**Museo Storico della Città**
**Martedì 2 Giugno 2015**
**Lushnja, Ore 10**

# Conferenza scientifica sulla TALASSEMIA

## Nuove terapie farmacologiche nella TALASSEMIA

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# Main Concepts

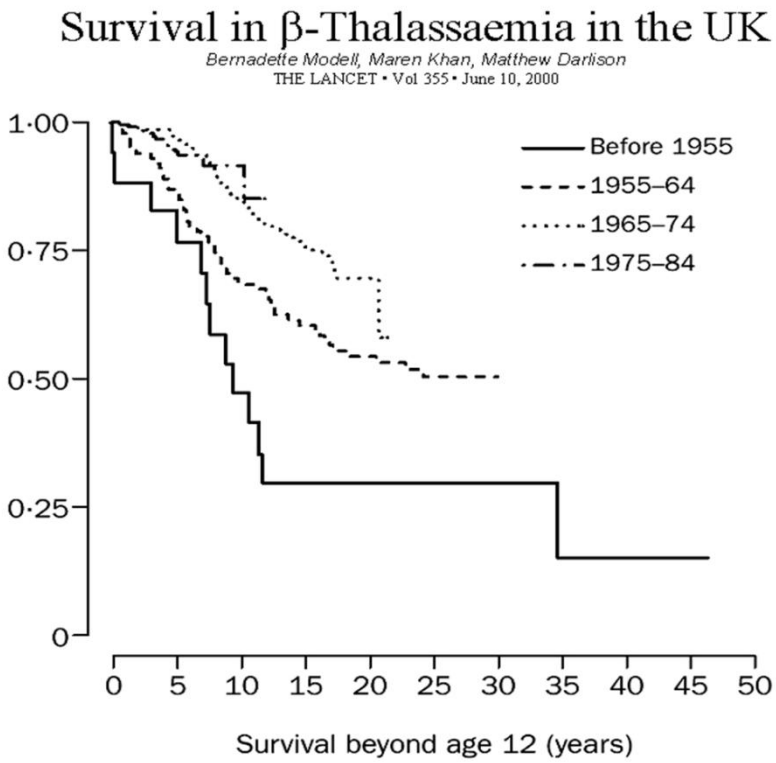
- Approximately 7% of the global population is a carrier for Haemoglobin disorders
- A carrier of a pathological Hb gene encounters no health problems
- Between 300,000 – 500,000 children are born annually with a severe haemoglobin disorder
- About 80% of affected children are born in middle and low income countries
- About 70% are born with sickle cell and the rest with thalassaemia disorders
- 50 – 80% of children with sickle cell anaemia and 50,000 – 100,000 children with β-thalassaemia major die each year in low and middle income countries

(World Bank 2006, report of a joint WHO-March of Dimes meeting 2006)

# Main Concepts

HPs (including thalassaemia major and sickle cell disease) are endemic disorders affecting **the Mediterranean, African and Asian regions** and currently the most common rare diseases of genetic origin in Europe

