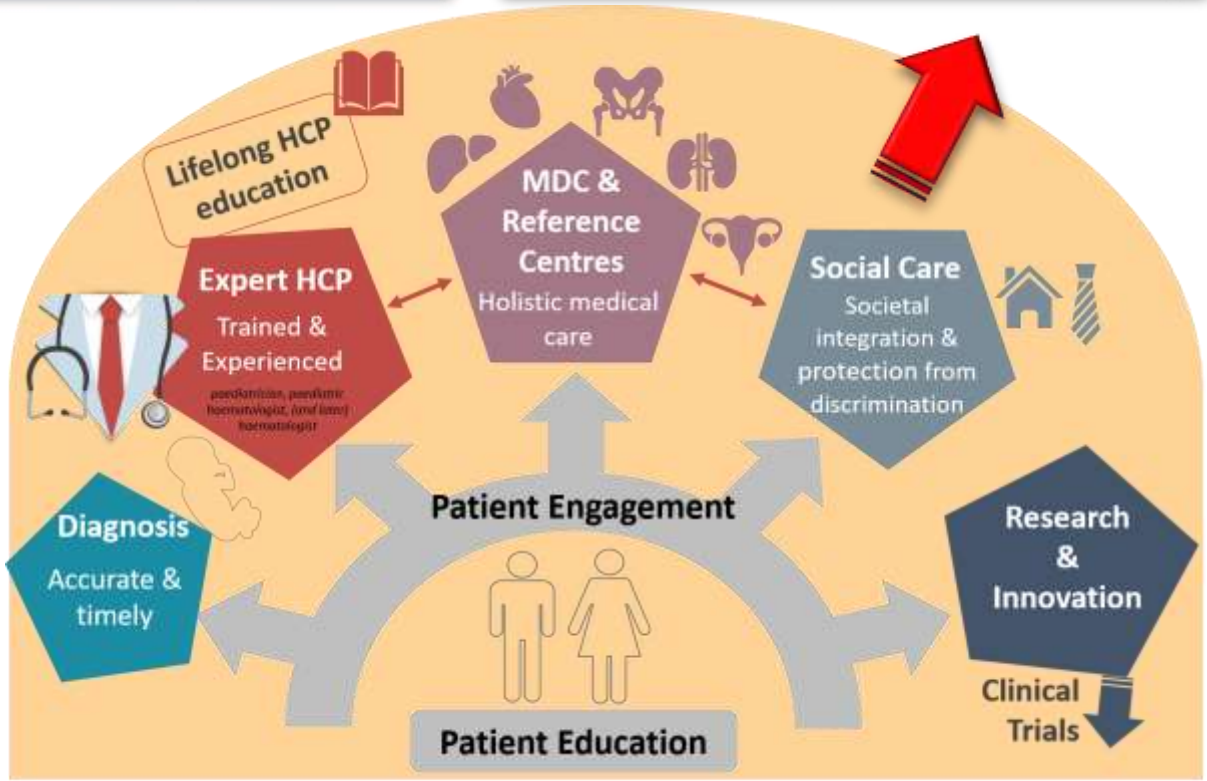




The patient journey: The example of Thalassaemia – TD & NTD

Evidence in countries with success in patient survival & quality of life support these parameters

- **UHC Healthcare Systems**
- **Disease-specific National Registries**
- **Surveillance Programmes**
- **Prevention Strategies**



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Heterogeneity in extent & quality of care globally – including the EU!

LIC

In **100%** of countries:

- Suboptimal care
- High morbidity & premature death
- Prevention absent
- High no. of annual affected births

