Challenges in drug development for haemoglobinopathies

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Public Declaration of transparency/interests*

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Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

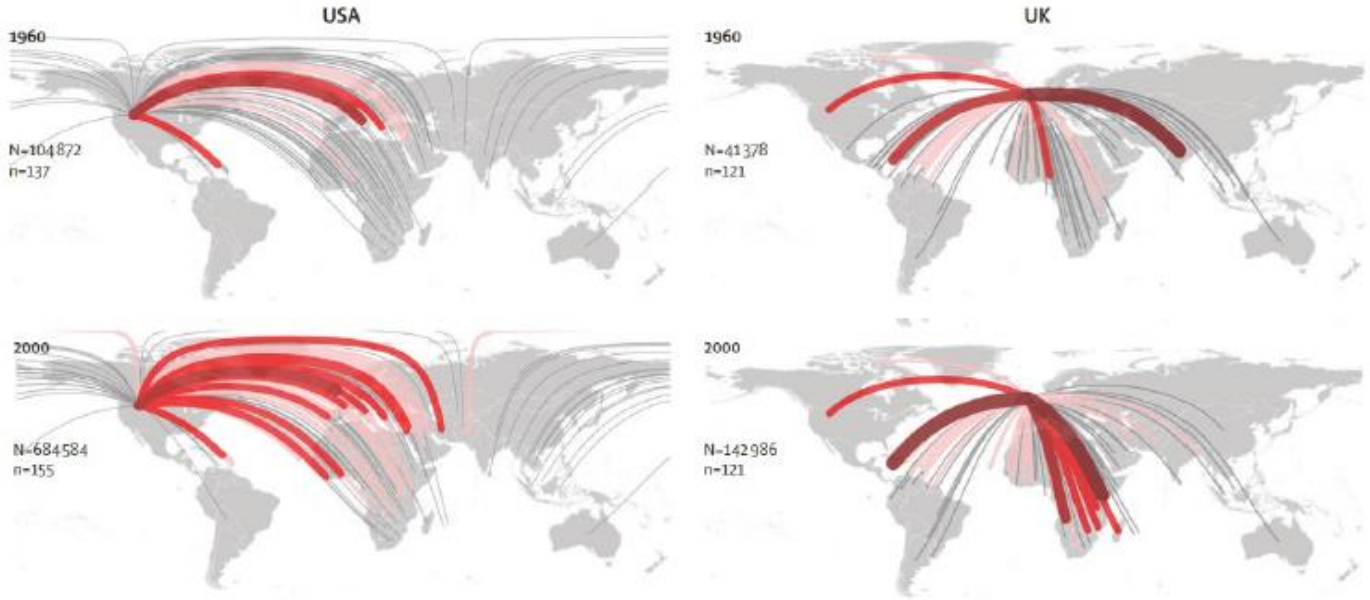
*Antonella Isgrò, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (Resolution n. 37 dated 13/10/2020).

N.B. I am not receiving any compensation

In recent decades, the globalization of migration has contributed to generate multiethnic European societies.

Global migration and the changing distribution of sickle haemoglobin: a quantitative study of temporal trends between 1960 and 2000

Frédéric B Piel, Andrew J Tatem, Zhuojie Huang, Sunetra Gupta, Thomas N Williams, David J Weatherall



(*Lancet Glob Health 2014; 2: e80–89*)

The advancements in clinical trials using new drugs and therapeutic procedures could ameliorate the quality of life of these patients and increase their life expectancy, but....

Hemoglobinopathies are rare and phenotypically diverse.

A trial that targets a clinical problem occurring in a subgroup restricts the number of eligible participants

