

# Oncologic Drugs Advisory Committee

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September 14, 2011  
FDA White Oak Campus

# Introduction

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Michael Spino, PharmD  
President, ApoPharma Inc.

## Proposed Indication for Deferiprone

- *“Ferriprox<sup>®</sup> (deferiprone) is an iron chelator indicated for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate.”*

Inadequate chelation:

Increasing iron load, or maintenance of a clinically undesirable iron load, or intolerance to a chelator

# Agenda

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## Introduction

### **Michael Spino, PharmD**

President, ApoPharma Inc.

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## Medical Need

### **Ellis Neufeld, MD, PhD**

Associate Chief, Division of Hematology  
Children's Hospital of Boston

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## Efficacy & Safety

## Benefit/Risk

## Risk Management

### **Fernando Tricta, MD**

Vice President, Medical Affairs  
ApoPharma Inc.

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## Clinical Perspective

### **Renzo Galanello, MD**

Professor of Pediatrics, University Hospital  
Cagliari, Sardinia

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## Conclusion

### **Michael Spino, PharmD**

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# Additional Clinical Experts

**Jean T. Barbey, MD**

Medical Director, Social and Scientific Systems,  
Silver Spring, MD

**Avital Cnaan, PhD, MS**

Professor, Pediatrics, Epidemiology & Biostatistics,  
George Washington University  
Director Multi-Center Studies Section,  
Children's National Medical Center

**James Freston, MD**

Chair of Clinical Pharmacology, University of  
Connecticut Health Sciences Center

**James H. Lewis, MD**

Professor of Medicine, Gastroenterology and Director  
of Hepatology, Georgetown University

**Antonio Piga, MD**

Chief, Division of Pediatrics & Thalassemia Center, St.  
Luigi Hospital of Orbassano, Italy

**Jack Uetrecht, MD, PhD**

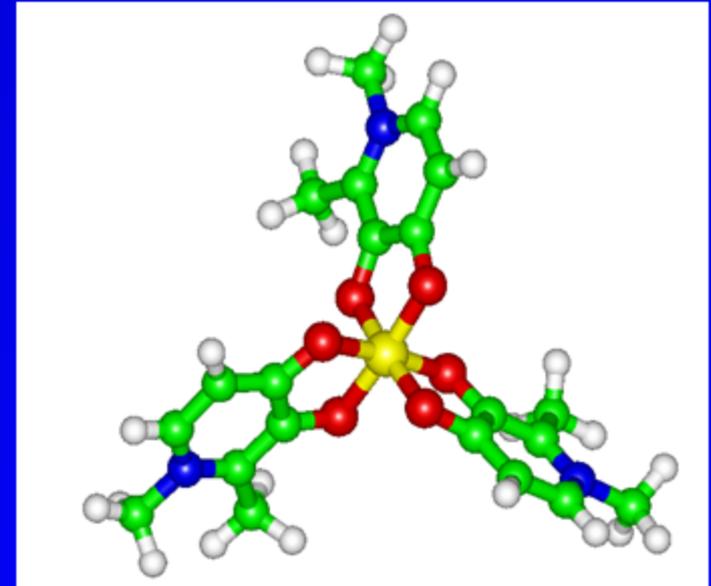
Professor, Clinical Pharmacology/Toxicology,  
University of Toronto

**John Wood, MD, PhD**

Associate Professor, Division of Cardiology,  
Children's Hospital of Los Angeles

# Deferiprone Characteristics

- High affinity for trivalent iron
- Low molecular weight (139 Daltons)
- Physicochemical properties facilitate cell and organelle penetration
- Removes excess iron from tissues



## Brief Development History

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- ApoPharma began formal development – 1993
- Ferriprox<sup>®</sup> was approved by the EMEA – 1999
- Ferriprox now approved in > 60 countries
- Orphan drug status for transfusional iron overload
- NDA submitted as first-line therapy due to ability to reduce cardiac iron better than deferoxamine
- FDA concluded data insufficient for 1<sup>st</sup> line – 2009
- Changed the indication to 2<sup>nd</sup> line therapy

## Medical Need

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Dr. Ellis J Neufeld

Egan Family Foundation Professor of Transitional Medicine,  
Harvard Medical School

Associate Chief, Hematology and Director, Thalassemia Program,  
Children's Hospital Boston

Associate in Hematology, Brigham and Women's Hospital, Boston  
Chair Medical Advisory Board, Cooley's Anemia Foundation

# Prevalence of Transfusion Dependency in the U.S.

	<b>Thalassemia Major<sup>a</sup></b>	<b>Sickle Cell Disease<sup>b</sup></b>
<b>Number of Patients</b>	<b>500 – 1,000</b>	<b>80,000</b>
<b>Number of Patients Transfused</b>	<b>500 – 1,000</b>	<b>5,000 – 10,000</b>

<sup>a</sup>Pakbaz, 2010

<sup>a,b</sup>Brittenham, 2011

<sup>b</sup>Taylor, 2010

<sup>b</sup>Strouse, 2008

# Measurements of Iron Overload

	Undesirable Levels
<b>Serum Ferritin</b>	<b>&gt; 2,500 <math>\mu\text{g/L}</math><sup>a,b,c</sup></b>
<b>Liver Iron Concentration</b>	<b>&gt; 7 mg/g dry weight<sup>c</sup></b>
<b>Cardiac MRI T2*</b>	<b>&lt; 20 ms<sup>d</sup></b>

<sup>a</sup>Olivieri, 1994

<sup>b</sup>Borgna-Pignatti, 2004

<sup>c</sup>Telfer, 2000

<sup>d</sup>Kirk, 2009

# Current Treatment Options in the U.S.

	<b>Deferoxamine</b>	<b>Deferasirox</b>
<b>Delivery</b>	Subcutaneous	Oral
<b>Regimen</b>	10-12 hours/ 5-7 nights a week	Once daily
<b>Chelator Efficacy</b>	Improves long-term survival	At higher doses, non-inferior to deferoxamine for serum ferritin, and liver iron concentration
<b>Relevant Limitations</b>	<ul style="list-style-type: none"> <li>• Inadequate compliance</li> <li>• Inadequate efficacy in some</li> <li>• Infusion site local reactions</li> <li>• Auditory &amp; visual disturbances</li> <li>• Yersinia and other infections</li> </ul>	<ul style="list-style-type: none"> <li>• Inadequate efficacy in some</li> <li>• Risk of kidney and liver failure</li> <li>• GI hemorrhage</li> <li>• Increase in serum creatinine</li> <li>• Increase in serum transaminases</li> </ul>