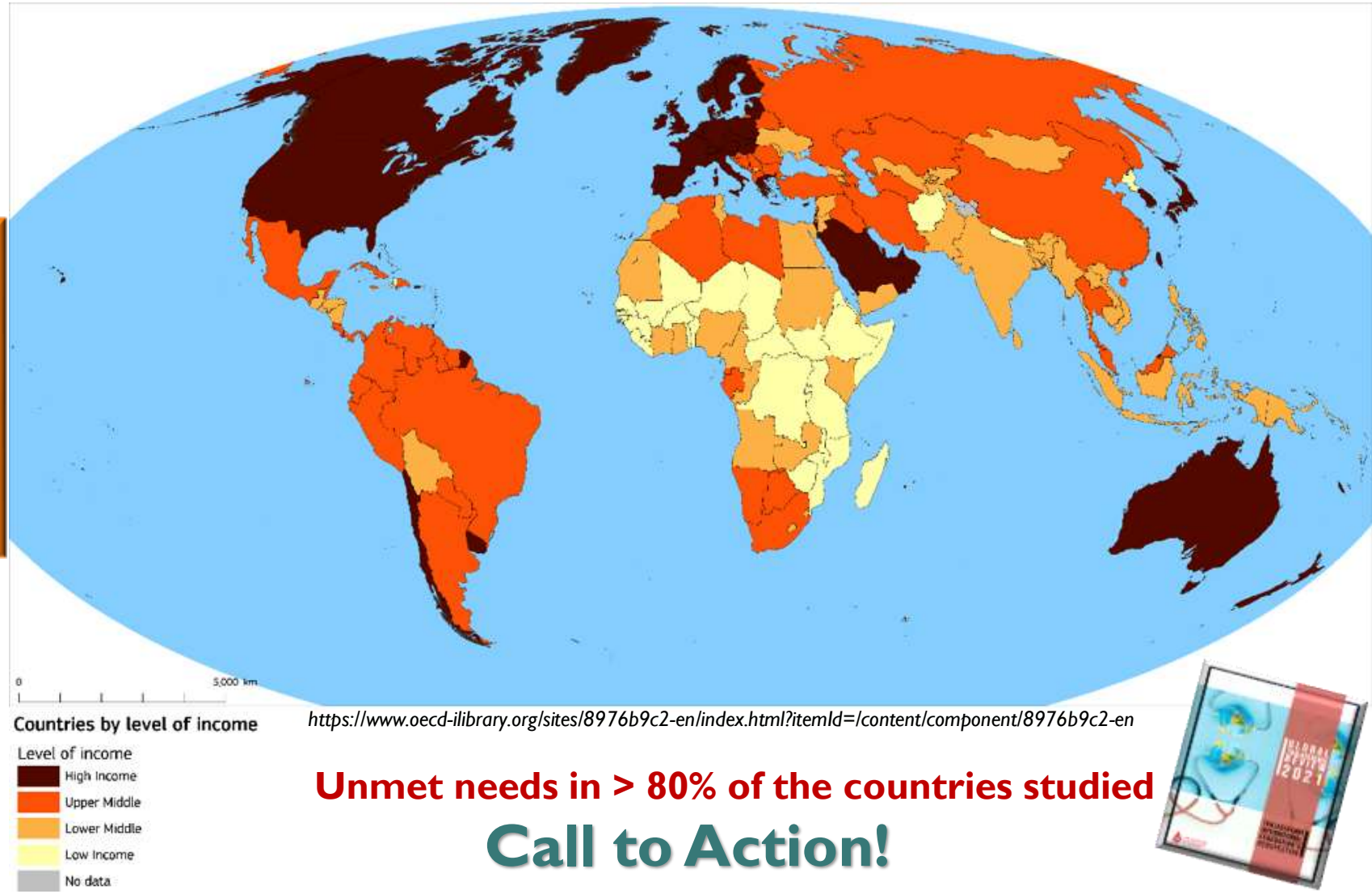
MIC

- **75%** provide suboptimal care
- **19%** nearly appropriate / basic care
- **6%** optimal care

HIC

- **6%** nearly appropriate / basic care
- **78%** near optimal care
- **16%** optimal care

LIC: Low Income Countries; MIC: Middle Income Countries; HIC: High Income Countries, defined by World Bank



https://www.oecd-ilibrary.org/sites/8976b9c2-en/index.html?itemId=/content/component/8976b9c2-en

Unmet needs in > 80% of the countries studied

Call to Action!