Limits for CTs

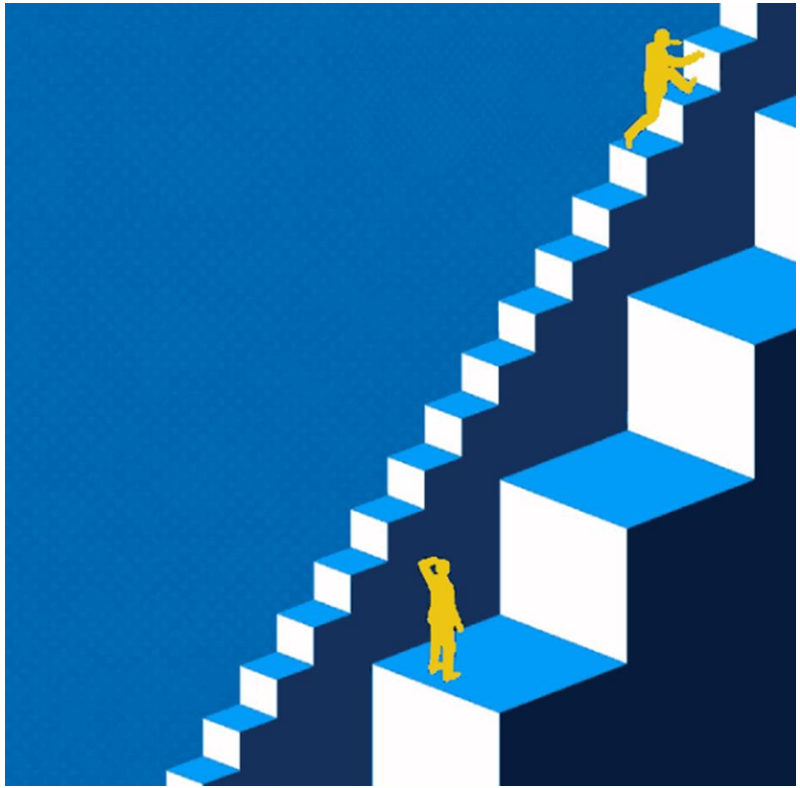
The clinical problem addressed by a specific trial (such as VOC or ACS) may be an acute event with a frequency that is not predictable

Investigators may overestimate the number of participants (feasibility)

Haemoglobinopathies: an opportunity for Academia

Therapies targeting different pathophysiological mechanisms of SCD:

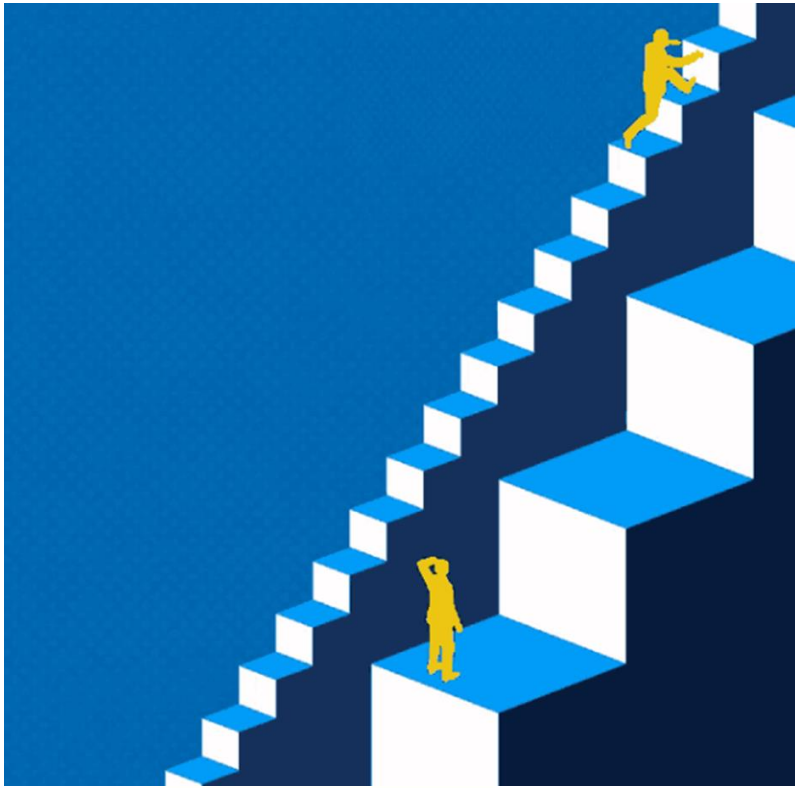
- modulation of Hb polymerization, erythrocyte dehydration, and Hb oxygen affinity
- prevention of vasal occlusion by inhibiting cell interactions
- prevention of endothelial dysfunction
- modulation of inflammation