## Unmet Medical Need

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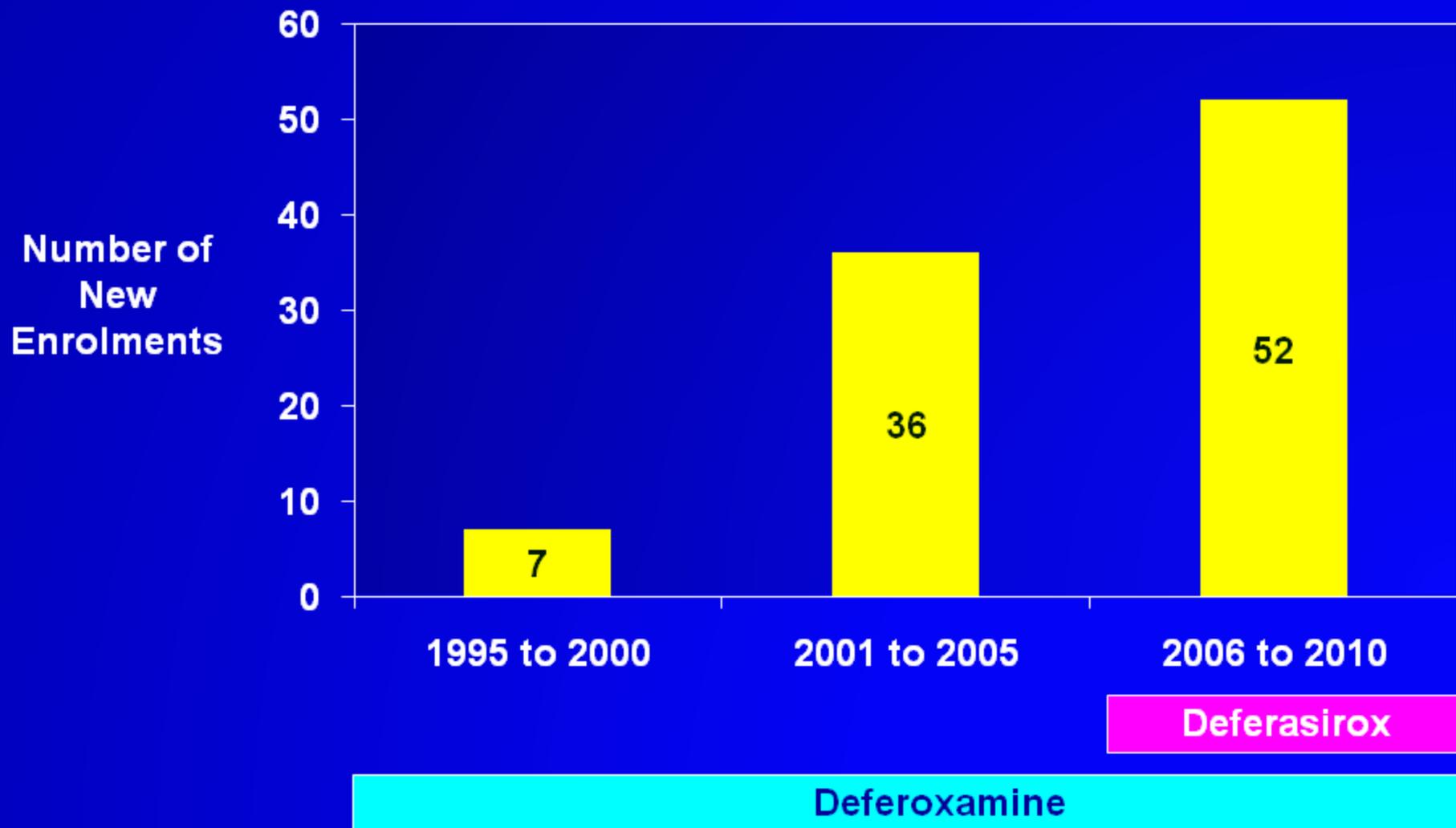
- Patients receiving chelation therapy continue to develop transfusion-related iron overload
- 25% of patients treated with 30-40 mg/kg/day of deferasirox for up to one year in the EPIC trial had no improvement in their ferritin level<sup>1</sup>

# Continued Cardiac Morbidity and Mortality in Thalassemia

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- Thalassemia Clinical Research Network
  - Inadequate chelation
    - 30% deferasirox
    - 25% deferoxamine
  - 32% of patients have had clinical heart disease
- Cooley's Anemia Foundation
  - 80 of 724 registered patients died between 1998 and 2008

# U.S. Patients Enrolled in Compassionate-Use Program for Deferiprone



## Conclusion

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- Iron overload remains a significant problem
- Not all patients are successfully treated with current chelators
  - Insufficient response
  - Intolerant
- Deferiprone needed for patients in U.S. whose current chelation therapy is inadequate

**Efficacy & Safety**  
**Benefit/Risk**  
**Risk Management**

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Fernando Tricta

Vice President of Medical Affairs

ApoPharma Inc.

# Presentation Overview

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- Efficacy
  - LA36
    - LA16
    - Other studies
- Safety
  - Clinical trials (1993-2010)
  - Post-market experience (1999-2010)
- Benefit/Risk Assessment
- Risk Management Plan

# Deferiprone Efficacy Studies

Type of Study	Study ID	Deferiprone Regimen (Dose mg/kg/d)	Duration (years)	Efficacy Indices		
				SF	LIC	Card. T2*
Randomized Trials	LA-01 <sup>†</sup>	Monotherapy (75)	2	✓	✓	
	LA08	Alternate (75)	1	✓	✓	
	LA16	Monotherapy (50 -100)	1	✓	✓	✓
	LA12	Monotherapy (75)	5	✓	✓	
	LA-02/06	Monotherapy (75)	1-7	✓		
	LA30	Monotherapy (50 -100)	0.5	✓		
Non- Randomized Trials	LA-03 <sup>†</sup>	Monotherapy (75)	7	✓		
	LA-04/06B <sup>†</sup>	Mono or Combined (50 -100)	Up to 14	✓	✓	✓
	LA-11 <sup>†</sup>	Monotherapy 50	2	✓		
	LA15 <sup>†</sup>	Monotherapy (75)	0.25	✓		
	LA28	Monotherapy (50 -100)	3	✓		
	Borgna-Pignatti <sup>†</sup>	Monotherapy (75)	9	✓		

<sup>†</sup>Non-GCP studies:

LA-01 & LA-03: non-compliance with protocol

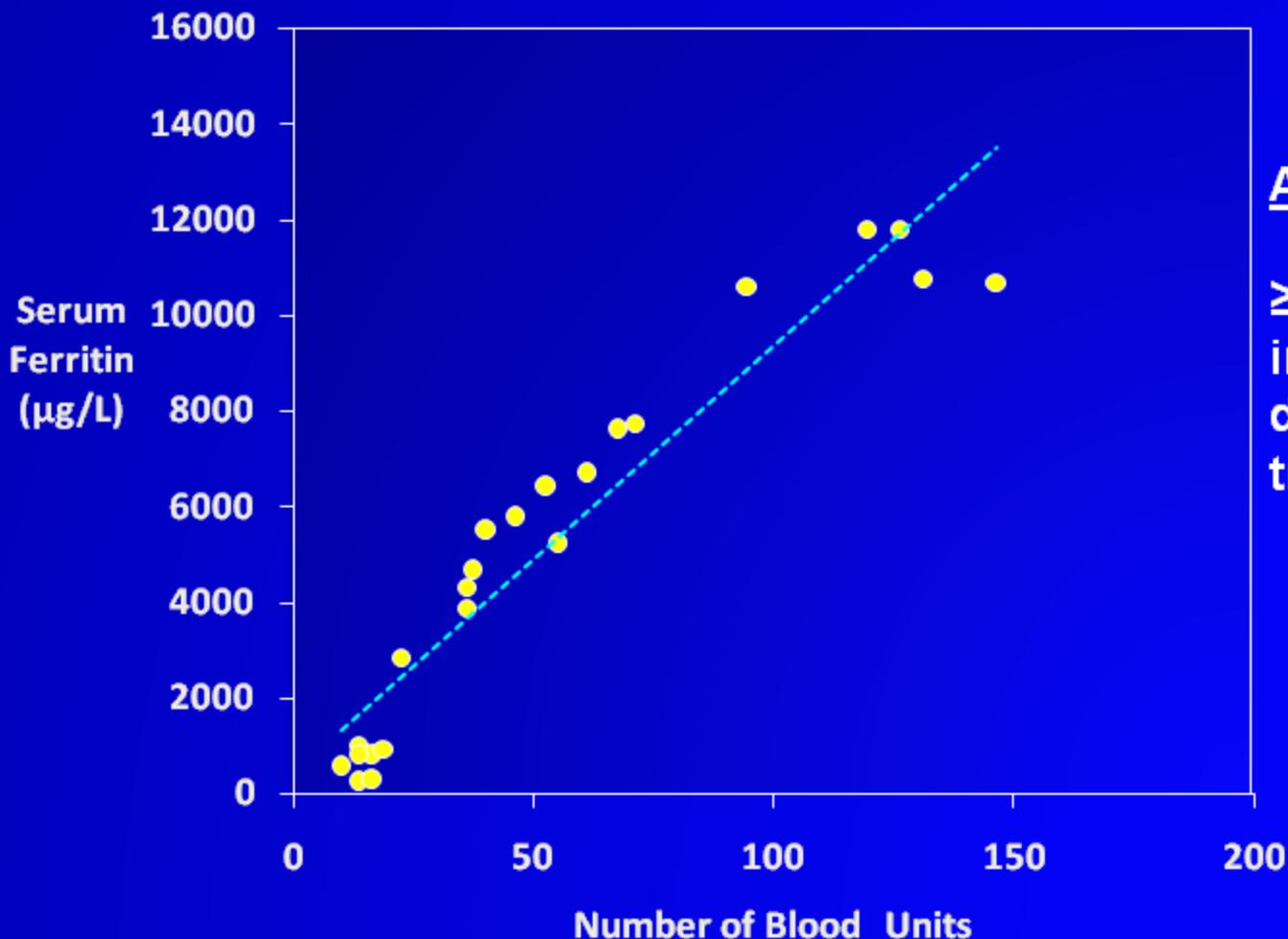
LA-03, LA-04/6B, LA-11, LA15, LA28, Borgna-Pignatti: source data not monitored by sponsor