THE PATIENTS' PERSPECTIVE: WHY A CURATIVE APPROACH IS NEEDED

What they say:

'…*hooked* to regular, life-long blood transfusions'

'…iron overload complications and medications which I cannot afford'

'Frequent monitoring tests'

'daily chelation adherence is difficult to keep up with'

'…sometimes I feel that I spend all of my time at transfusion units…'

…reflects their challenges & concerns:

- × Blood Adequacy & Safety
- × Medical Expertise
- × Appropriate iron monitoring tools
- × Out-of-pocket expenses
- × Emerging complications with ageing
- × Social stigma / marginalisation

…in addition to:

- Development of complications, need for extra care / hospital stays
- Extensive & life-long *intrusion* in personal, family, professional, educational, social life

- Sentiments are **common** to all patients, irrespective of their eligibility for GT
- **Quality of Life** is severely impaired
- **2019:** 1st gene-based therapy to cure thalassaemia is approved by EMA
- **Allogenic HSCT** is the only other curative option – but varying success, eligibility limitations (only ~25% of patients) & 5 – 20% transplant related morbidity and mortality risks.

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ADVANCED THERAPIES FOR HB DISORDERS – AN OVERVIEW

Selected milestones of ex vivo gene therapy for Hb disorders

First in men ex vivo retroviral gene transfer in lymphocytes
Rosenberg et al. 1990

Stem cell-directed ex vivo retroviral gene transfer for newborns with ADA-SCID
Kohn et al. 1995

Lymphocyte-directed ex vivo retroviral gene transfer for patients with ADA-SCID
Blaese et al. 1995

First patients with SCD treated with lentiviral gene addition
Ribeil et al. 2017
Kanter et al. 2017

First patient with thalassemia reaches transfusion independence after lentiviral gene addition
Cavazzana-Calvo et al. 2010

Patients with SCD successfully treated with lentiviral gene addition
Kanter et al. 2019
Walters et al. 2019

Patients with β-thalassemia successfully treated with lentiviral gene addition
Thompson et al. 2018

Set back

Leukemogenesis after retroviral gene therapy for SCID-X1 and for WAS
Howe et al. 2008
Braun et al. 2014

Clonal T-cell proliferation after retroviral gene therapy for SCID-X1
Hacein-Bey-Abina et al. 2003

Clonal hematopoiesis after lentiviral gene therapy for thalassemia
Cavazzana-Calvo et al. 2010

Potential inefficient erythropoiesis in thalassemia patients who reached transfusion independence after gene therapy
Thompson et al. 2019

1990 2000 2010 2020

Regulatory decisions

Approval of Strimvelis for treatment of ADA-SCID
2016 *2017* FDA

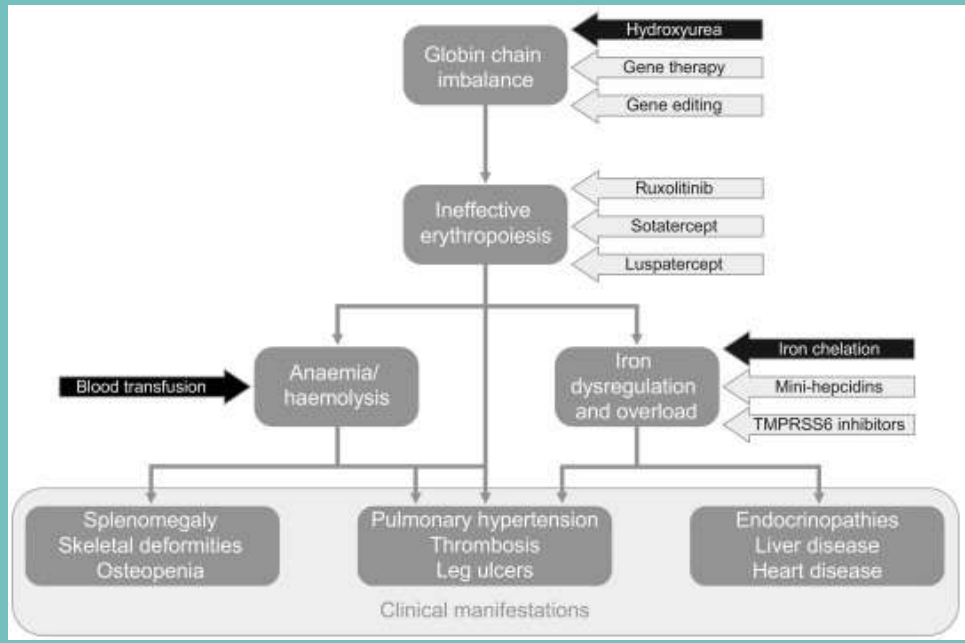
Approval of Zynteglo for treatment of β-thalassemia
2019

Approval of Oxbryta for treatment of SCD
2021 *2019* FDA

Approval of Reblozyl for treatment of β-thalassaemia
2020 FDA

Approval of Adakveo for treatment of SCD
2019 FDA

Adapted from: Kunz, Joachim & Kulozik, Andreas. (2020). Gene Therapy of the Hemoglobinopathies. HemaSphere. 4. e479. 10.1097/HS9.0000000000000479.