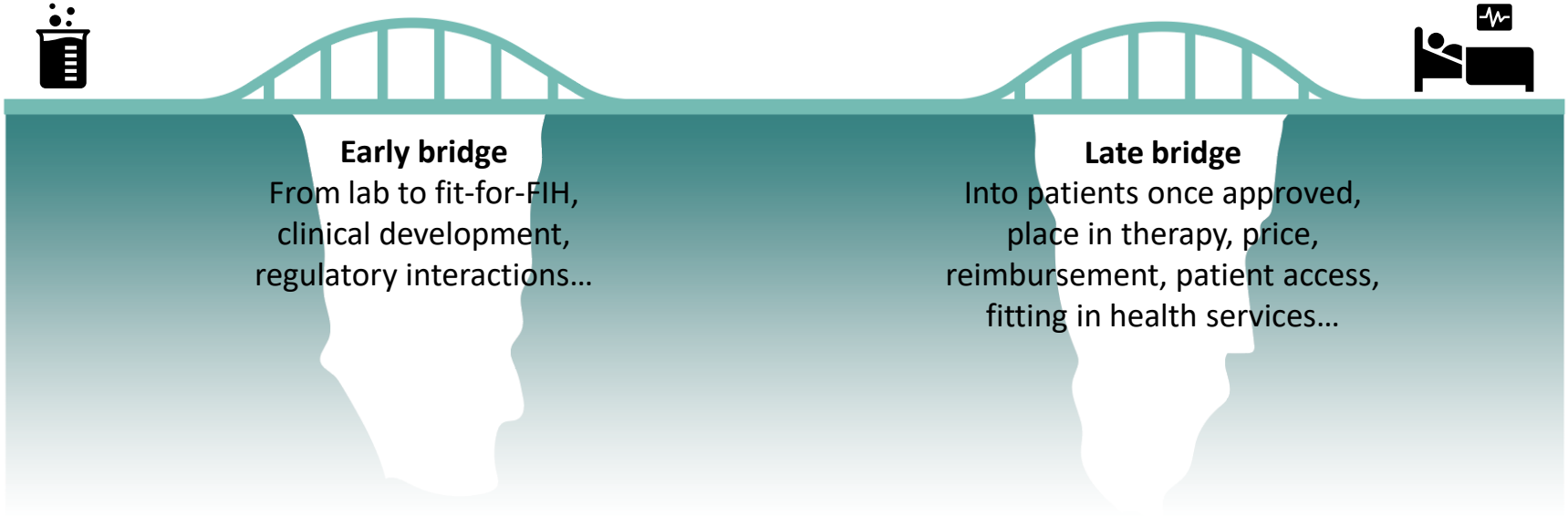
Haemoglobinopathies: an opportunity for Academia

Emerging therapies for thalassaemias based on their pathological target:

- addressing ineffective erythropoiesis and/or hemolysis (TDT and NTDT)
- modifying iron metabolism
- altering globin gene expression



Evidence from Academic/Pharma industrial research for translation needs to be solid and serve several masters



ODDs have stimulated research efforts in the area of rare diseases

10 of 28 ODDs for β-THAL (36%) have been discontinued (2 in the preclinical stage and 8 in Phase II);

12 (42%) are active (1 in the preclinical stage, 3 in Phase I and 8 in Phase II).

Six ODDs, relating to four APIs, are now licensed for the treatment of β-THAL.