## LA36 - Criteria for “Inadequate” Therapy

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- Have failed therapy with another chelator
  - Baseline serum ferritin  $> 2,500 \mu\text{g/L}$ , or
  - Baseline liver iron concentration  $>7 \text{ mg/g}$  dry weight, or
  - Baseline cardiac MRI T2\*  $< 20 \text{ ms}$

# Progressive Increase in Serum Ferritin Based on Cumulative Number of Blood Units Transfused



Adequate chelation:

≥ 20% decline  
in iron load,  
despite continued  
transfusional iron input

## LA36 - Endpoints (I)

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- Primary:
  - $\geq 20\%$  decline per patient in serum ferritin concentration after deferiprone therapy for up to 1 year
- Secondary:
  - $\geq 20\%$  decline per patient in liver iron
  - $\geq 20\%$  increase per patient in cardiac T2\*

## LA36 - Endpoints (II)

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- Criteria for positive trial:
  - $\geq 20\%$  of all patients met the primary efficacy endpoint for serum ferritin
  - For added assurance, the lower limit of the 95% confidence interval for the success rate should be greater than the pre-defined 20% criterion for treatment success

# LA36 - Patient Selection

ApoPharma Studies		Ferritin > 2500 µg/L	LIC > 7mg/g d w	MRI T2* < 20 ms
Studies	Patients			
LA-01	35	8	15	
LA-02/06	151	65		
LA-03	25	8	12	
LA-04	157	56	11	10
LA08-9701	25	7	21	
LA-11	23	12	3	
LA-12-9907	69	19	35	
LA-15-002	29	18		
LA16-0102	29	5	20	29
LA28-CMP	8	3		
LA30-0307	100	36		
Borgna-Pignatti	96	27		
		<b>264</b>	<b>117</b>	<b>39</b>

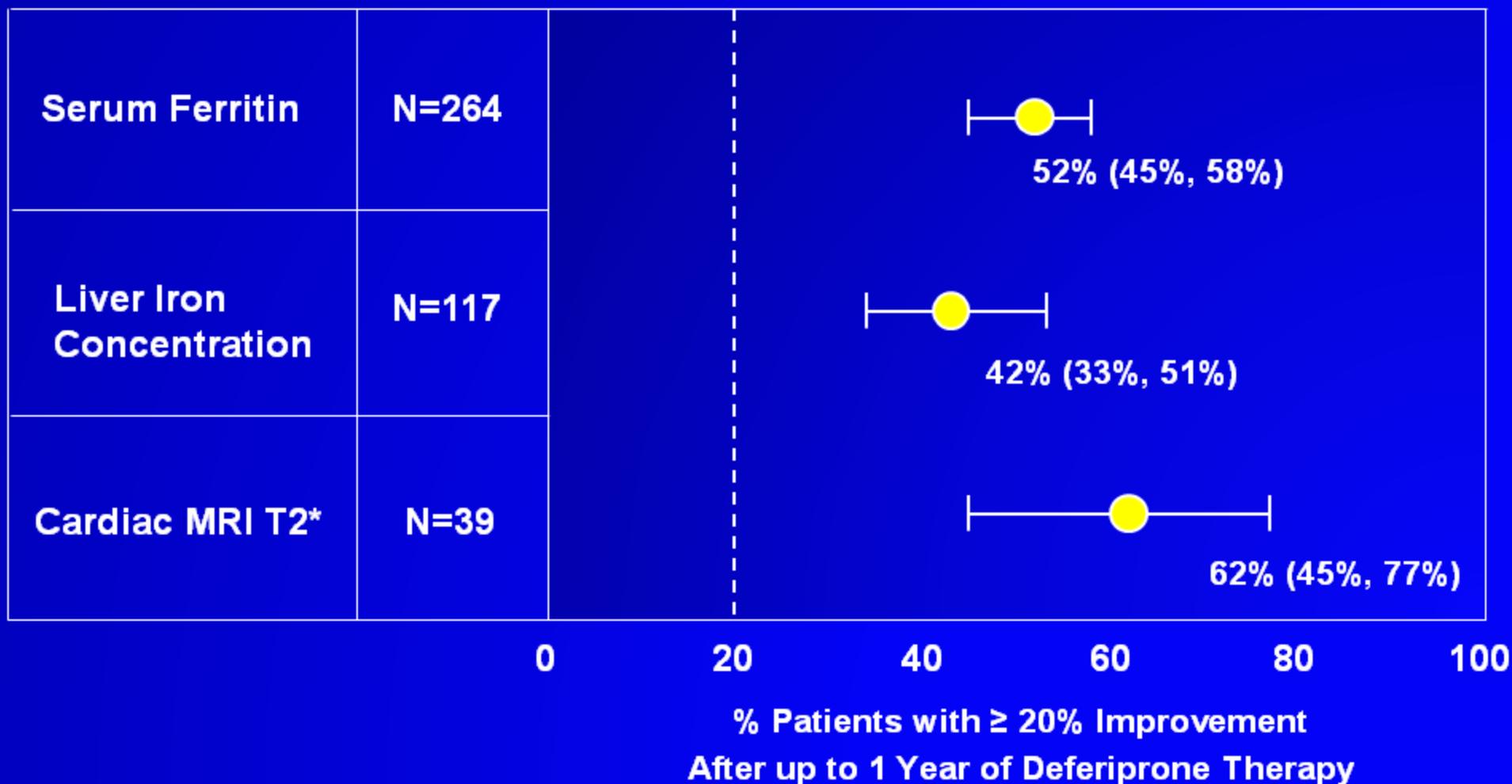
Independent Committee

## LA36 - Demographic Data

Cohorts	Age (years)			Gender (N)	
	Min.	Max.	Mean	Male	Female
Serum Ferritin	2	76	20.1	119	145
Liver Iron Concentration	6	52	19.4	62	55
Cardiac MRI T2*	12	33	24.3	21	18