Pathogenesis of beta-thalassaemia and targets for current and novel therapeutic strategies

Maria Domenica Cappellini, John B. Porter, Vip Viprakasit, Ali T. Taher, A paradigm shift on beta-thalassaemia treatment: How will we manage this old disease with new therapies?, Blood Reviews, Volume 32, Issue 4, 2018, Pages 300-311, ISSN 0268-960X, https://doi.org/10.1016/j.blre.2018.02.001.

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ZYNTEGLO™: A LONG-AWAITED CURE FOR THALASSAEMIA

Until Zynteglo's authorization, in 2019 by the EMA (in EU), the allogeneic HSCT was the only curative option – BUT:

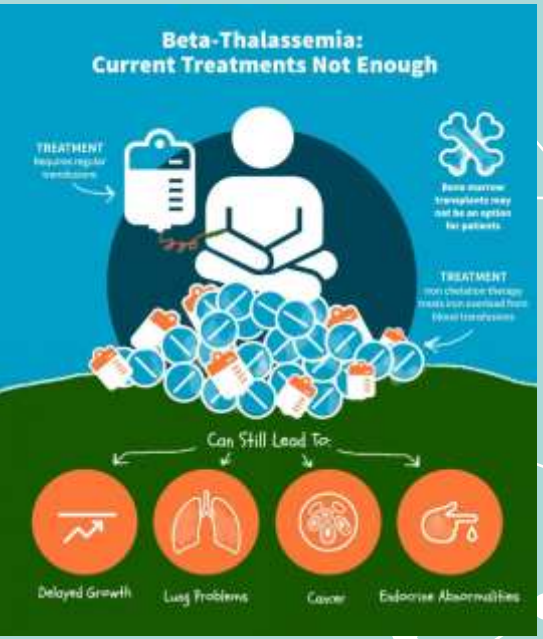
- **Required a fully matched donor for high level of success**

<25% of patients have access to HSCT even when "state-of-art" care is provided

CHALLENGES REGARDING QUALITY OF LIFE

The patients' perspective – How they feel

- **Patients "attached" to the healthcare system** (often necessary to move or live near an expert medical centre)
- Consultations, programming, monitoring, **regular transfusions**, regular visits to hospitals/clinics
- Adequacy of blood, **blood transfusion-related challenges** (side effects, incompatibilities, reactions etc.)
- Availability of/ accessibility to everyday, lifelong, safe and effective **iron load monitoring and chelation**
- **Schooling/ professional/ family life interrupted** (on many occasions damaged/ destroyed)
- **Marginalisation**/ "stigma" with regard to a genetic/hereditary disease
- Availability of / accessibility to **trained**, **experienced** treating, medical and other healthcare professionals across scientific and medical disciplines
- Addressing **"new" complications** with ageing
- **Cannot benefit from the existing SoC**