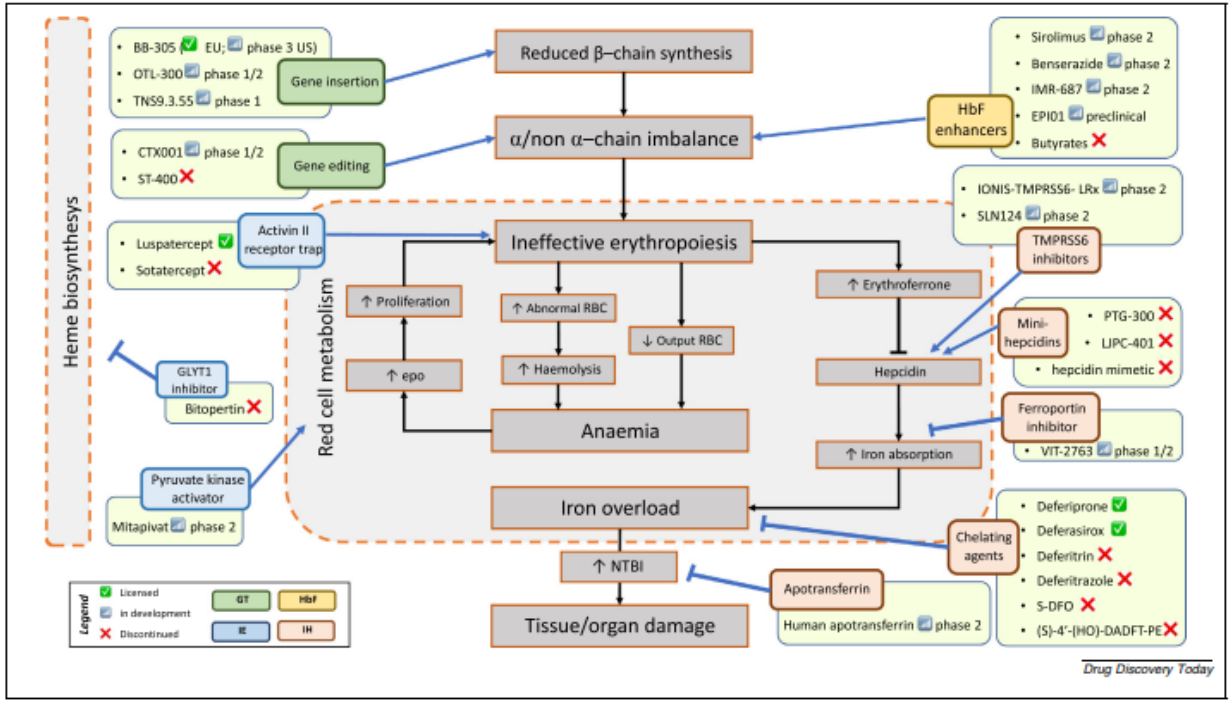


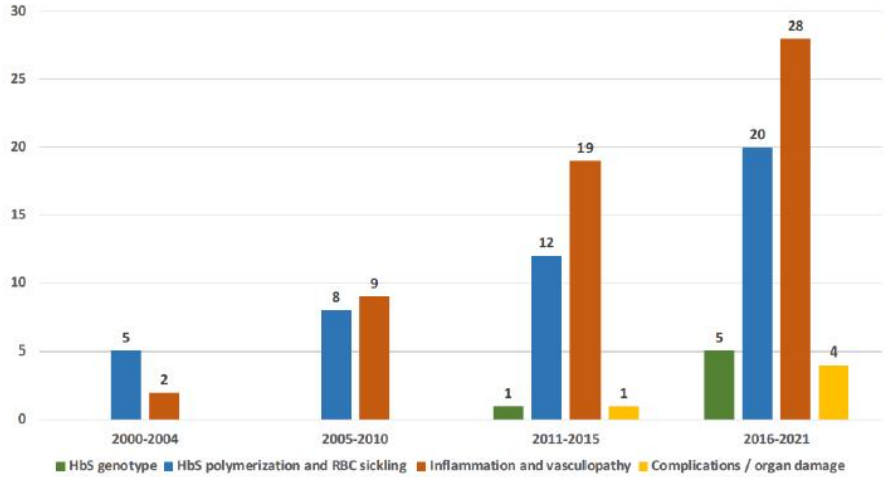
FIGURE 3

Pathophysiology of β-thalassemia (β-THAL) and therapeutic targets of Orphan Drug Designations (ODDs). In graph details all ODDs granted in the US and the European Union (EU) from 1983 to 2020; how the respective drugs work; and the outcome of each ODD. Abbreviations: GT, gene therapy; HbF, fetal hemoglobin; IE, ineffective erythropoiesis; IH, iron homeostasis; NTBI, Non-transferrin-bound iron; RBC, red blood cell.

(Costa et al. Drug Discov Today. 2022 Nov;27(11):103342)