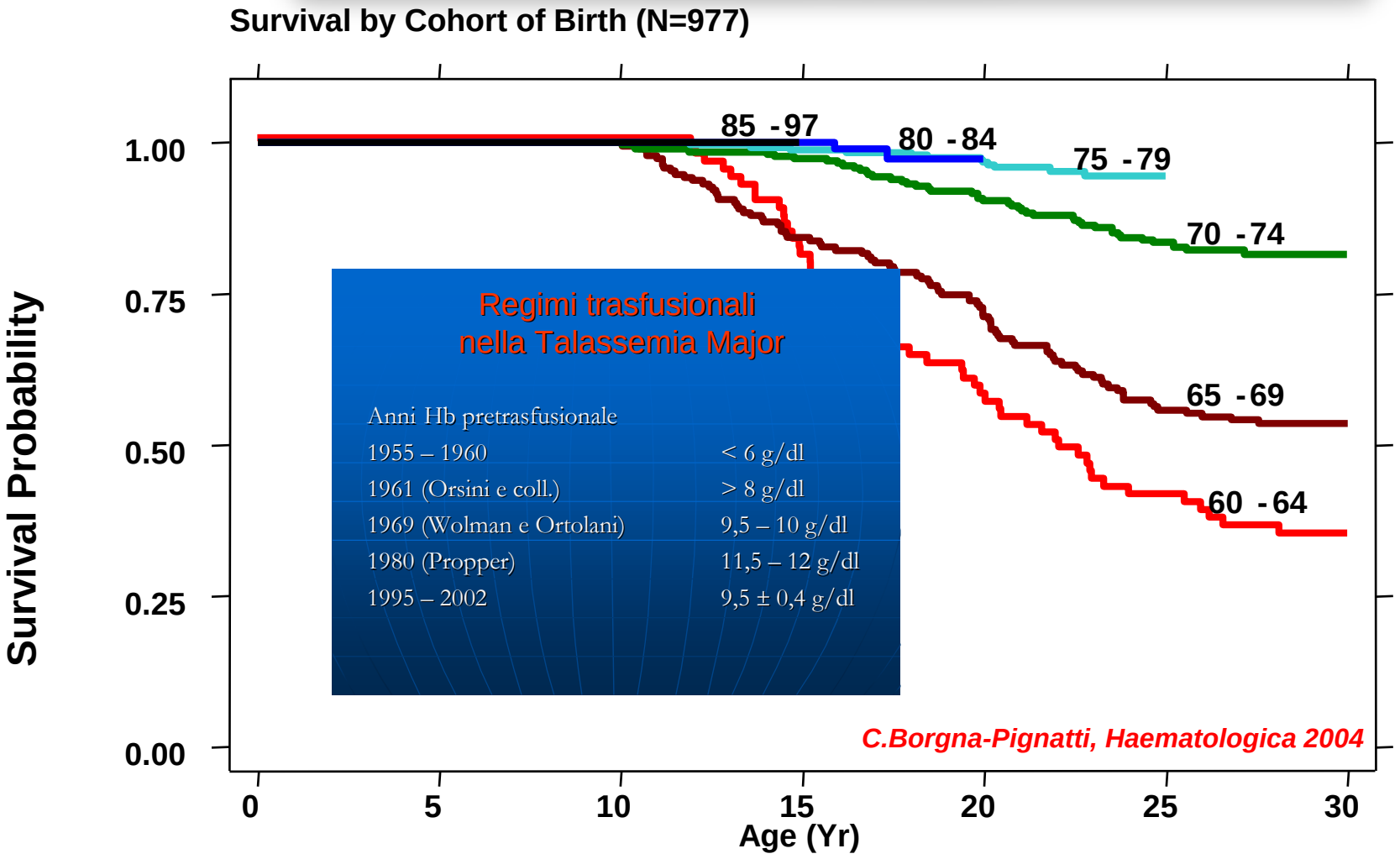
The growing migration flows have led to a global spread of many different HPs carriers and patients




For many years Thalassemia has lead to precocious death in infancy or adolescence

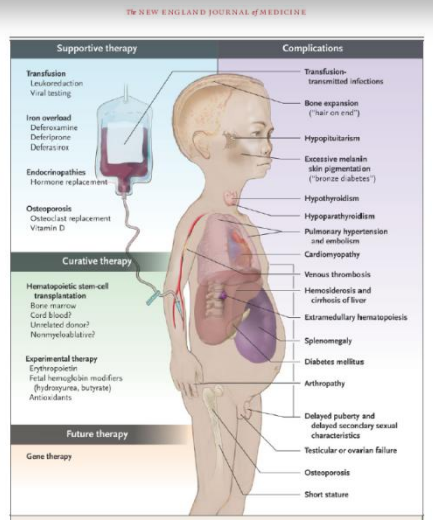
# Main Concepts

**Relevant improvement in patients survival due to chelation and blood transfusion**



# Main Concepts

Notwithstanding relevant results in survival, Thalassemia is not yet cured!
Death rate in transfused adult subjects is 3 times greater than the general population