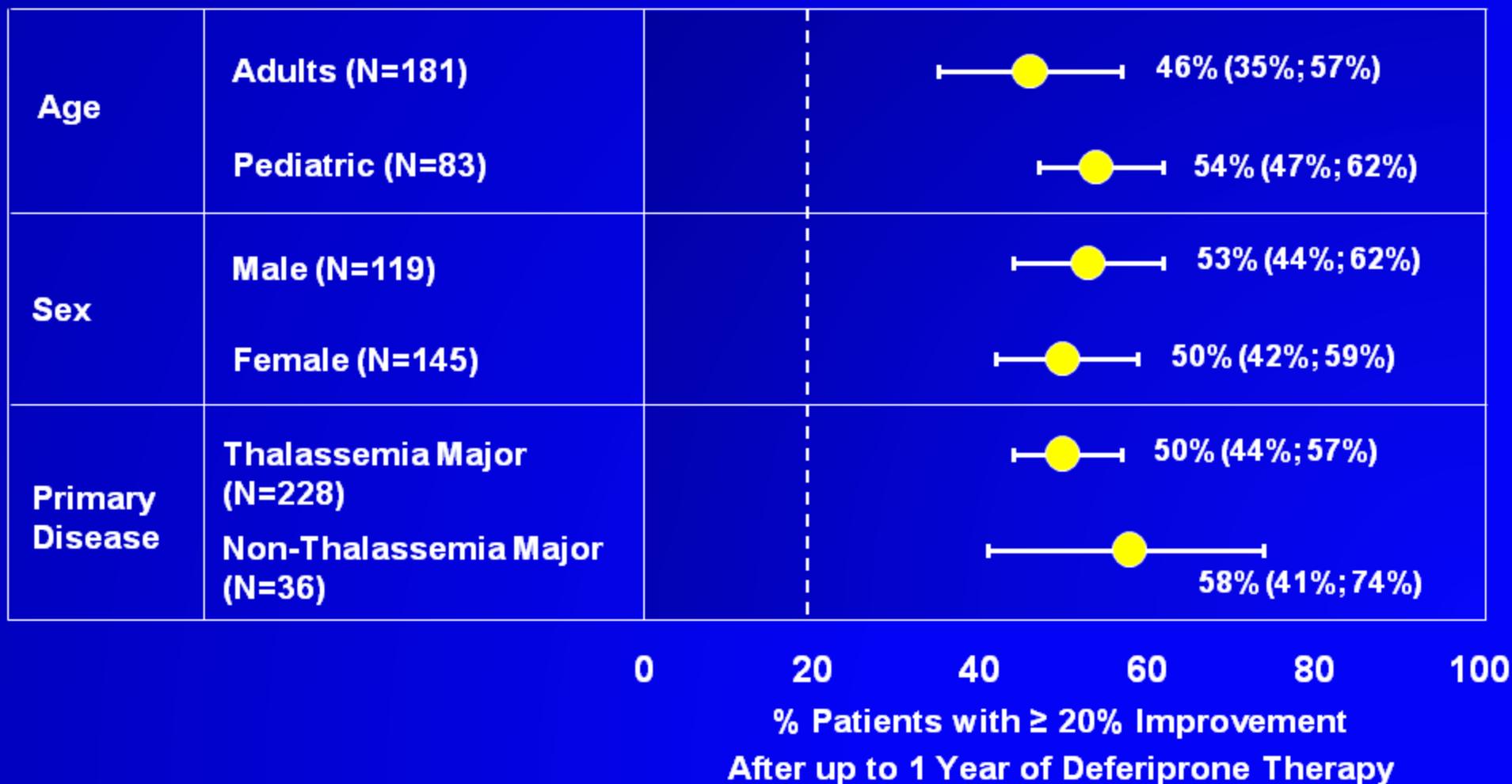
# LA36 - Success Rate (% of patients) (I)

Success Rate with 95% Confidence Interval

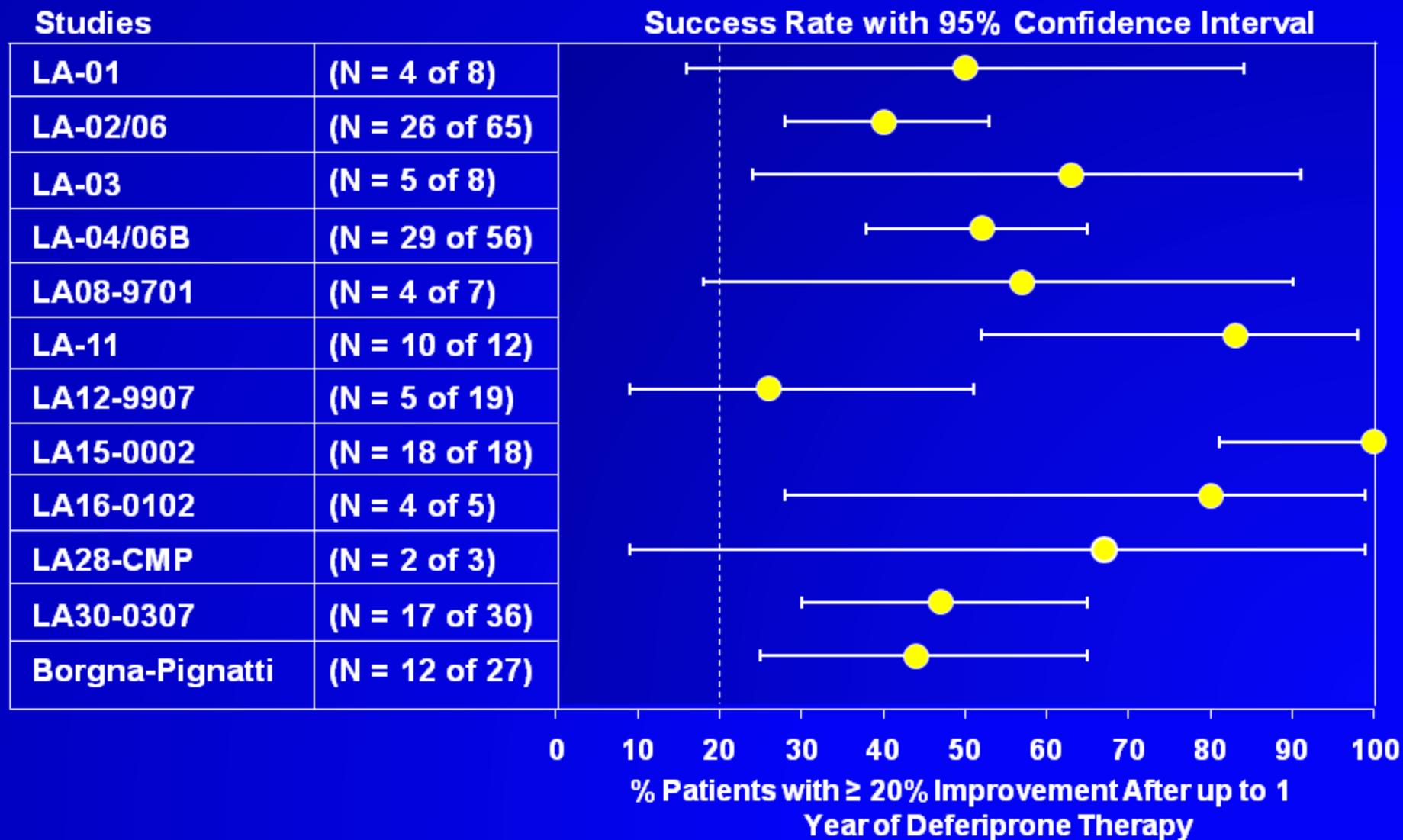


# LA36 - Success Rate (% of patients) (II)

Success Rate with 95% Confidence Interval



# Success Rate (%) by Study for Serum Ferritin - ITT Population



## LA36 - Conclusion

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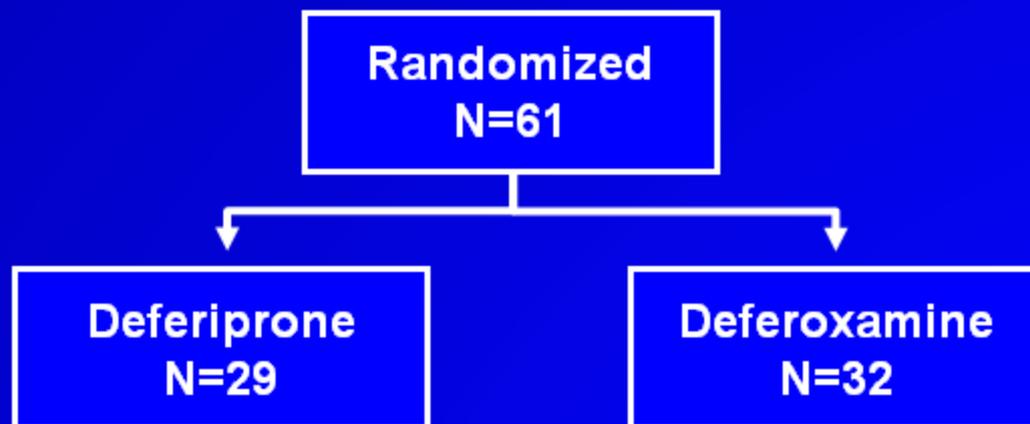
- The results met the success criteria for primary and secondary endpoints
- The results indicated
  - Deferiprone was an effective treatment in patients who failed other chelation therapy
  - Deferiprone was effective in diverse populations