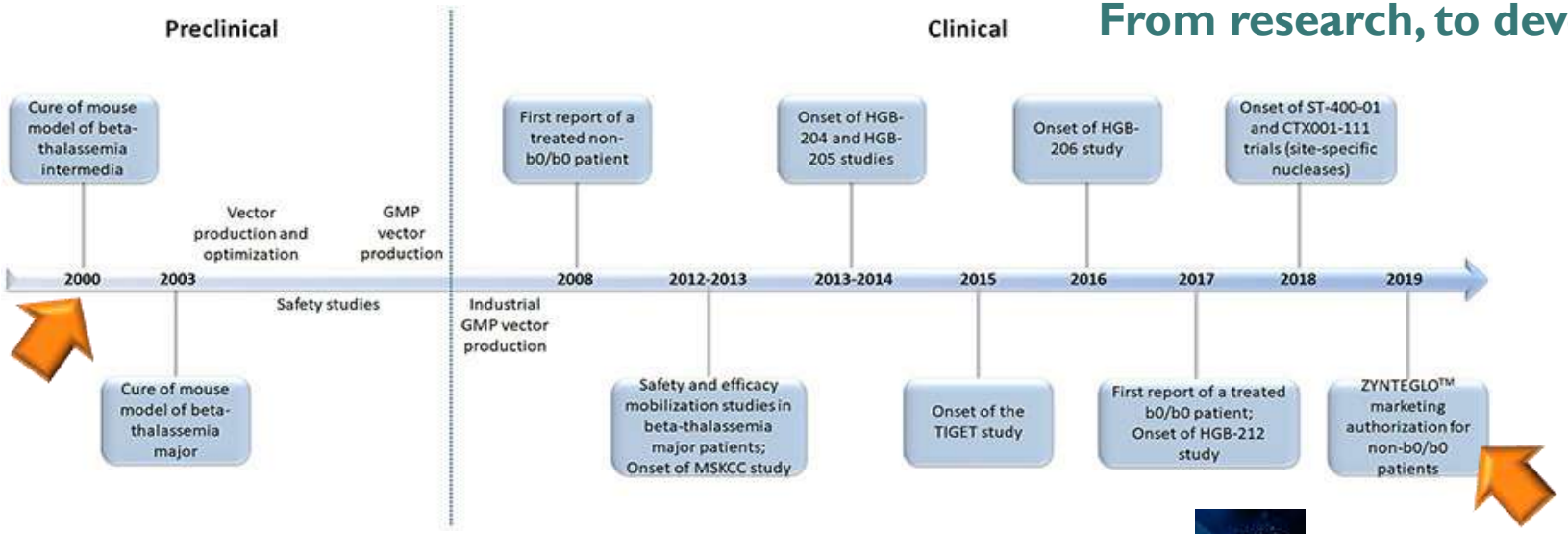


https://www.mybiosource.com/learn/therapeutic-approaches-beta-thalassemia/

"Gene-based and other advanced therapies and drugs MUST NOT BECOME A PRIVILEGE OF SOME BUT A RIGHT FOR ALL"

Mr. George Constantinou
Member of TIF's Board of Directors
Statement at the World Health Assembly (Geneva), May 2019

From research, to development and marketing authorisation



Since 2012, TIF has been raising awareness on gene therapy.

Clinical Trials:

- 2 phase 1 / 2 trials
- 2 phase 3 trials
- 1 long-term follow up study of trial participants

Between phase 1 / 2 and phase 3, a manufacturing change occurred.

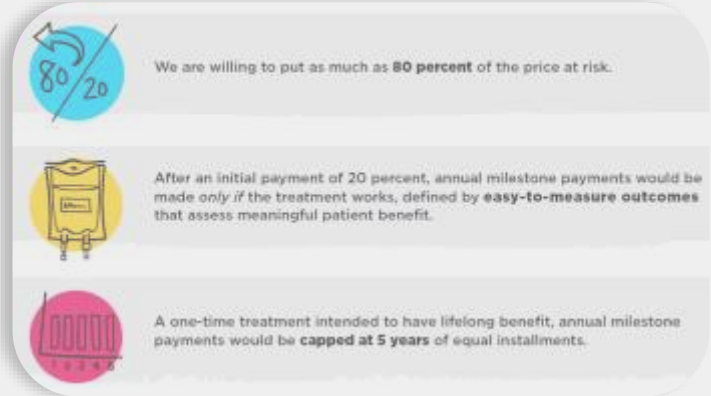
Results: TI achieved in **89%** (phase 3 trial) and was sustained (phase 1 / 2 & phase 3) for a median length of follow up of **42 months** (range: 23-87)

zynteglo
(autologous CD34+ cells encoding β^{A-T87Q}-globin gene)

ZYNTEGLO (autologous $CD34^+$ cells encoding β^{A-T87Q}-globin gene†) **is the first and only one-time gene therapy for transfusion dependent β-thalassaemia by Bluebird Bio** that gives patients the potential to reach transfusion independence. This medicine received a **"conditional marketing authorisation"** by the EMA in 2019.