Morbidity and mortality from transfusional Iron Overload

# TRENDS IN THALASSEMIA THERAPY

- **New or updated chelation Therapy**

**An** optimal chelation therapy for the treatment of iron overload in haemoglobinopathies is to be identified

- **Reduced RBC intake**

methods to induce production of non-thalassemia red blood cells or the modify the Hb-chains proportion are under development

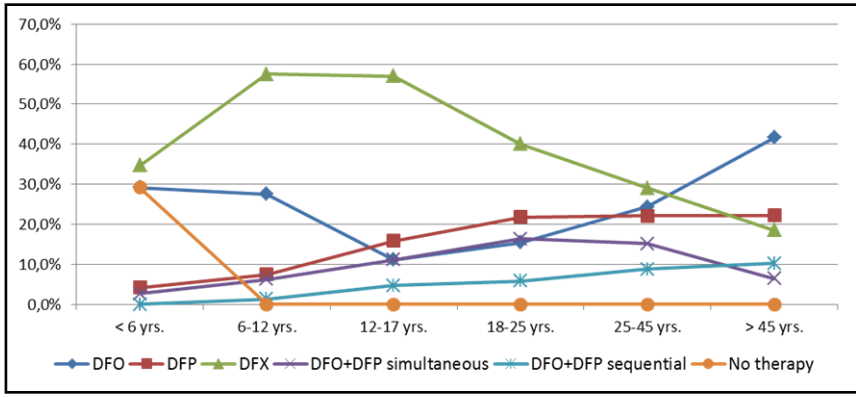
- **Provide curative therapy**

Bone Marrow Transplantation, stemcell and gene therapy can result curative

# New Chelation Therapy: why it still needed?

| | DFO | | DFX | | DFP | | Combined | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % |
| **N** | 448 | 23.9 | 616 | 32.9 | 383 | 20.4 | 399 | 21.3 | 1873 | 100 |
| **Age (*mean ± SD*)** | 32.2 ± 12 | | 27.7 ± 11.5 | | 32.4 ± 9.4 | | 31.7 ± 8.5 | | 30.4 ± 11.3 | |
| **Gender** | | | | | | | | | | |
| **Male** | 206 | 46 | 299 | 48.5 | 202 | 52.7 | 171 | 42.8 | 887 | 47.4 |
| **Female** | 242 | 54 | 317 | 51.5 | 181 | 47.3 | 227 | 57.2 | 983 | 52.6 |

Patients included in HTA-Thal Registry
(age-gender and chelators)




**The Italian Multiregional Thalassaemia Registry: centres characteristics, services and patients' population**
R. Conte, L. Ruggeri, A. Gambino, F. Bartoloni, P. Baiardi, D. Bonifazi, F. Bonifazi, M.G. Felisi, V. Giannuzzi, R. Padula, C. Putti, G. Del Vecchio, A. Maggio, L. Mangiarini, A. Ceci, *on behalf of the HTA-THAL Multiregional Registry (submitted 2014)*

# New Chelation Therapy still needed

The introduction of the oral chelators has progressively changes the prescription habits in children and young patients:

- **DFO** is progressively excluded from the chelation treatment in young patients
- **DFX** is the preferred therapeutic approach because well accepted
- **DFP** is acknoledged as the most appropriate for reducing the cardiac risk . Currently used in association with DFO
- **Optimal** chelation therapy has not been yet identified