## Study LA16 – Study Objectives

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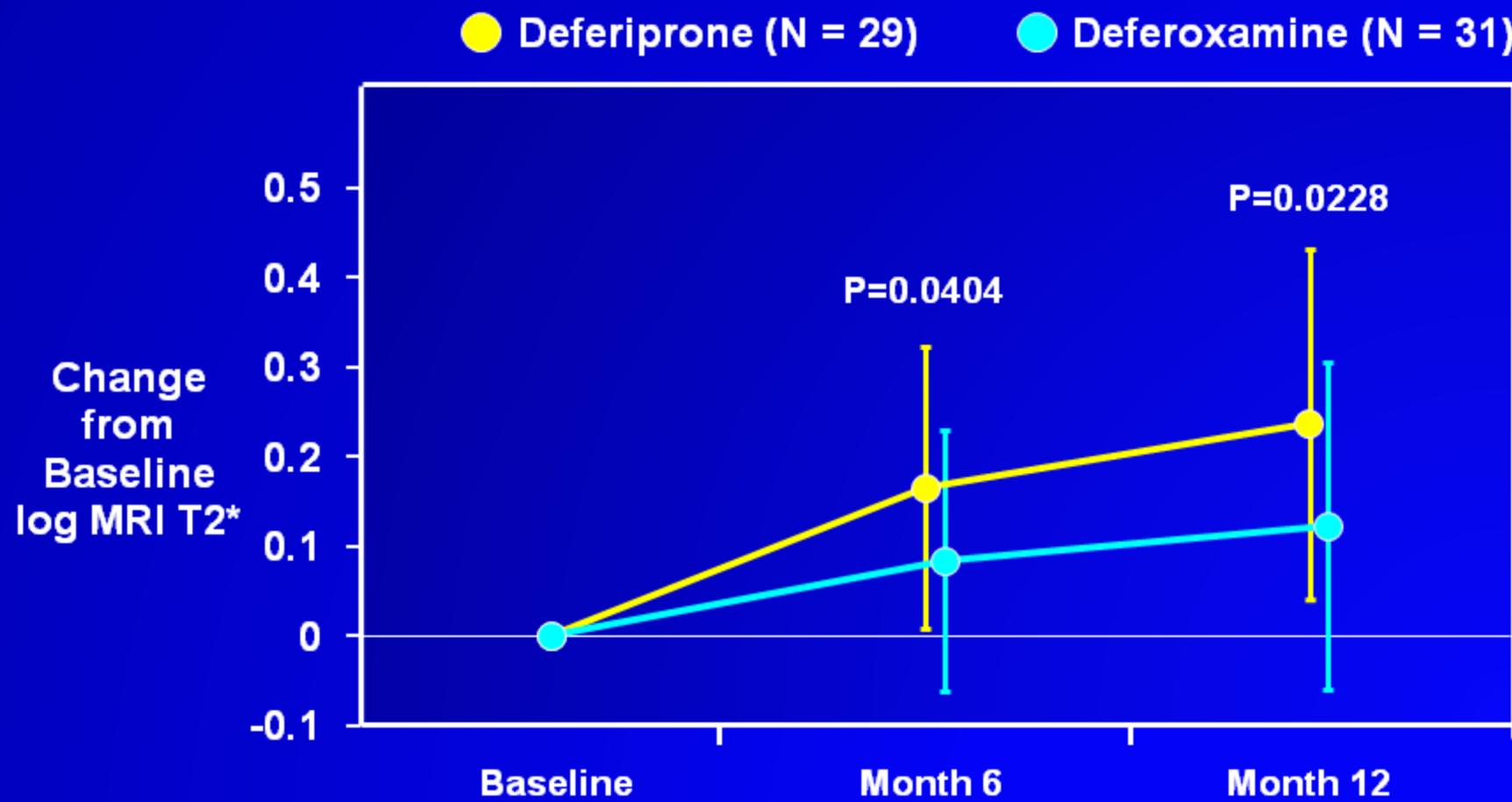
- Primary objective: to confirm superiority of deferiprone over deferoxamine in removing excess iron from the heart (MRI T2\*)
- Secondary and tertiary objectives: to evaluate efficacy of deferiprone vs deferoxamine in controlling serum ferritin and liver iron concentration and in improving cardiac LVEF

# LA16: Randomization & Efficacy Measurements

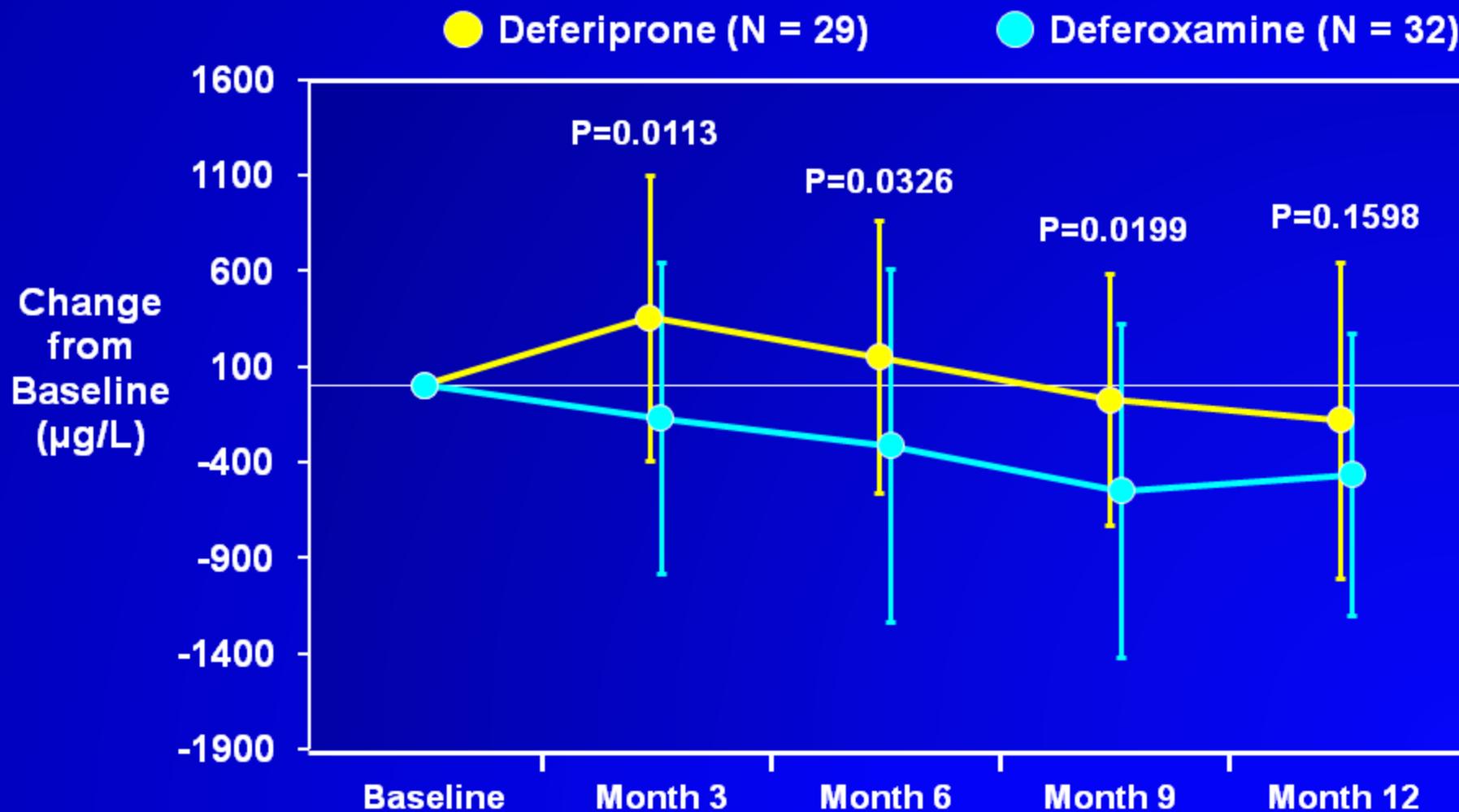


	Cardiac T2*	Serum Ferritin	Liver Iron Concentration	Cardiac Function
Baseline	✓	✓	✓	✓
3 months		✓		
6 months	✓	✓		✓
9 months		✓		
12 months	✓	✓	✓	✓