Eligibility Criteria

Payment Model



- **All those eligible may not want to undergo GT.**

TIF Survey Results (2020)

- 28%: No, even if they met eligibility criteria
- 37.6%: Yes, at any risk
- 39.6%: Possibly Yes, if sufficient/convincing information is provided to satisfy their concerns

Patient concerns:

- Short/Long-term side effects
- Fertility impact
- Durability of effectiveness
- Revert to TD & IC
- Post-GT Hb levels not sufficient & TI not achieved
- Not eligible for any other ATMPs
- Costs / Decisions of govts & HTA bodies

Is it an option that needs to be provided?

- For those who do not respond / adversely respond to SoC methods
- It is a basic human right to benefit of scientific advancements

On a rocky road after authorisation
What we know

PATIENTS were WELL-VERSED but NOT ACTIVELY INVOLVED in INTERACTION and ADVOCACY with their treating physicians and competent authorities (health & regulatory) on this new long-awaited treatment

WHY?

DID NOT BELIEVE IN ITS SAFETY AND EFFICACY – **18.6%**
SATISFIED WITH STANDARDS OF CARE – 49.6%
AFRAID/ CONCERNED ABOUT **SIDE EFFECTS/ FERTILITY – 32.8%**
WORRIED ABOUT **COSTS – 14.8%**
WORRIED ABOUT **PROCESS – 62%**
RISKS OF TREATMENT AND/OR MYELOABLATIVE CONDITIONING (**FERTILITY**) – **82.4%**
ONCOGENESIS AS A SAFETY CONCERN – **71.5%**

Status of negotiations at the time of the wind-down of operations (August 2021)

COUNTRY	STATUS
Germany	No agreement on price (April 2021)
Greece	Pending HTA report (July 2021)
Cyprus	Intention to submit dossier (July 2021)
France	Pending HTA report (June 2021)
UK	Negative NICE appraisal (February 2021)
Italy	Pause of negotiations due to suspension of EU Marketing Authorisation (March 2021)
Norway, Finland, Iceland	Termination of negotiations (Dec 2020)
Denmark	Pause of negotiations due to suspension of EU Marketing Authorisation (March 2021)
Sweden	Pause of negotiations due to suspension of EU Marketing Authorisation (March 2021)

Health Technology Assessment (HTA) Opinions

Country(-ies)	HTA Body	Opinion
Finland, Norway, Sweden	FINOSE	Negative
United Kingdom	NICE	Negative
France	HAS	Positive
Netherlands	Zorginstituut	Negative

FACTORS HAVING CONTRIBUTED TO THE WIND-DOWN OF OPERATIONS – TIF'S PERSPECTIVE

COMPETENT HEALTH AUTHORITIES/ HTA/ PAYERS

1. Demonstrated a **belated/** no response to-date.
2. Limited knowledge on the **process** required for patients to have access to gene therapy
3. Confined knowledge on the different **concerns of patients** and HCPs
4. Limited to no knowledge on how to address **costs** (cost-effective VS clinical value studies)
5. Unaddressed concerns on the **durability of effectiveness and safety** of cure
6. Other **pharmaceutical advances** and the COVID-19 pandemic were on the table

INDUSTRY

1. **Very good interaction** with the patient community but not sufficiently transparent (pricing and costs)
2. **Not sufficient** and appropriate **interaction** with competent authorities/ HTAs/ Payers and HCPs on the frontline
3. **Overreliance on patient's advocacy**
4. Very **expensive** product production stages with **no** expressed or **planned strategies** on addressing this in future
5. Confined knowledge and consideration on multiple challenges of **cross-border collaboration** and services between EU members
6. **Poor** financial and other **management** policies of the company based on **unrealistic estimations** of numbers (absence of national registries)
7. Companies **shortcomings** and adverse events (SCD) delayed process and evoked uncertainties

INEFFECTIVE INTERACTION BETWEEN ACADEMIA

HCPs

1. **Belated/** no response to-date
2. Confused/ **concerned** on procedures related to **cross-border** services
3. Concerns on the **prioritisation** of eligible/ interested patients/ competencies, capacities of centres and manufacturing of the product
4. Uncertainty of the **durability** of safety and effect
5. Uncertainties on the degree of **risk** in **real-world** practice
6. **Limited interaction** with competent authorities, manufacturing company and academia