REGULAR ARTICLE
blood advances
Check for updates

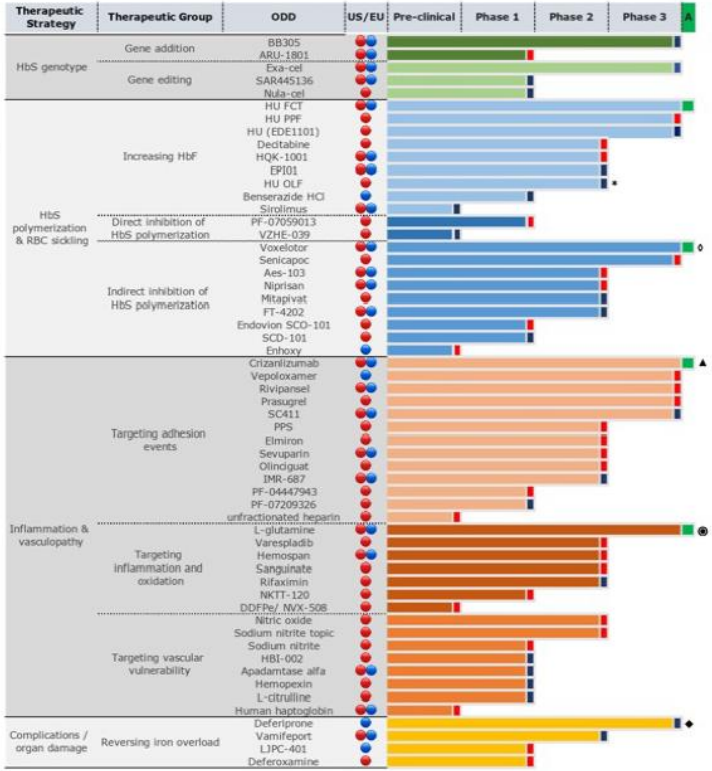
…and for SCD



- 20 years of sickle cell orphan drug development has ~12% success rate, with highest rates when targeting early pathophysiological steps.
- Failure rates for lack of efficacy were highest in late stages of drug development when vaso-occlusive crisis was the key clinical endpoint.

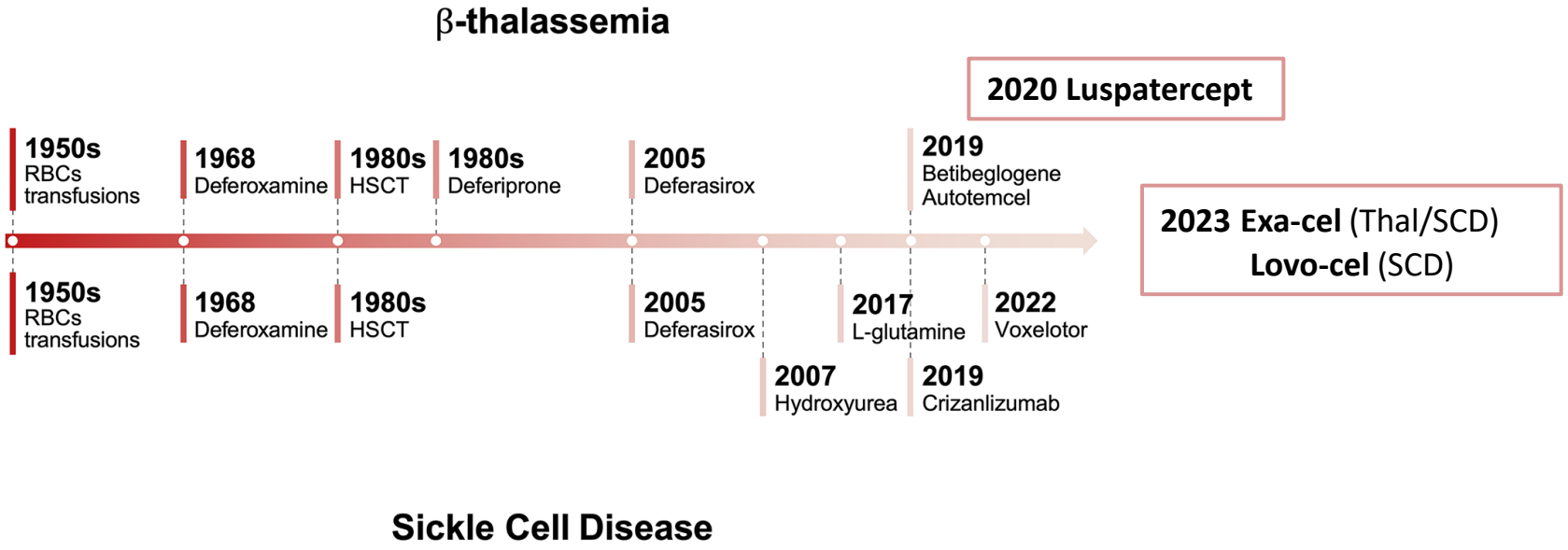
Successes and pitfalls in orphan drug development for sickle cell disease