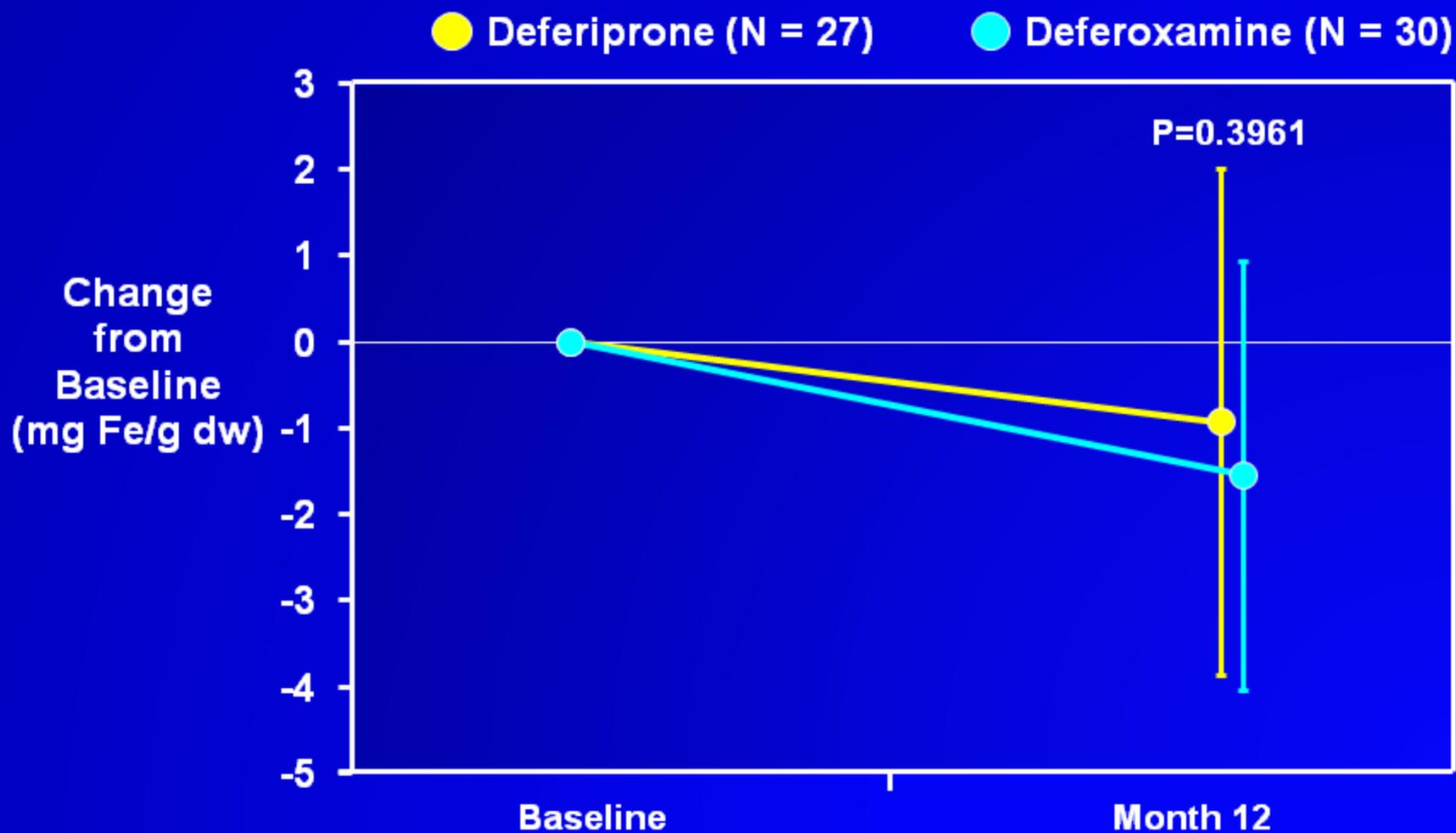
# Change in Log Cardiac MRI T2\* in Deferiprone or Deferoxamine-treated Patients - LA16



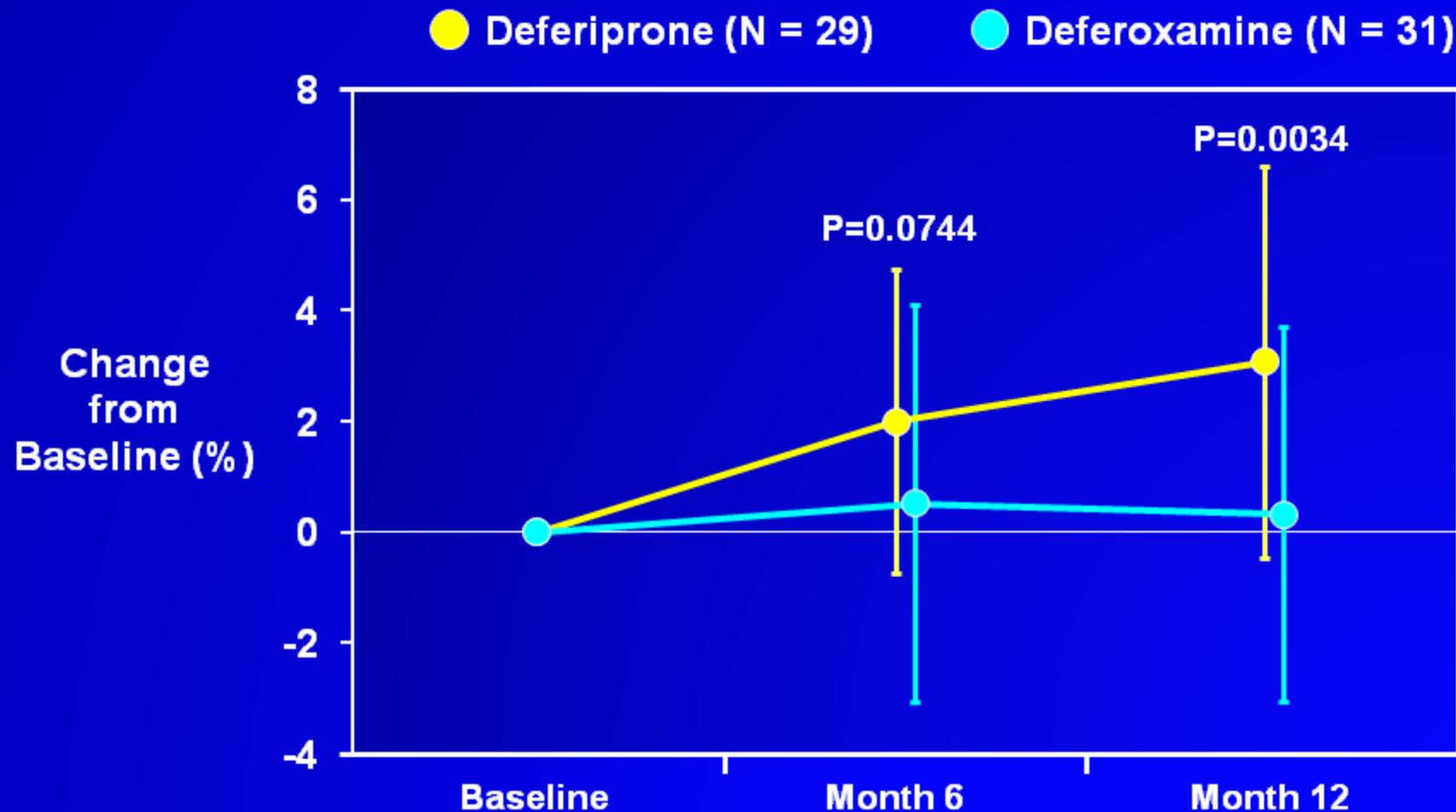
# Change in Serum Ferritin in Deferiprone or Deferoxamine-treated Patients - LA16