# New Chelation Therapy still needed

***THE INTEREST OF THE SCIENTIFIC COMMUNITY IS STILL RELEVANT:***

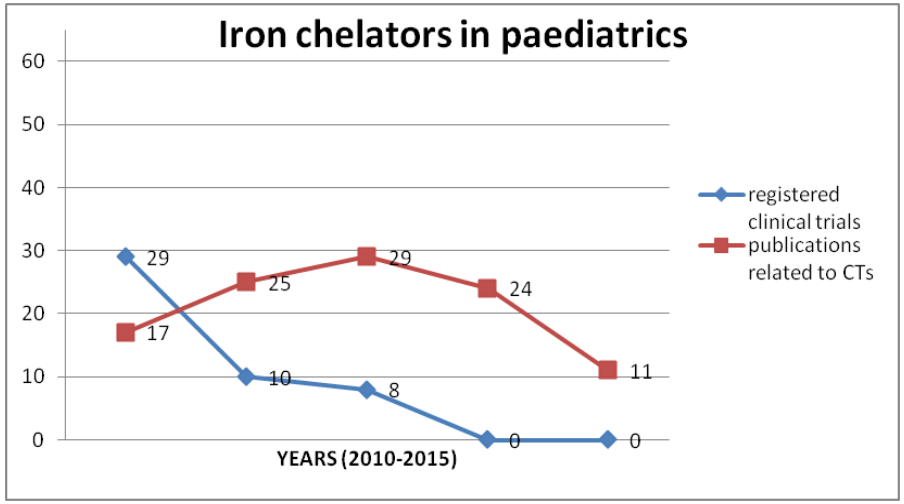
•In the last five years, 106 articles related to clinical trials in the paediatric population testin iron chelators have been published.

*(source: Pubmed, update 15/05/2015)*

***THE CLINICAL RESEARCH STATE OF THE ART:***

•In the last five years, 47 interventional studies testing iron chelators in paediatrics are reported in the global database of CTs

*(source: clinicaltrials.gov, update 15/05/2015)*



# New Chelation Therapy still needed

*Three paediatric investigation plans are ongoing testing new and old substances for chelation*

| Agreed PIP | FBS0701 | Deferiprone (DEEP) | Deferasirox |
|---|---|---|---|
| Indications/ Conditions | Treatment of chronic transfusional iron overload | Treatment of chronic transfusional iron overload | Treatment of chronic **non transfusion dependent** iron overload |
| Age groups | > 2 yrs | > 1 month | > 10 yrs |
| N° of clinical studies | 2 | 3 | 1 |
| Studies type and design | - E/S/Dose/PK Open Label,<br>- E/S Comparator-Controlled | -PK including modelling<br>-E/S randomised, open label, non-inferiority active-controlled<br>-Large, long-term safety | -Double-blind, randomised, multicentre, placebo-controlled study<br>- 5-year observational study (registry)<br>- Meta-analysis of safety and efficacy profiles |
| Comparator | Active: deferoxamine | Active: **deferasirox** | Active: deferoxamine |

# DEFERIPRONE (DEEP) EXPECTED ADVANCEMENT

| Product | Approved Indication and main SPmC variations |
|---|---|
| **FERRIPROX® (deferiprone)**<br><br>**MA under exceptional circumstances**: Ottobre 1999<br>The exceptional circumstances removed: May 2002 | ○ Ferriprox is indicated for the treatment of iron overload **in patients with thalassaemia** major when deferoxamine therapy is contraindicated or inadequate.<br><br>○ Paediatric population. **There are limited data available on the use of deferiprone in children** between 6 and 10 years of age, and no data on deferiprone use in children under 6 years of age. |
| Variation:26/01/2007<br><br>Variation:23/04/2008 | ○ Information pertaining to **chronic overdose** and the risk of neurological disorders<br><br>○ Following the review of the 15th Periodic Safety Update Report , the CHMP requested that the product information should be amended to include **headache** (common) and **fatigue** (common) |
| Variation: 20/05/2010 | ○ Update of section 5.1 of the Summary of Product Characteristics (SmPC) with new information from two clinical studies demonstrating that in **Ferriprox is effective** in protecting myocardial tissue |

# DEFERIPRONE (DEEP) EXPECTED ADVANCEMENT

To extend the existing indication to children <6 years

To develop comparative data on efficacy-safety in children >18 years

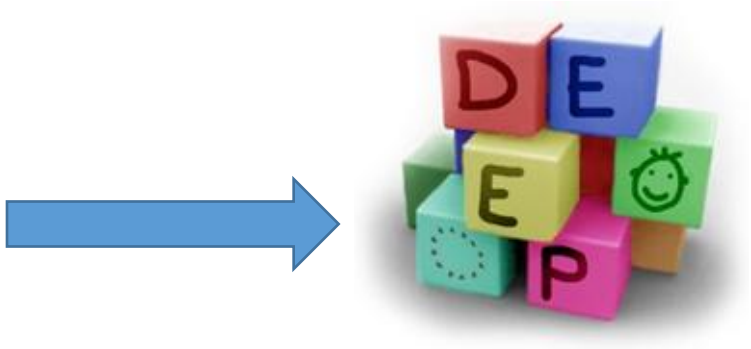
To develop PK/Efficacy/ long term Safety studies in this all Hb pathies population