Enrico Costa,[1] Antonella Isgrò,[2] Mariane de Montalembert,[3] Hubert G. M. Leufkens,[4] Russell E. Ware,[5] and Lucia De Franceschi[6]



(*Costa et al. Blood Adv. 2024 May 28;8(10):2455-2465*)

Milestones in the development of treatments for THAL and SCD



(modified from *Ferraresi et al. European Journal of Pediatrics (2023) 182:2509–2519*)

Challenges

TRIAL POPULATION

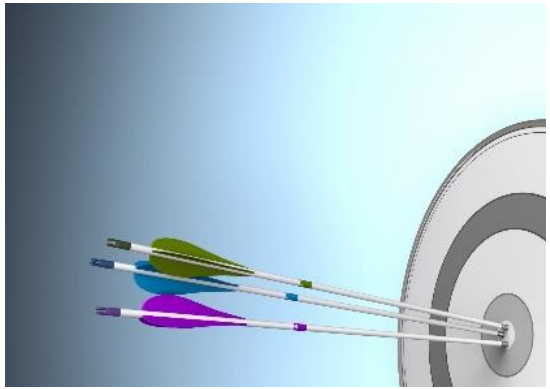
Regulatory perspective: For clinical research results to be generalizable, the enrolled participants in the research study should reflect the population affected by the condition or those for whom the treatment or intervention is intended.

Haemoglobinopathies have substantial genotypic and/or phenotypic heterogeneity. Different phenotypes may present with involvement of different organ systems, with different severity or rate of deterioration. In addition, metabolism and interindividual response variability seem linked to genetics of poorly characterized enzymes and differences between races cannot be excluded (*Pharmacogenomics J. 2018 Dec;18(6):730-739. doi: 10.1038/s41397-018-0045-1).*

Impact on representativeness of early clinical data

Clinical trials

- In accordance with principles of guidelines for specific therapeutic area
- For EMA scientific advice (or MAA national advice)
- RCT preferable over SATs but may not be feasible



Efficacy primary endpoints

- established and validated disease-specific endpoints accepted
- non-validated clinical or biomarker endpoint would have to be validated before being accepted in a clinical trial
- need for long-term follow-up for efficacy/safety also to assess durability of effect (i.e., ATMP)

In the era of gene therapy and gene editing as a potential cure

Primary endpoints

- Primary endpoint
  - Thalassaemia: TI12 = achieving transfusion independence, i.e. proportion of patients with weighted average Hb ≥ 9 g/dl without transfusion for at least 12 consecutive months any time after CTX001 infusion
  - Sickle cell disease: VF12 = being VOC free, i.e. proportion of patients that did not experience severe vaso-occlusive crisis for at least 12 months after CTX001 infusion

Specific clinical endpoints of cure related to SCD phenotype

VOC

PROS:

- Tracking the frequency and severity of VOCs (in terms of hospitalization and opioid use)
- Development of prior pharmacological therapies exclusively utilized VOC as a clinical efficacy endpoint

CONS:

- Focus on VOC did not capture the full extent of disease symptomatology and complications and slowed the development of new therapies
- Most SCD patients (94.8%) have infrequent VOCs requiring hospitalization (< 3 annually) and are excluded from VOC-focused trials
- SCD patients can have lifelong complications in addition to pain (i.e., anaemia)