# Change in LIC in Deferiprone or Deferoxamine-treated Patients - LA16



# Change in LVEF in Deferiprone or Deferoxamine-treated Patients - LA16



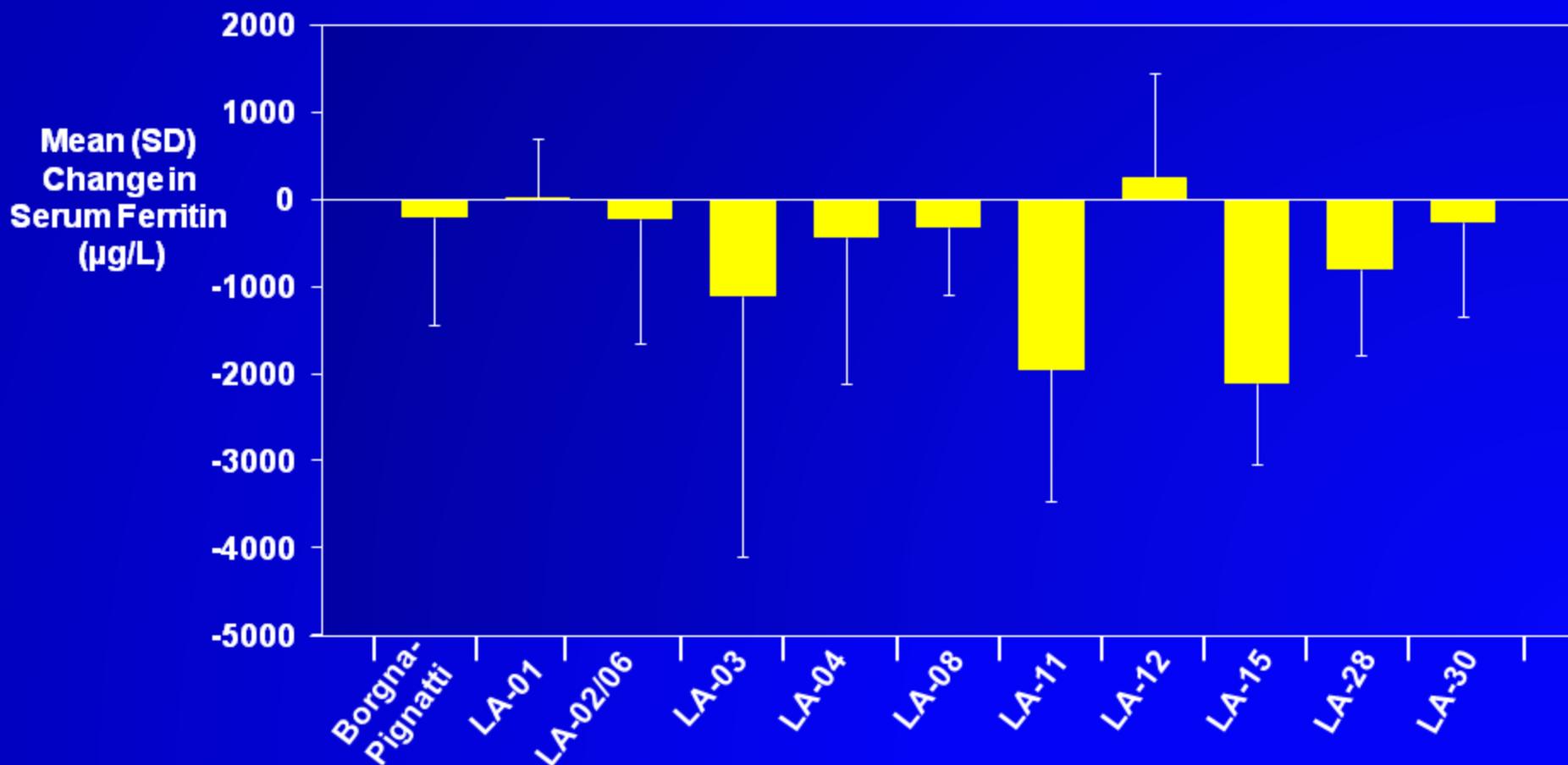
## LA16 - Conclusions

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- Deferiprone was superior to deferoxamine in removing excess cardiac iron
- Deferiprone was not significantly different from deferoxamine in controlling serum ferritin and liver iron concentration

# Changes in Serum Ferritin After up to 1 Year of Deferiprone Therapy (Submitted in NDA)

P- Value	0.1532	0.8781	0.0541	0.1466	0.0052	0.0531	0.0006	0.1040	<.0001	0.1448	0.0184
No. of Patients	75	35	151	17	122	25	21	64	28	5	99



## Deferiprone Efficacy Summary

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- LA36 provides evidence that deferiprone reduces iron load in approximately 50% of patients who had failed previous therapy
- Results of a randomized controlled trial (LA16) and of other clinical trials support the efficacy of deferiprone

# Deferiprone Safety

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- Demographics
- Deaths
- Adverse events
- Historical question
- Post-marketing safety changes to the label
- Risk Management Plan

# Deferiprone Safety

	<b>Time Frame</b>	<b>Exposure</b>
<b>Pooled Safety Database</b>	<b>1993 to 2010</b>	<b>All patients treated with &gt;1 dose</b> <ul style="list-style-type: none"><li>• <b>Clinical Trials (N=443)</b></li><li>• <b>Compassionate Use (N=199)</b></li></ul> <b>Total number of patients = 642</b> <b>Mean Exposure in Years <math>\pm</math> SD</b> <b>(Range): 2.09 <math>\pm</math> 2.13 (0.00,14.89)</b>
<b>Post-market Experience</b>	<b>1999 to 2010</b>	<b>Exposure: 34,043 patient-years</b>

# Pooled Safety Data Demographics

		Patients, N (%)		
		Total	Adults	Pediatrics
All Patients		642 (100%)	420 (65%)	222 (35%)
Primary Diagnosis	Thalassemia Major	560 (87%)	352 (63%)	208 (37%)
	Non- Thalassemia Major*	82 (13%)	68 (83%)	14 (17%)

\* Non Thalassemia Major primary diagnosis consists of hemoglobin E- $\beta$  thalassemia disease (n=42), myelodysplasia (n=15), sickle cell disease (n=5), thalassemia intermedia (n=5), myelofibrosis (n=4), congenital anemia (n=2), refractory anemia (n=2), and in 1 patient each with pure red cell aplasia, aplastic anemia, Blackfan-Diamond anemia, chronic lymphocytic leukemia, hereditary hemochromatosis, severe hemolytic anemia, transfusion-dependent  $\alpha$ ase syndrome

## Deaths in Clinical Trials (1993 - 2010)

<b>Subject ID</b>	<b>Year</b>	<b>Primary Diagnosis</b>	<b>Age (Years)</b>	<b>Days on Therapy</b>	<b>Cause of Death</b>
LA01-61	1994	Thal. Major	27	170 (30)*	Cardiac Failure
LA02/06-604	1999	Thal. Major	22	1706 (20)*	Internal Injury
LA11-107	2001	Hb E-Thal	33	146 (2)*	Diarrhea

\*Number of days from the date of discontinuation of deferasirox to the date of death