ADDITIONAL FACTORS

Qualified Treatment Centres (QTCs) in countries where thalassaemia is rare and/or not a priority:
Germany (1) – Discussions for more QTCs in Denmark, Sweden, Beneluxa countries, France)

Safety Concerns:
The Temporary Suspension of Marketing of ZYNTEGLO™ in Europe due to a Suspected Unexpected Serious Adverse Reaction (SUSAR) of acute myeloid leukemia and myelodysplastic syndrome in HGB-206 for SCD caused a series of delays in many countries, as negotiations stopped and in many never resumed.

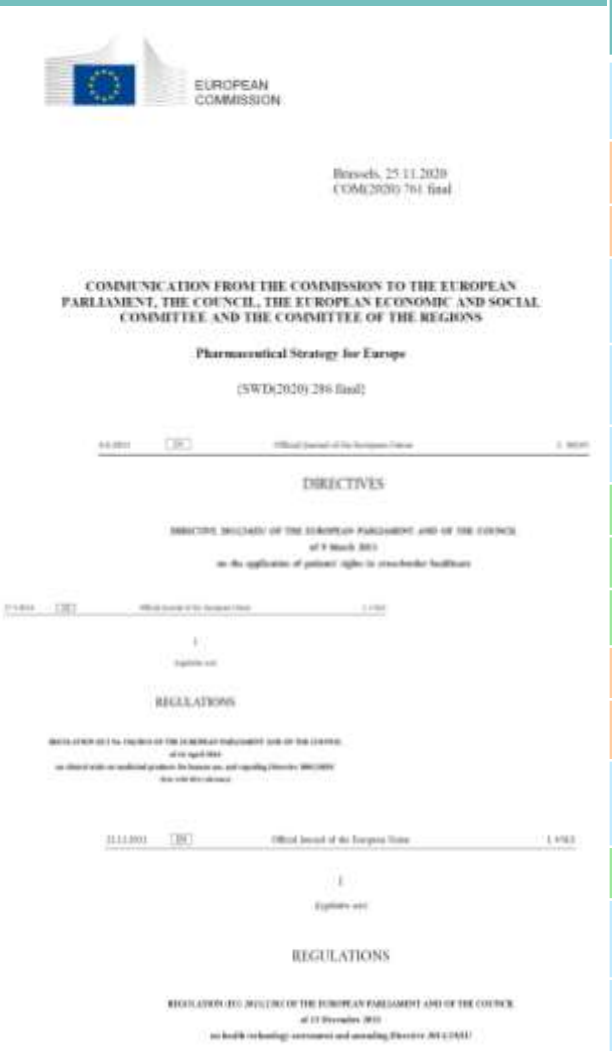
Health Technology Assessment (HTA) Opinions mostly negative because of:
- absence of patient participation;
- the hefty price tag;
- the existence of conventional treatment;
- the limited number of patients participating in clinical trials;
- the unknown number of patients living in each country due to the absence of registries;
- limited RWE.

No early dialogue or transparency:
When the product was granted market access, it already was too late for payers, healthcare professionals and patients to solve the access puzzle.

