DEEP-2 preliminary results: a best practice in FP7

Antonis Kattamis

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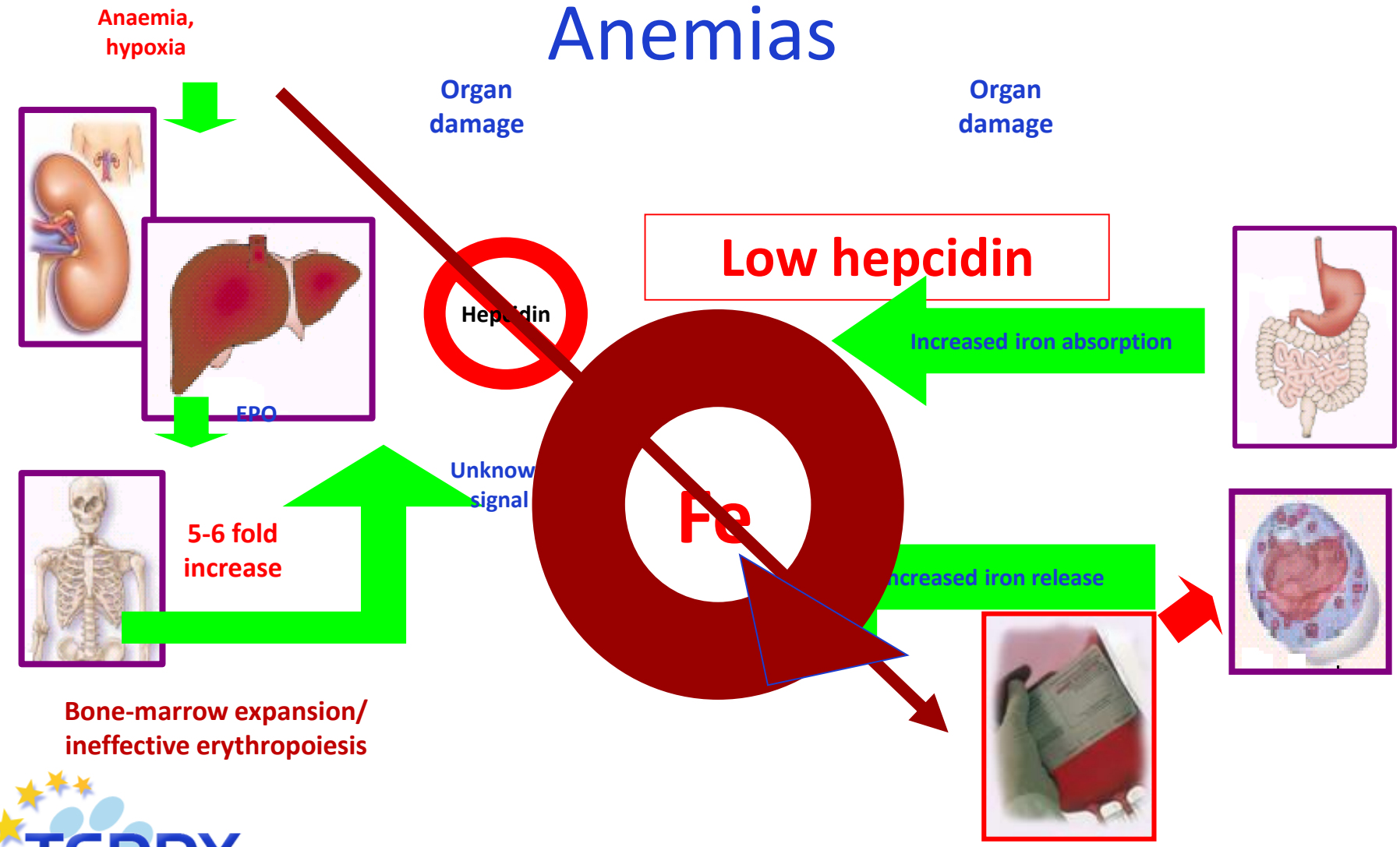
Iron Load in Transfusion Dependent Anemias