**To move DFP to first line indication**

**To incorporate DFP benefits**

**in registrative trials**

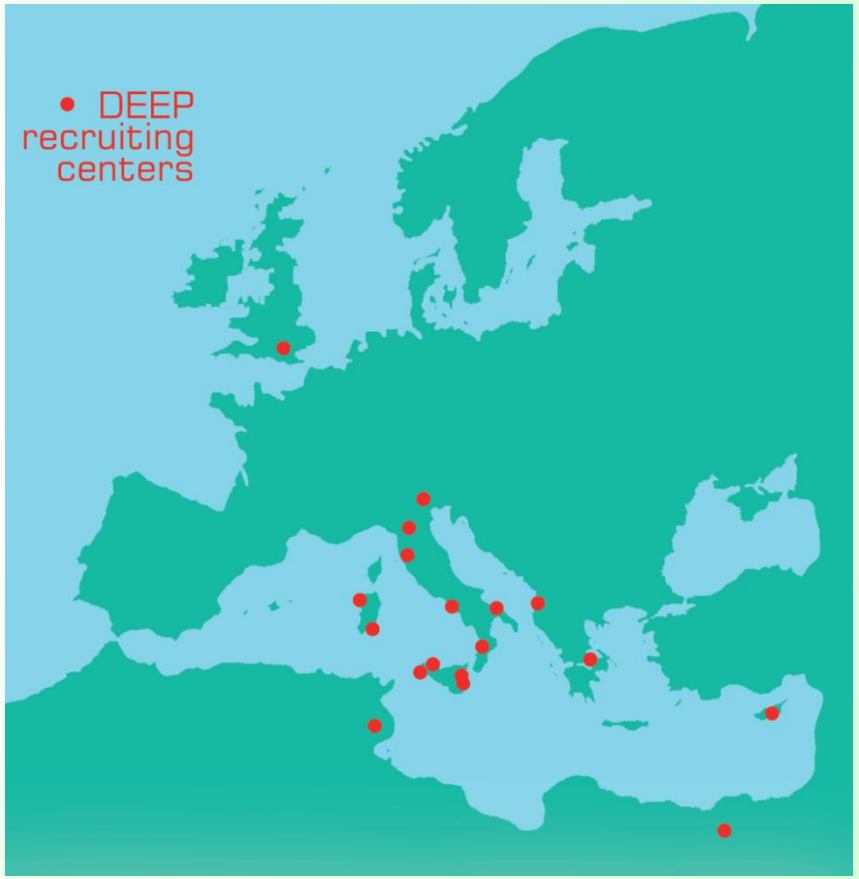
**To apply for a new marketing authorization devoted to children (PUMA)**



**SEVENTH FRAMEWORK**
**PROGRAMME**
**THEME [HEALTH.2010.4.2-1] [Off-Patent Medicines for Children.**
**FP7-HEALTH-2010-single-stage]**
Grant agreement for: Collaborative project*

A large researchers-driven Network including centres from :

- EU: Cyprus, Greece, Italy, UK (new)
- non-EU: Albania, Egypt, Tunisia, Morocco (new)
- probably new centres will be activate in Lebanon and Turkey
- industrial partners: to guarantee the commercial development of the drug (Apopharma-Apotex)




**Congenital Haemoglobinopathies including Thalassemia and Sickle Cell Disease: the more frequent congenital anaemias whose cradle is the Mediterraneum**

# DEFERIPRONE (DEEP) EXPECTED ADVANCEMENT

**Objective** to perform paediatric studies on ***deferiprone*** and to develop a new liquid formulation specific for the paediatric population

## Project contents:

**New Liquid Formulation**

**2 Clinical Trails:**

-PK trial providing dose definition (DEEP-1)