COVID-19-related burden on national health systems

EU MEMBER STATES WERE NOT READY TO INCLUDE A TRANSFORMATIVE THERAPY INTO THEIR NATIONAL HEALTH SYSTEMS

INITIATIVES SUPPORTING ACCESS TO NOVEL THERAPIES


EUROPEAN COMMISSION

Brussels, 25.11.2020
COM(2020) 761 final

COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS

Pharmaceutical Strategy for Europe

{SWD(2020) 286 final}

DIRECTIVES

REGULATIONS

REGULATIONS

Relevant EU Initiatives	Relevant Stakeholder Initiatives
European Industrial Strategy	European Expert Group for Orphan Drug Incentives – Recommendations for Action
Revision of the EU General Pharmaceutical Legislation	European Rare Disease Research Coordination and Support Action (ERICA)
Evaluation of the Orphan and Paediatric Legislation	International Rare Diseases Research Consortium (IRDiRC)
Horizon Europe	European Paediatric Translational Research Instrastructure – Paediatric Research Manifesto
HTA Regulation	ACCELERATE International Multi-stakeholder Platform – Paediatric Strategy Forum
Pharmaceutical Strategy for Europe	SIOP Europe Essential Medicines and HTA Evaluation Project
Implementation of the EU Clinical Trials Regulation	SIOPE Clinical Research Council (SIOPE CRC)
Implementation of the Medical Devices Regulation (MDR)	RARE IMPACT
Implementation of the In-Vitro Diagnostics Regulation (IVDR)	**TRANSFORM Alliance**
Revision of the EU Legislation on Blood, Tissues and Cells	RWE4Decisions
Revision of the Paediatric and Orphan Regulations	Get Real Institute
European Health Data Space	EAHAD-EHC Joint Statement on Promoting hub-and-spoke model for the treatment of haemophilia and rare bleeding disorders using gene therapies
EMA's DARWIN EU (Data Analytics and Real World Interrogation Network)	World Federation of Hemophilia Global Gene Therapy Registry
INSPIRE Knowledge Base	Screen 4 Rare
European Reference Networks	European Alliance for Newborn Screening for Spinal Muscular Atrophy (SMA NBS Alliance)
Evaluation of the Cross-Border Healthcare Directive	EURORDIS Key Principles for Newborn Screening
Cross-country collaborations such as BeneluxA or FINOSE	**Thalassaemia International Federation - TIF.ACCESS**
	ACN: Addressing the sustainability of ATMPs in a European perspective to broaden an equal access to highly innovative therapies

CONCLUSIONS

1. Lack of or confined **policy planning** prior to development and authorisation of the drug

2. Lack of or confined, transparent and extended **dialogue** between the producing company, regulators, HTA bodies and payers on:

a) The **high cost** and how to reduce it

b) How to best capture and translate the **value** of the product, understanding fully the **implications**, steps and **processes** involved in the treatment protocol

c) The value of promoting national **registries**

d) Complex legislative framework of **cross-border healthcare services**

e) Specific funds for ATMPs

f) Contribution/ use of ERNs

3. Lack of collaboration between countries that had HTA bodies and the competency to support other but also share experiences with them

4. Inability to address the **concerns** of HCPs, patients, families, competent authorities on limited data

- **Uncertainties** for long-term safety and efficacy

5. Lack of or confined deep and transparent involvement of first-line physicians to capture and understand the process of the therapy, the uncertainties and need for more Real World Evidence (RWE)

- to support their interaction with the patients/families and with regulatory authorities/ payers.

6. Limited to confined interaction of treating physicians, academics (scientists involved in clinical trials) with the patients and their families to discuss uncertainties – need for collection of more RWE

THE EUROPEAN COMPETENT AUTHORITIES, HCPS, ACADEMIA, PATIENTS/FAMILIES WERE NOT **"READY" (PROACTIVE ENOUGH)** TO ADDRESS THE EXISTING CHALLENGES.

The producing company was NOT READY either but had some **shortcomings**, **delays** and several **uncertainties**:

a) False, not well-grounded anticipations (**numbers**)

b) **Poor interaction** with competent authorities and HCPs.

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How will Europe avoid a repetition of such a failure and address the issue of providing access of patients to innovation?

- ✓ Must act proactively, in a patient-centred way to demonstrate patient benefit.
- ✓ Early dialogue, continuous and meaningful, with the involvement and interaction of Patients, HCPs HTAs, competent authorities & industry is imperative.
- ✓ Must promote collaborative work between EU Member States, HTA co-ordination, horizon scanning, price negotiation & reimbursement within a dedicated EU policy and regulatory framework
- ✓ Must always integrate a holistic disease cycle approach in assessment and HTA studies
- ✓ Promote a patient-focused new economic model for the development, marketing, pricing and reimbursement of advanced therapies – An EU fund proposal
- ✓ Ensuring the competitive pharmaceutical environment is strengthened without violating the rights of patients to have a safe and effective cure that is made **available** and **affordable** – affordability is crucial for achieving **access**.

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ACKNOWLEDGEMENTS

TIF BOARD OF DIRECTORS

TIF STAFF

TIF International Scientific Advisory Board & HCP Community across countries

TIF Members & every Patient/Parent Organization & Advocate

Thank you!