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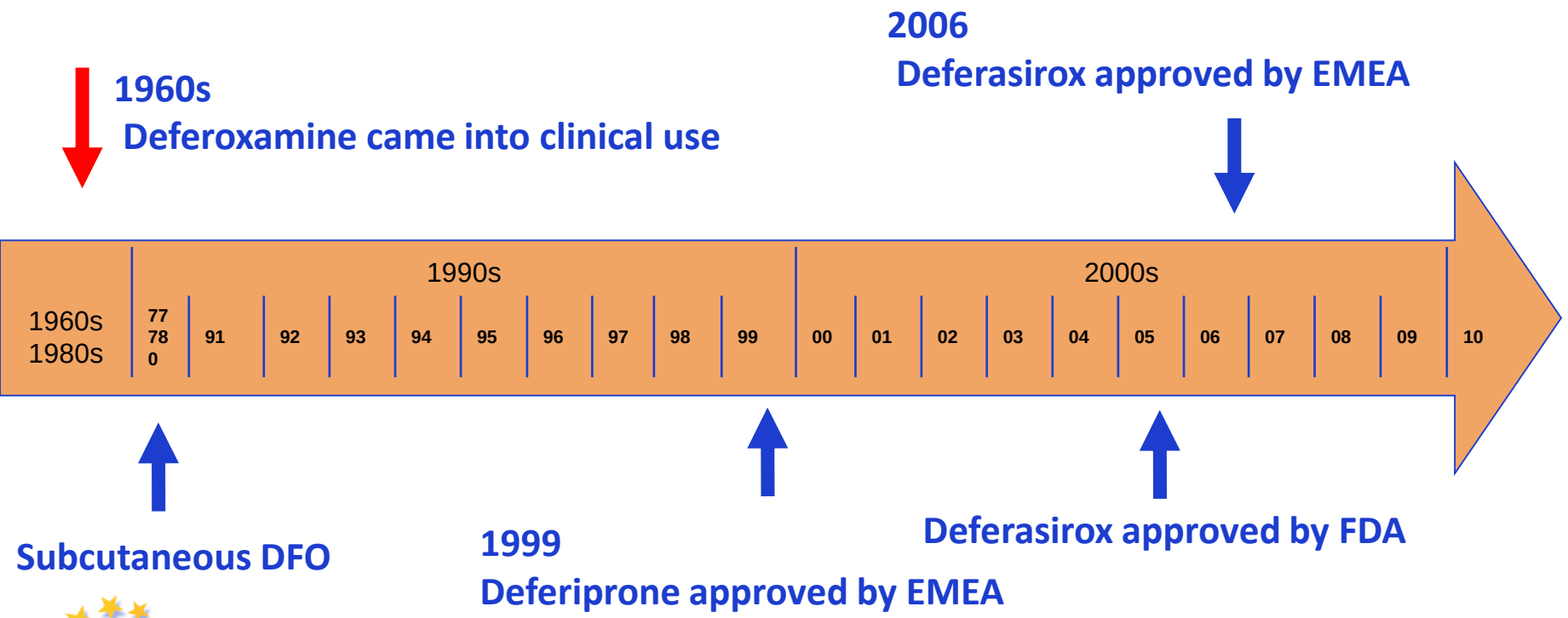
TOTAL = x20 times more Fe than healthy individuals

Evolution in Iron Chelation



FDA, Food and Drug Administration, USA

EMEA, European Medicines Agency;

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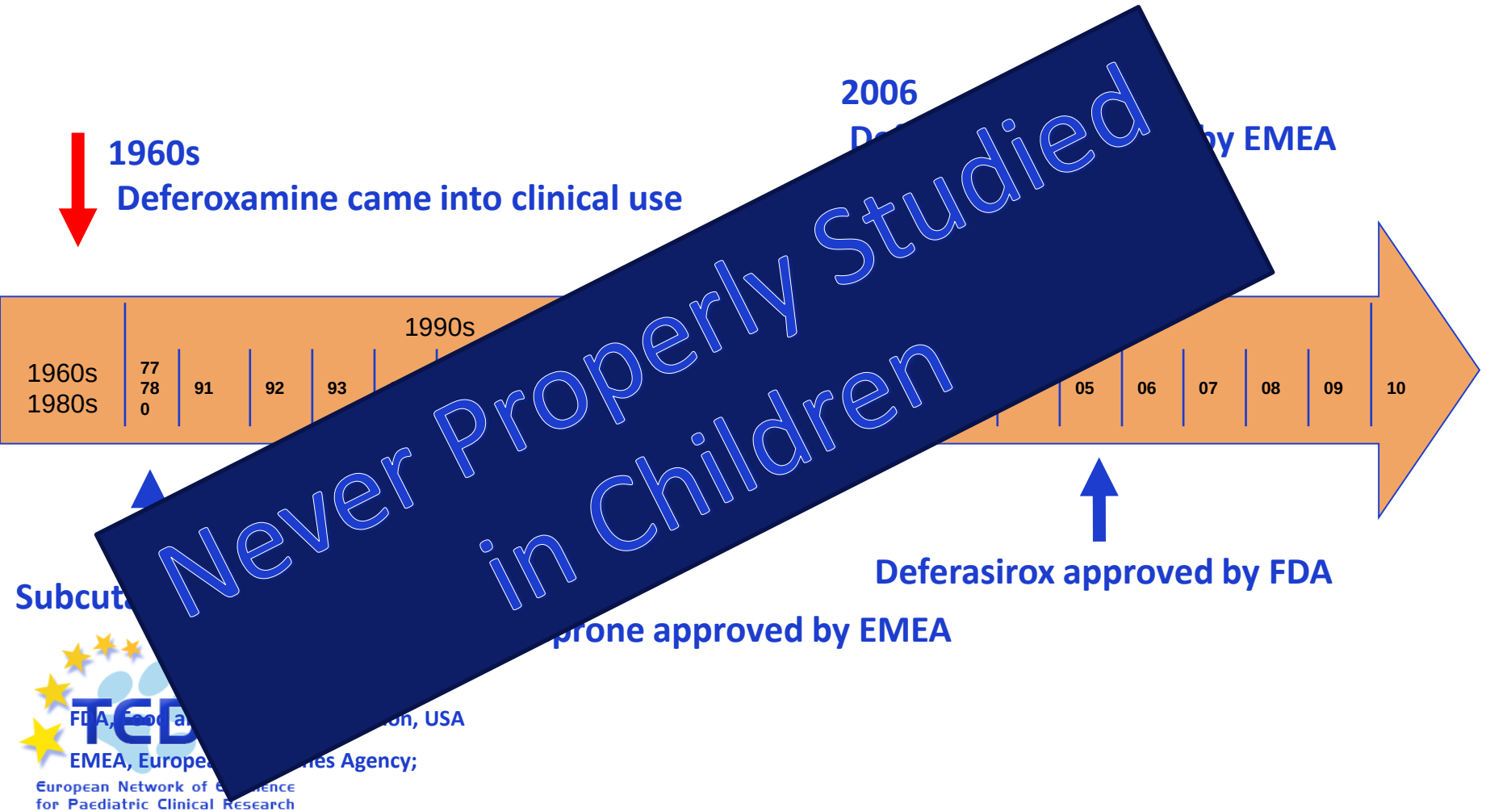
Evolution in Iron Chelation