-efficacy-safety multicentre, controlled, active comparator trial (DEEP-2)

2 post marketing studies

long-term safety non-interventional study (DEEP-3)

pharmacoeconomic study

**A new Marketing Authorisation (PUMA)**

# DEFERIPRONE (DEEP) EXPECTED ADVANCEMENT

- Innovative approaches in CTs: ***DEEP-1*** **PK modeling/simulation** study to define the drug exposure and appropriate dosage of deferiprone for children aged < 6yr
- Deletion of the age-cut off. Inclusion criteria based only on number on **transfusional Fe** intake
- First time comparison between the **two oral available comparators**: ***DEEP-2****:* the **larger RCT** in *paediatric patients* comparing deferiprone vs deferasirox
- **Cardiac MRI-T2* as co-primary endpoint and liver MRI as secondary in children >10 years**

At the end of the proposed set of studies, deferiprone, will be available at efficacious dosages in children < 18 years as first line treatment. In addition a three year safety study will evaluate all deferiprone uses in the clinical setting

# (S)-3'-(OH)-desazadesferrithiocin-polyether, magnesium

EMA/609581/2010
Paediatric Committee (PDCO) and Human Medicines Development and Evaluation

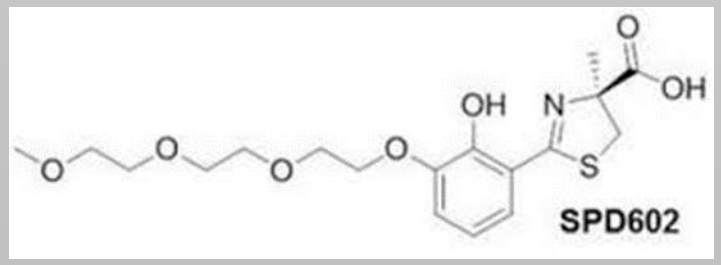
## EMA/PDCO Summary Report

on an application for a Paediatric Investigation Plan including a waiver

(S)-3'-(OH)-desazadesferrithiocin-polyether, magnesium salt

(FBS0701)

EMEA-001057-PIP01-10

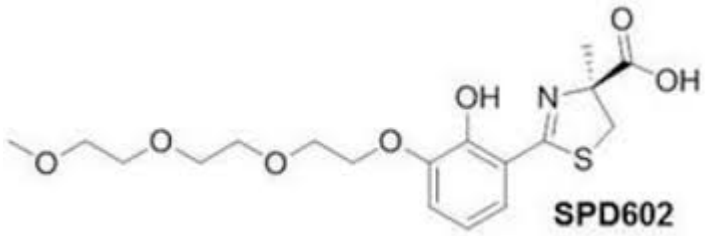



FerroKin BioSciences Ltd

It work by binding under physiologic conditions iron with high affinity.
It is a tridentate (like deferasirox) chelator and the resultant complex is extremely stable and excreted intact.

# SPD602 (SHIRE) EXPECTED ADVANCEMENT

A once-a-day, oral iron chelator with an anticipated improved safety profile versus Deferasirox.



SPD602

Developmental status.

- One phase 2 study has completed
- Two additional phase 2 studies currently ongoing to assess safety, efficacy & tolerability of SPD602 in the following patient populations:
  - pediatric and adolescent patients
  - adult patients with transfusional iron overload

- A long-term safety extension study (SPD602-301).

# Drugs aimed to reduce the RBC intake

## ***Substance: GSK1278863***

N-[(1,3-dicyclohexyl-6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-5- pyrimidinyl)carbonyl]glycine

*Class: HIF-Prolyl hydroxylase inhibitors (PHIs)*

*an emerging new class of therapies for the treatment of anaemia*

## ***Mode of action***

PHIs

**PHIs stimulate erythropoiesis**

*inhibition* ⇩ hypoxia inducing factor (HIF)-prolyl hydroxylases EGLN1, EGLN2, & EGLN3

*accumulation* ⇨ HIFα transcription factors

*increased* ⇨ transcription of **HIF-responsive genes**

This biological activity stimulates components of the natural response to hypoxia, stimulating endogenous erythropoietin (EPO) production and improving iron metabolism and utilization (hepcidin, hemojuvelin, ferroportin).