management of uncertainties

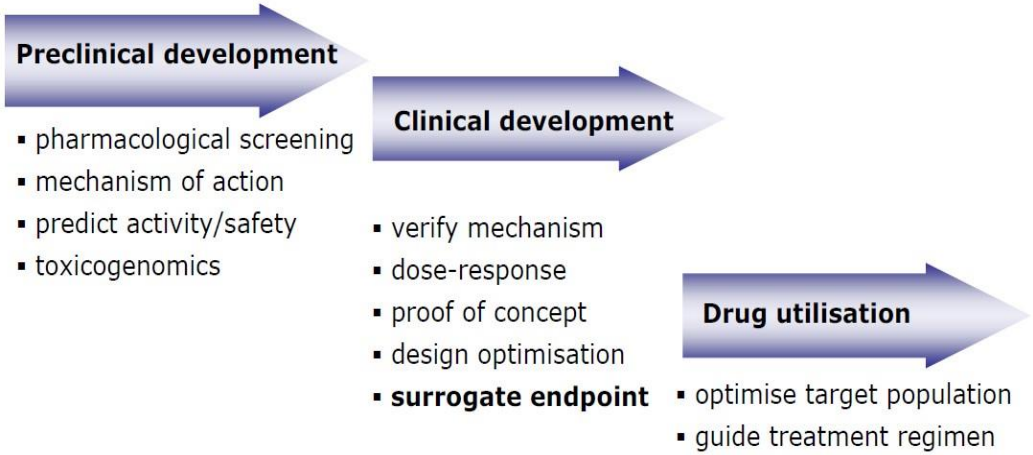
	Voxelotor	Crizanlizumab	
Full MA	The primary efficacy endpoint of **Hb response (percentage of subjects achieving a >1 g/dL increase in Hb from baseline at Week 24), together with secondary endpoint (change from baseline in Hb and clinical measures of haemolysis at Week 24)**, served as the basis for the marketing authorization of voxelotor in the EU for the treatment of haemolytic anaemia due to SCD in adults and paediatric patients 12 years of age and older.	For crizanlizumab, the primary efficacy endpoint was **the annual rate of sickle cell related pain crises (SCPC or VOC)**. The key secondary efficacy endpoint was the **annualised rate of days hospitalised.** At time of its approval in the EU, data supporting the effects of crizanlizumab were not considered comprehensive due to some uncertainty about the size of crizanlizumab's effect. The medicine was therefore granted a **marketing authorisation on condition** that the company provided data from the STAND (CSEG101A2301) study in order to confirm the efficacy and safety of the medicine.	**CMA & confirmatory trial**
	Voxelotor received a full marketing authorisation valid throughout the EU on 14 February 2022.	Crizanlizumab: revocation of EU marketing authorisation due to lack of therapeutic efficacy (03/08/2023).	

ASH-FDA consensus recommendations for SCD endpoints & Lancet Haematology Commission

- The ASH and FDA developed consensus recommendations for trial endpoints, resulting from the SCD Clinical Endpoints Workshop.
- Recommendations were focused on endpoints in PROs, pain, specific clinical endpoints related to SCD phenotype, and endpoints in low-resource settings (*Farrell et al. Blood Adv. 3 (23) (2019) 4002–4020; Farrell et al. Blood Adv. 3 (23) (2019) 3982–4001*).
- "Defining global strategies to improve outcomes in sickle cell disease: a Lancet Haematology Commission“ (https://www.thelancet.com/commissions/sickle-cell-disease).

(Lancet Haematology July 2023)

Qualification Advice & Opinion - Novel methodologies



- **Identification and Development of Biomarkers** (as intermediate endpoint or surrogate endpoints in clinical trials).
- **Long-term endpoints concerning organ function** (e.g., cardiac, pulmonary, endocrine, renal, neurological, bone and splenic function).
- **PROs** can be determined with **patient and caregiver** input using validated measures.

High standards of evidence in the interest of patients and society: a joint effort

Post-Authorisation, Registry Data

Due to the rare nature of the disease and patient availability for clinical studies, efficacy/safety data could be limited to pre-approval. Therefore, additional data may need to be collected in the post-marketing through dedicated PASS/PAES and/or Registries

Information obtained from Registries play an important role at every stage of drug development, from drug discovery to the design of clinical studies intended to support MA of a drug and beyond into the post marketing period.

Three main areas for which RWD analyses can support EMA committees' decision-making

1 Understand the clinical context	2 Support the planning and validity	3 Investigate associations and impact
Disease epidemiology	Design and feasibility of planned studies	Effectiveness and safety studies
Clinical management	Representativeness and validity of completed studies	Impact of regulatory actions
Drug utilisation		

WE CAN DO MORE...

- Increase the synergy between European research teams working on the pathophysiology of THAL/SCD at preclinical levels and the subsequent clinical development (i.e., initial orphan designations, protocol assistance, COMP, SAWP).

- Involve a larger number of patients in clinical trials (i.e., α-thalassaemia major or intermedia, HbS/C, HbS/β etc.).

- Data on new therapies regarding children are currently limited and access to new therapeutic approaches in children is often delayed since most clinical trials involve only adults at first. This should be carefully considered.

- Generate common action at the European level to ensure optimal care of THAL/SCD patients (especially for those who do not currently have access to specialist clinical services in many parts of Europe).