DEFERIPRONE EVALUATION IN PAEDIATRICS

Unmet Medical Need

5-years research project funded by the European Commission within the 7th Framework Program (Health 2010.4.2-1)

A **multinational project** aimed to make more reliable treatments available to children for
beta-thalassaemia, sickle cell disease and other congenital haemoglobinopathies
which represent the most severe forms of anaemia in the world with specific reference to the Mediterranean Area

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Project contents

- **new liquid formulation – Partnership with ApoPharma**

- **2 clinical trials:**
  - PK trial providing dose definition (DEEP-1)
  - efficacy-safety multicentre, with active comparator, controlled trial (DEEP-2)
- **a post-marketing study**
  - long-term safety non-interventional study (DEEP-3)
- **pharmacoeconomic evaluation**

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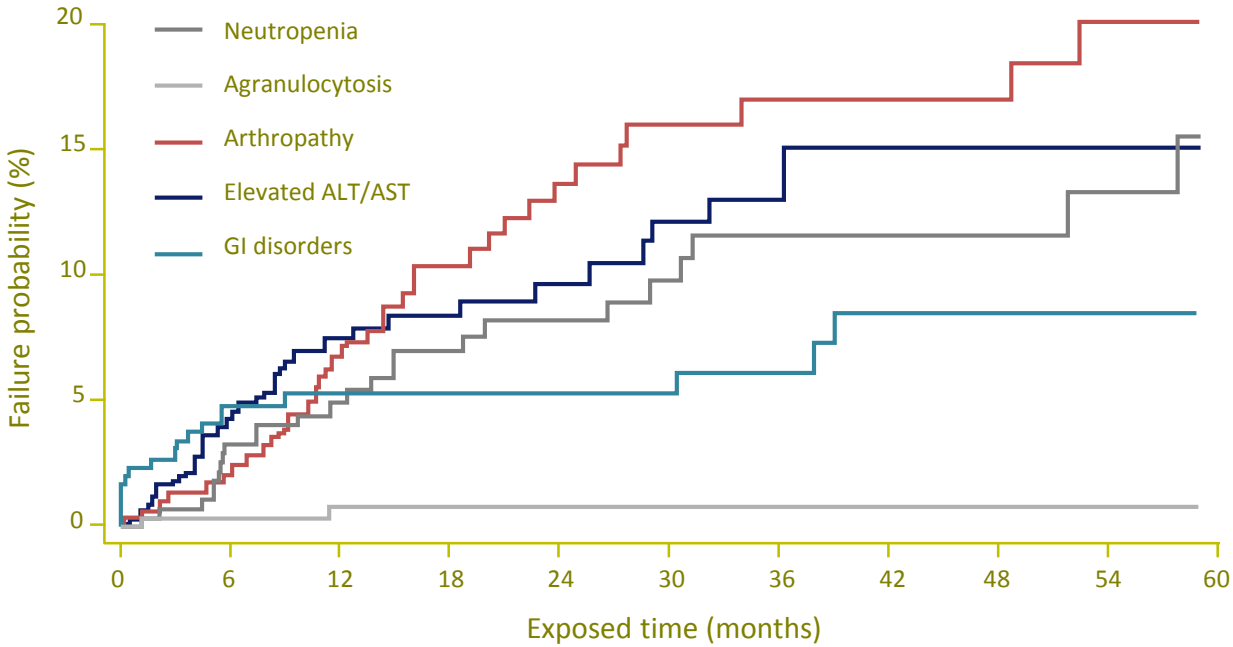
DEEP-3
multi-center observational safety study

Longitudinal safety analysis in 297 DFP-treated patients showed that the incidence of some AEs increased over time; most resolved following dose reduction, interruption or withdrawal



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Botzenhardt S *et al Haematologica* 2017; Epub ahead of print

DEEP-1 Study

Multi-centre, oral single dose experimental and modelling study to evaluate the pharmacokinetics of deferiprone in patients aged from 1 month to less than 6 years of age affected by transfusion-dependent haemoglobinopathies

The DEEP-1 PK-study, was concluded on February 2014, providing scientific evidence that the dosage of deferiprone used in adults can provide sufficient exposure to ensure efficacy also in small children and allowing children aged under 6 years of age to start to be recruited in DEEP-2 safety/efficacy study