➔ **increased erythropoiesis and elevation in haemoglobin (Hgb) concentrations.**

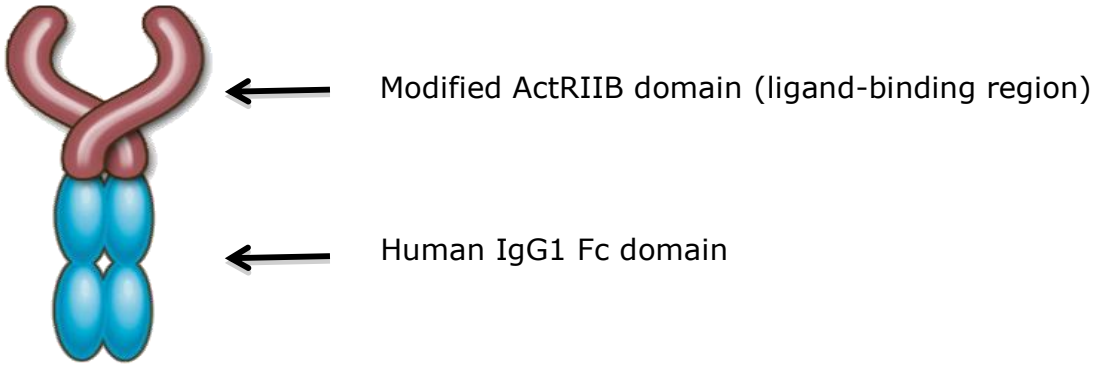
# Drugs aimed to reduce the RBC intake

- ACE-011: Phase 2 Trial of Sotatercept in Beta-Thalassemia at 2013 American Society of Hematology Annual Meeting. (non transfusion dependent)
- Luspatercept (ACE-536) has increased Hemoglobin and decreased the transfusion burden and serum ferritin levels in Adults with Beta-Thalassemia.

# Drugs aimed to reduce the RBC intake

ACE 11 and 536 are **recombinant soluble fusion proteis** with a modified form of the extracellular domain of **human activin receptor IIB** linked to the human IgG1 Fc domain involved in **modulating the differentiation of late-stage erythrocyte** precursors (normoblasts) in the bone marrow

**Figure 1. Illustration of xxxxx Structure**



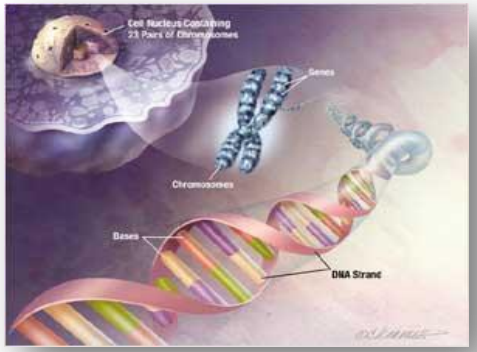

**Condition: Anaemias due to chronic disorders**

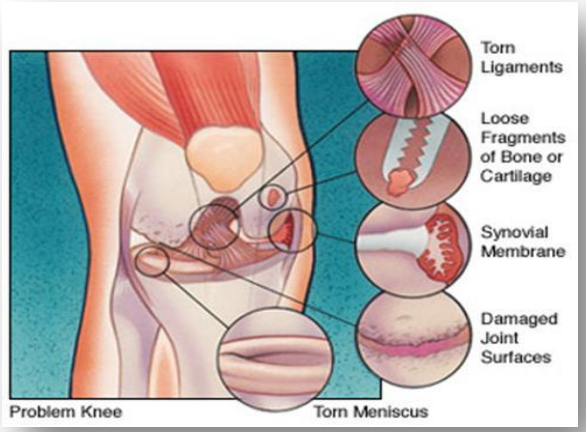
Proposed indication(s) in children: Treatment of anemia in patients with β-thalassemia

# Gene and cell therapies in Thalassema

'Advanced therapy medicinal product' means any of the following medicinal products for human use:

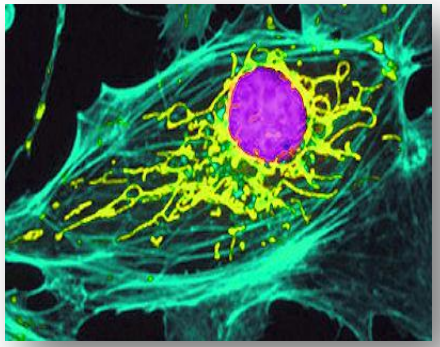
*Gene therapy product*




*Tissue engineered product*

*Somatic cell therapy product*



*Combined – in medical devices (Dir. 93/42/EEC; Dir. 90/385/EC)*

*– Regulation (EC) 1394/2007 –*

# Gene and Cell Therapies

| ACTIVE SUBSTANCE | Agency | designation date | ORPHAN INDICATION | SPONSOR |
|---|---|---|---|---|
| Autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human betaA-T87Q-globin gene | EMA | 24/01/2013 | Treatment of beta thalassaemia intermedia and major | Bluebird Bio |
| Autologous CD34+ hematopoietic stem cells transduced with LentiGlobin BB305 lentiviral vector encoding the human BA-T87Q-globin gene | FDA | 18/03/2013 | | Bluebird Bio |
| Autologous haematopoietic stem cells transduced with lentiviral vector encoding the human beta-globin gene | EMA | 29/04/2009 | | EGT San Rocco Italia SRL |
| Lentiviral vector encoded with a human beta-globin gene plasmid | FDA | 11/01/2006 | | Errant Gene Therapeutics, LLC |
| Human Autologous Bone-Forming Cell Derived From Bone Marrow Stem Cells | FDA | 24/03/2008 | Treatment of severe congenital Factor XI deficiency | Lab. français du Fractionnement et des Biotechnologies |
| Lentiviral vector carrying the Fanconi anaemia-A (FANCA) gene | EMA | 17/12/2010 | Treatment of Fanconi anaemia type A | CIBERER |
| Adeno-Associated Viral Vector Containing A Codon-Optimised Human Factor Ix Gene (Aav5-Hfixco) | FDA | 22/12/2011 | Treatment of haemophilia B | uniQure biopharma B.V. |
| Adeno-associated viral vector containing the human factor-IX gene | EMA | 11/01/2012 | | Amsterdam Mol. Therapeutics |
| Adeno-associated Viral vector containing the gene for human coagulation factor IX | FDA | 13/06/2001 | I.m. treatment of patients with moderate to severe haemophilia | Avigen, Inc. |

# *Gene and Cell Therapies*

**HGB-205:** New clinical data from bluebird bio gene therapy studies was released at 56th American Society of Hematology (ASH) Annual Meeting & Exposition, 7 December 2014, in San Francisco.

The first four Beta thalassemia major patients treated in these studies who have at least 3 months of follow-up are now all transfusion free, support by rapid and robust production of the therapeutic globin from the gene vector.

The first ever sickle cell disease patient was also treated with gene therapy in the HGB-205 study in October.

# Conclusions

After the Blood Transfusion, pharmacological agents (chelators) have represented the main factor to improve thalassemia patients survival and quality of life

At today additional improvement is expected by the Pharmacological research that is very active in the sector

Updating of existing chelators or discovery of new chelator agents could lead to personalize chelation treatment by age, complications and, may be, genetics

New emerging class of drugs could reduce the BRC intake and iron overload complications

Gene therapy could finally cure Thalassemia and other haemoglobinopathies patients

# Conclusions

**Attention should be paid to:**

Inequality still affecting low income populations where the priority is to have full access to the existing 'gold standard' treatments. This is not already achieved in many Mediterranean Countries.

Sustainability of the cure in all the European/non European countries. In fact the access to the cure is strongly affected by the increasing cost of the innovative treatments and the decreased budgets for the Government

*"The enjoyment of the highest attainable standard of health is one of the fundamental rights, of every human being, without distinction of…"*

**Word Health Organisation (WHO) in 1948 and behind!!**