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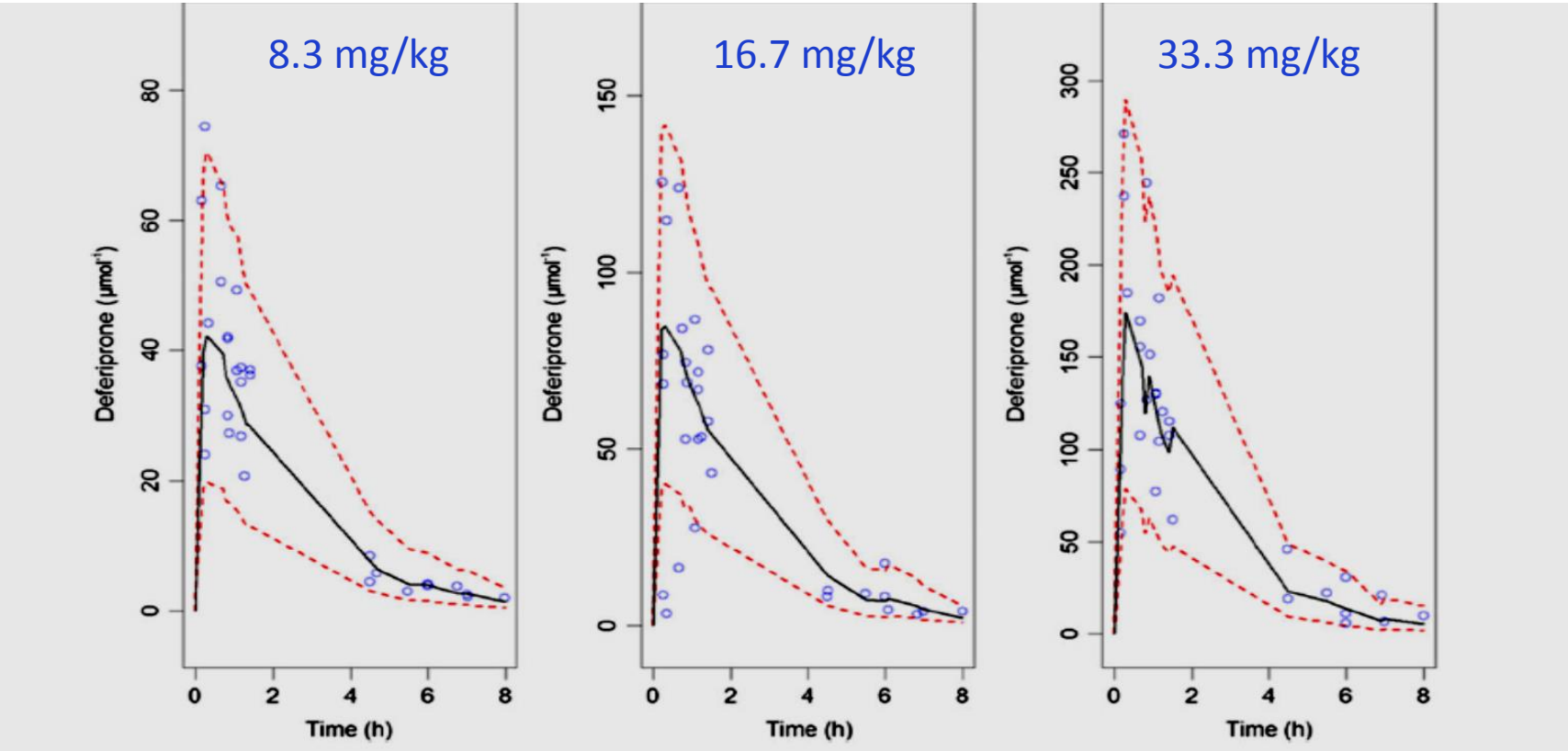
DEEP-1 Study



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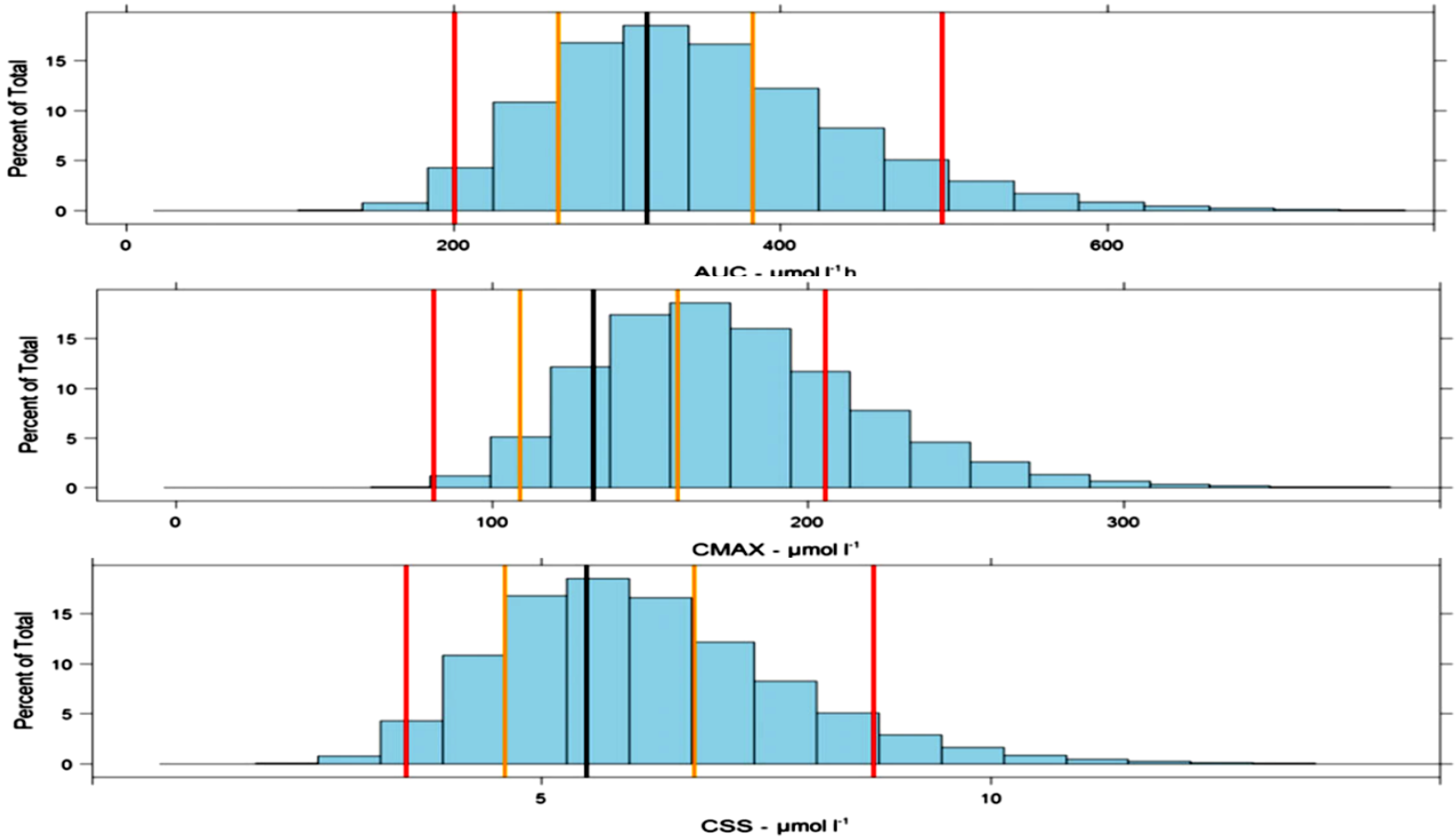
The DEEP-1 PK-study, was concluded on February 2014.

- Concentration showed linear dose dependency
- Kinetics verified the need for TID dosage

Bellanti et al; Br J Clin Pharmacol (2017) 83 593–602

DEEP-1 Study



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The dosage used in adults (25-33,3 mg.kg TID) can provide sufficient exposure to ensure efficacy also in small children

DEEP-2 Study

DEEP-2 study is a Phase III multicentre, randomised, open label, non-inferiority active-controlled trial aiming at comparing for the first time the efficacy of deferiprone (DFP) versus deferasirox (DFX) in paediatric patients aged from 1 month to less than 18 years, affected by hereditary haemoglobinopathies

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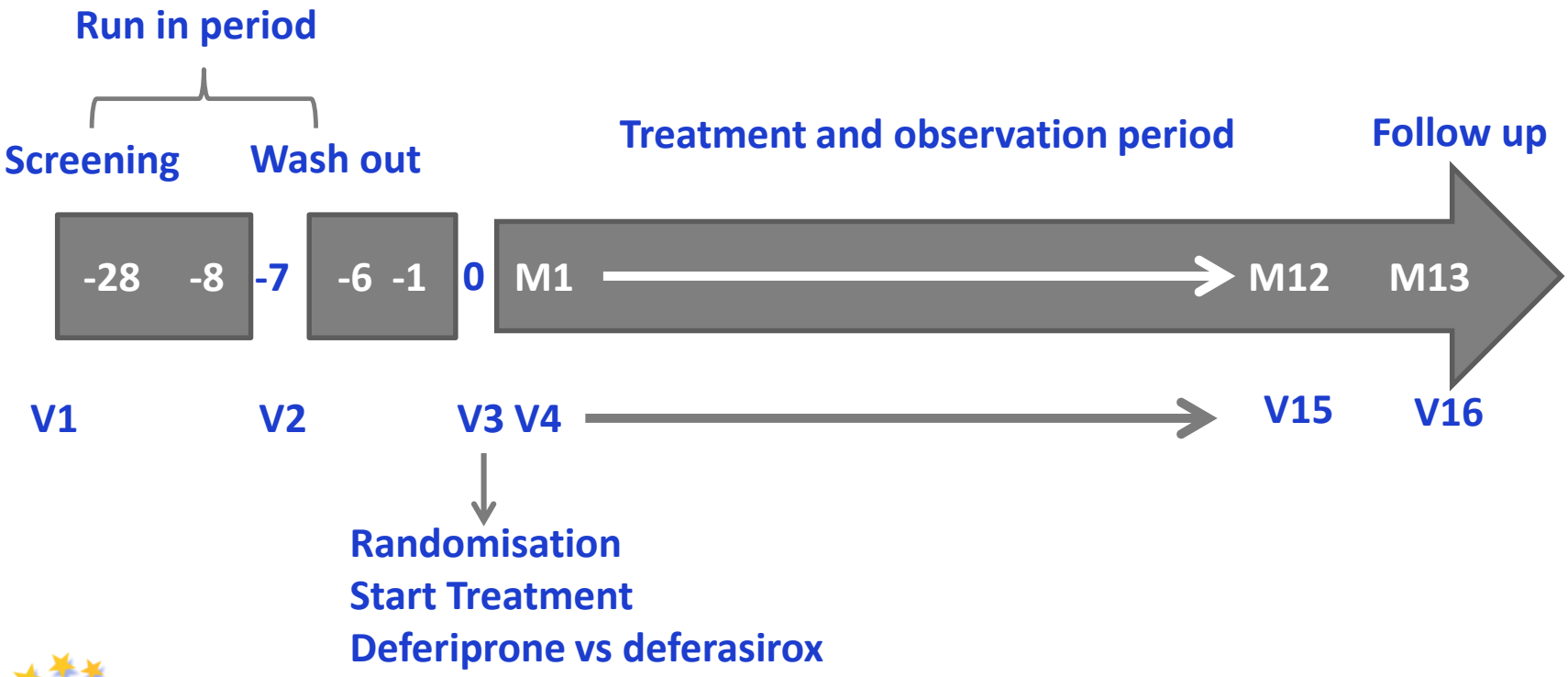
DEEP-2: Study Outline



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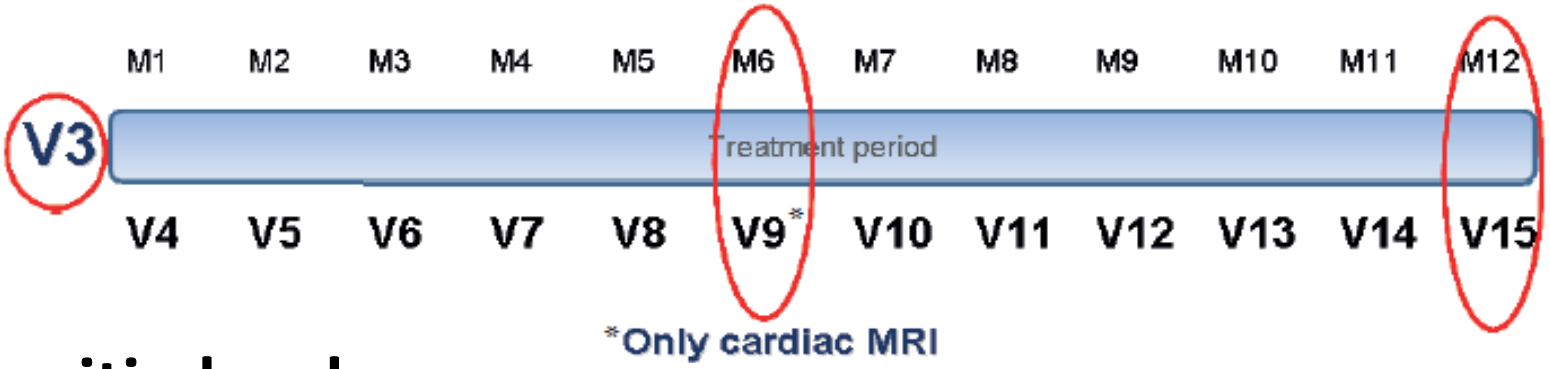
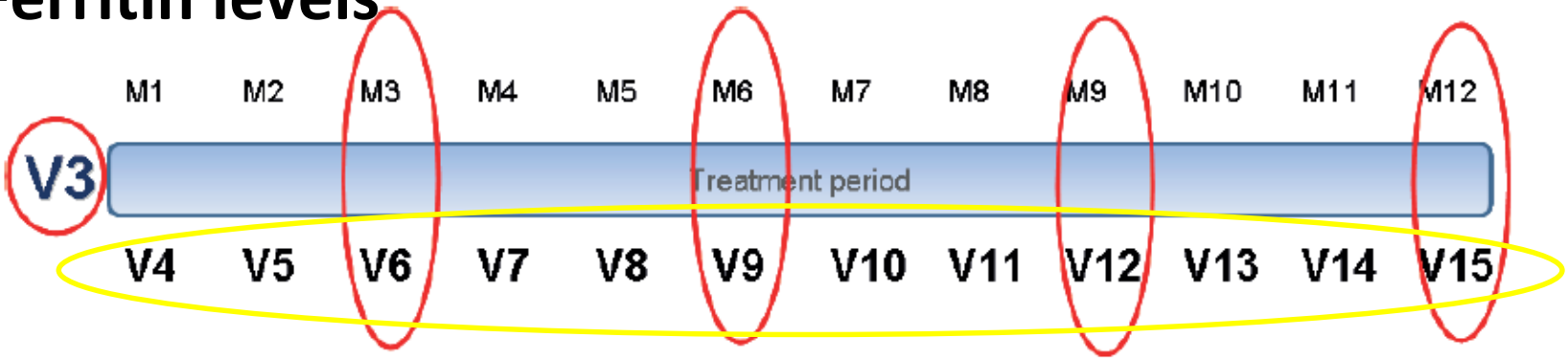
DEEP-2:Efficasy endpoints

Cardiac and Liver MRI



*Only cardiac MRI

Ferritin levels



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Challenges No 1

- Very few young patients with Transfusion dependent hemoglobinopathies in Europe
- Established access to iron chelation therapy in Europe → reluctance to participate

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Recruiting Centers: Partners

Acronym	Country (City)	Investigator	DEEP1	DEEP2
			Patients that could be enrolled	Patients that could be enrolled
PB	Italy (Bari)	G.C. Del Vecchio	4	16
CU	Egypt (Cairo)	A. El-Beshlawy	8	100
AORC	Italy (Palermo)	A. Maggio	4	12
CMoH	Cyprus (Nicosia)	S. Christou	5	11
AOC	Italy (Napoli)	A. Filosa	9	19
NKUA	Greece (Athens)	A. Kattamis	0	15
UHCT	Albania (Tirana)	E. Nastas	0	12
AODP	Italy (Padova)	M.C. Putti	3	11
CNGMO	Tunisia (Tunisi)	M. Bejaoui	0	120
TOTAL			**33**	**316**

Challenges-EU and non-EU countries

- **Different Health Care Systems**
  - Different access of the patients to therapies
- **Different relationship Physician/Patient**
- **Under-developed clinical research system in comparison to EU standards**
  - Research infrastructure
  - Dedicated staff
  - Quality standards
  - Facilities accrediatation
  - GCP adherence

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(slide from Dr Telfer)

Challenges-EU and non-EU countries

- **Varying national and local requirements and delays in obtaining trial authorizations**
- **Timeliness of recruitment**
- **Centralization of sample analysis**
- **Trial monitoring in very different health care settings across EU and Mediterranean**
- **Access to comparator (deferasirox)**

- **Unforeseen Major Challenge: Arab Spring**

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(slide from Dr Telfer)

How to bridge?

- Close surveillance
- Patience / flexibility
- Budget allocation
- Educational materials
  - Patients/family (according to age)-translated in all languages
- Ethics Board:
  - Common consent form
  - Emphasis on the assent form

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DEEP-2 Centres

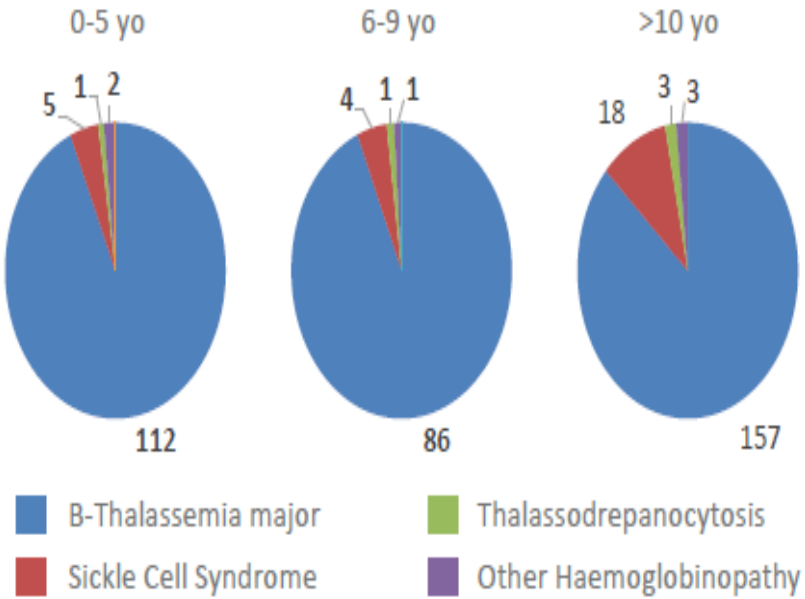
- 6 Countries
- 22 Clinical Sites

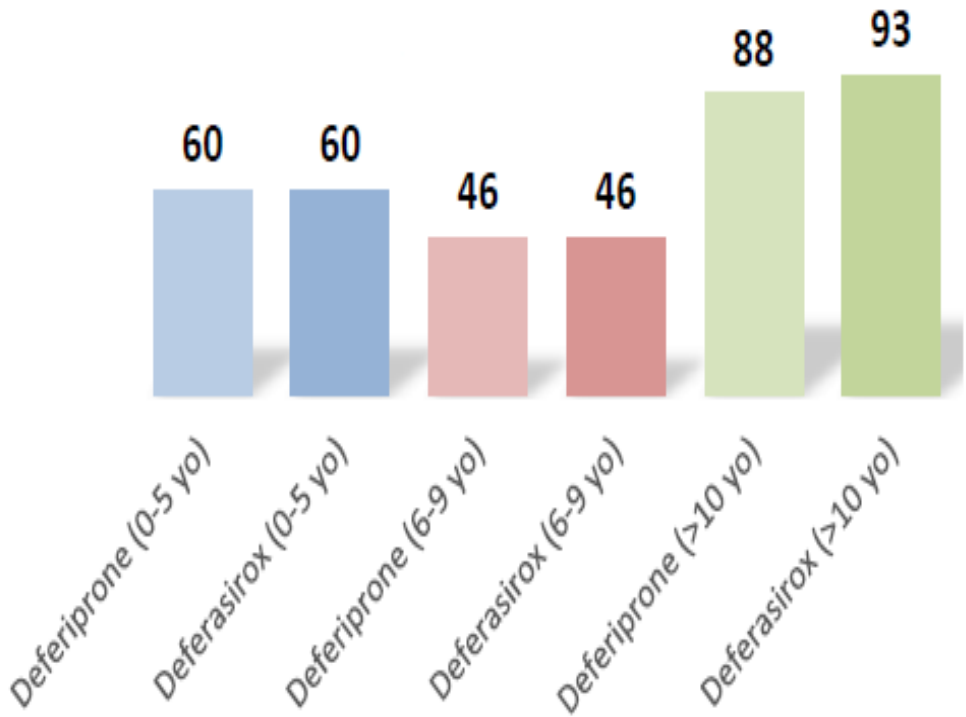
DEEP-2: Patients randomized per Clinical Site

Country	Town	Clinical Site	Patients randomized
ITALY	Palermo	Ospedali Riuniti Villa Sofia-Cervello	11
EGYPT	Cairo	Cairo University Faculty of Medicine	133
GREECE	Athens	National And Kapodistrian University of Athens	11
ALBANIA	Tirana	Qendra Spitalore Universitare "Nene Tereza"	27
CYPRUS	Nicosia	Cyprus Ministry of Health - Department of Medical and Public health Services of the Ministry of Health	8
ITALY	Napoli	Azienda Ospedaliera di Rilievo Nazionale "Antonio Cardarelli"	14
TUNIS	Tunis	Centre National de Greffe de Moelle Osseuse	56
ITALY	Padova	Azienda Ospedaliera di Padova	9
ITALY	Bari	Università di Bari - Facoltà di Medicina	6
ITALY	Palermo	U.O.C. Ematologia - Emoglobinopatie, Ospedale G. Di Cristina	3
ITALY	Cosenza	Presidio Ospedaliero "Annunziata", Centro di Studi della Microcitemia	1
ITALY	Lentini	Centro di Thalassemia, Ospedale Civile di Lentini	1
ITALY	Sassari	Clinica Pediatrica Università - ASL 1 D.H per Talassemia	5
ITALY	Cagliari	ASL Cagliari Ospedale Regionale per le Microcitemie	5
ITALY	Firenze	A.O.Universitaria Meyer	3
ITALY	Catania	Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione Garibaldi	2
UNITED KINGDOM	London	Barts Health NHS Trust, Department of Paediatric Haematology	19
UNITED KINGDOM	Romford	Queen's Hospital	4
UNITED KINGDOM	London	North Middlesex University Hospital NHS Trust	0
EGYPT	Zagazig	Zagazig University Hospitals Haematology outpatients Clinic	40
EGYPT	Alexandria	Alexandria University Hospital Faculty of Medicine	23
ALBANIA	Lushnja	Hospital "Ihsan Çabej"	12

DEEP-2: Enrollment on randomization arm

Randomized patients





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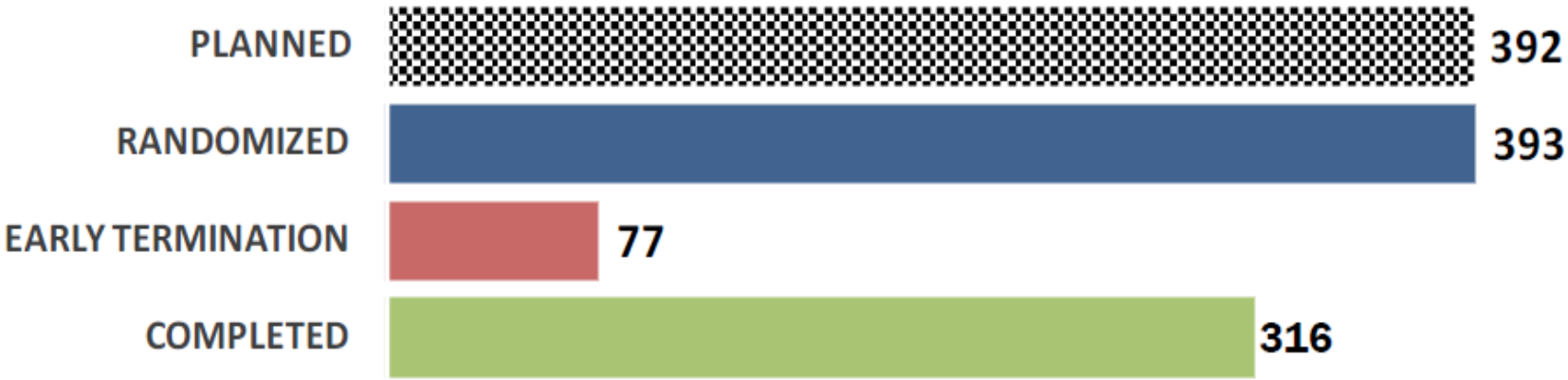
DEEP-2: Study Population



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LPLV : September 2018

DEEP:
Multinational clinical study

Reaching the End

How We Got here:

- Participate, Challenge and Collaborate
- Patient and Persevere
- Focused, committed and dedicated to the goals
- Trust
- United
- Team work
    - Democratic decision making process

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DEEP:
Multinational clinical study

Reaching the End: Achievements

- Set up an example to EC Research policies in promoting networking and public-private partnership
- Set up a new model for clinical research
- Disseminate competencies and technologies in European and non-European Countries

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DEEP:
Multinational clinical study

Reaching the End: Achievements

- Development of a consortium of **specialist centres** treating transfusion-dependent anemia
- Collaboration with **pharmaceutical company** (Apopharma) in developing a new liquid formulation for pediatric use
- Collaboration with **Resonance Health** in use of standardised and centralised MRI protocols for measuring iron overload (Liver and myocardial iron)

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DEEP:
Multinational clinical study

Reaching the End: Achievements

- Produce new knowledge, based on scientific solid, unbiased data
- Much needed from the medical community
- Direct clinical application
- Benefit young patients worldwide

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DEEP:
Multinational clinical study

Reaching the End: Achievements

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Great Collaborators
Good Friends