# Deaths in Compassionate Use (1993 - 2010)

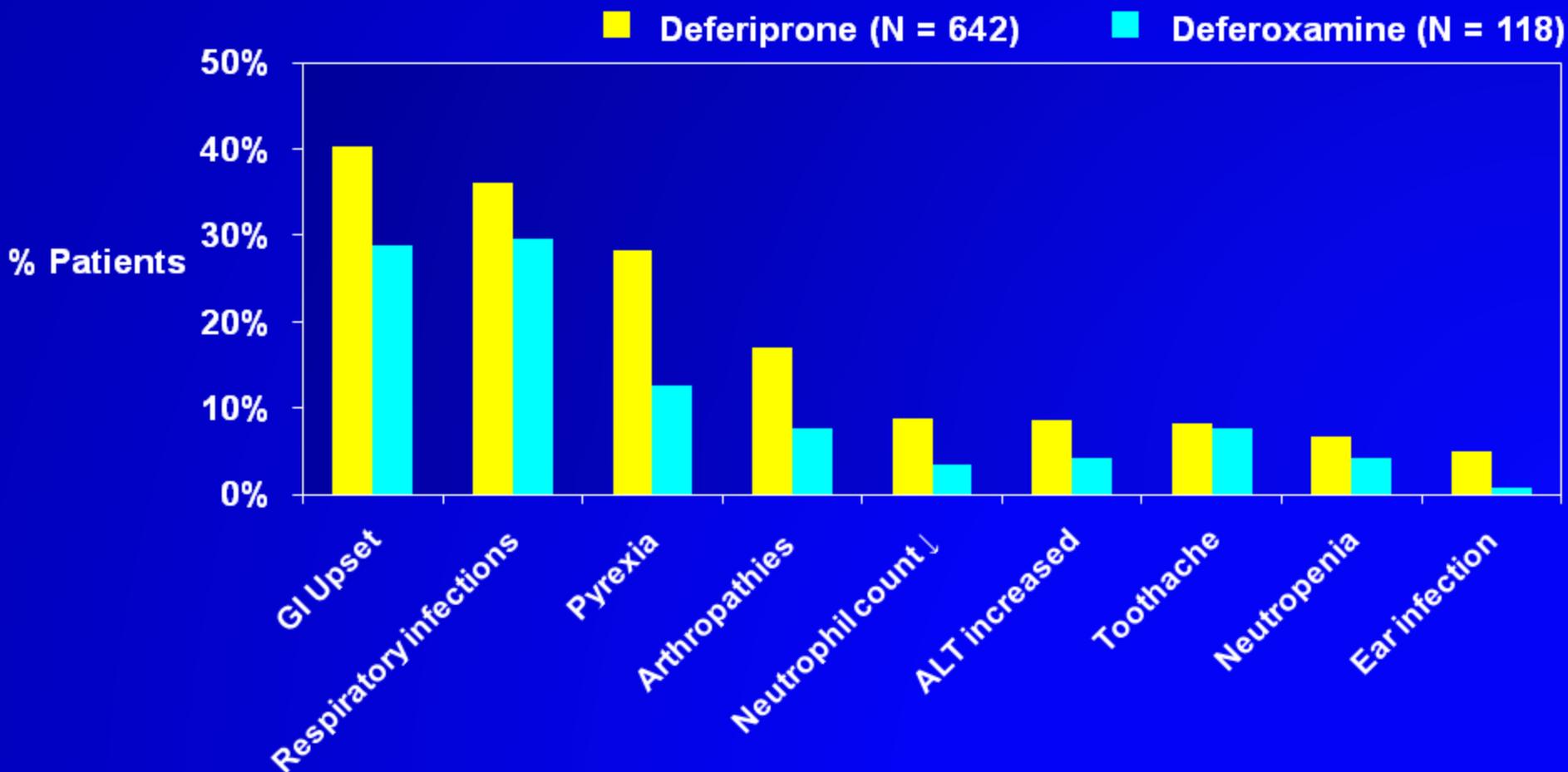
Cause of Death	N out of Total Deaths	Age	Days on Therapy	Time from Discontinuation of Deferiprone to the Time of Death (Days)
		Median (Range)	Median (Range)	Median (Range)
Cardiac Disease <sup>a</sup>	7/14	31 (18 - 45)	29 (2 - 242)	1 (1 - 7)
Malignancies <sup>b,c</sup>	4 /14	68.5 (53 - 74)	507.5 (257 - 2606)	30 (3 - 108)
Multi-organ Failure	1 /14	68	180	29
Intestinal Obstruction	1 /14	53	343	0
Procedural Complication	1/14	45	2861	23

<sup>a</sup>Primary diagnosis for cardiac disease: 5 thalassemia major, 1 Aase syndrome and 1 myelofibrosis.

<sup>b</sup>Primary diagnosis for malignancies: 3 myelodysplasia and 1 thalassemia major.

<sup>c</sup>Malignancies consists of acute myeloid leukemia, lung neoplasm malignant, pleural effusion, and adenocarcinoma.

# Most Common AEs ( $\geq 5\%$ of Patients) Where AEs More Common on Deferiprone



GI Upset consists of abdominal pain (incl. upper), vomiting, nausea, and diarrhea.  
Respiratory infection consists of pharyngitis, influenza, tonsillitis, and bronchitis.

## AEs in $\geq 5\%$ of Patients Where AEs More Common on Deferiprone

Adverse Event	N (%) patients	Rate events per 100 patient yrs	Median Onset (days)	Median Duration (days)	Withdrawals N (%)
GI Upset	258 (40.2)	58.3	37	2	10 (1.6)
Respiratory Infections	231 (36.0)	47.8	164	6	0 (0.0)
Pyrexia	181 (28.2)	35.6	176	3	0 (0.0)
Arthropathies	109 (17.0)	17.5	214	9	12 (1.9)
Neutrophil Count ↓	57 (8.9)	5.6	141	2	3 (0.5)
Increased ALT	56 (8.7)	6.4	176	22	6 (0.9)
Toothache	53 (8.3)	8.0	350	2	0 (0.0)
Neutropenia	43 (6.7)	3.7	280	10	27 (4.2)
Ear Infection	33 (5.1)	3.4	630	8	0 (0.0)

## **Agranulocytosis (ANC < 0.5 x 10<sup>9</sup>/L) (Irrespective of a Relationship to Deferiprone)**

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- Patients: 11 (1.7%)
- Median (range) time to onset:  
161 days (2.1 months - 9.2 years)
- Median (range) duration:  
10 days (3 days - 2.8 months)
- Discontinuations: 9 (1.4%)

## Agranulocytosis (ANC < 0.5 x 10<sup>9</sup>/L) (Irrespective of a Relationship to Deferiprone)

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- Re-challenges: 2
  - Subsequent mild neutropenia: 1 (ANC=1.4 x 10<sup>9</sup>/L). Deferiprone was discontinued
  - 3 episodes of neutropenia, no agranulocytosis observed during the 7 years of continued therapy

# Post-marketing Agranulocytosis (1999 - 2010)

- 94 episodes in >34,000 patient-years (0.28/100 patient-years of exposure) in 91 patients
- Median (range) time to onset (available in 87 episodes): 151 days (13 days - 9 years)
- Median (range) duration (available in 62 episodes): 10 days (3 days - 3.3 months)
- 13 episodes with fatal outcome (0.04/100 patient-years of exposure)
  - No monitoring of ANC at onset of infection
  - No discontinuation of therapy
  - Infection managed by professionals unaware of patients at risk of agranulocytosis

# Risk Mitigation in Europe

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- In 2006 instituted
  - Dear Dr. Letter
  - Detailing risk of agranulocytosis, need for monitoring neutrophil counts and interruption of therapy at signs of infection
  - Wallet-sized card to patients

# Wallet-size Card Distributed to Patients

## **Ferriprox**<sup>®</sup> deferiprone

### Instructions to Health Care Providers

This patient is currently taking Ferriprox for the condition of Iron Overload.

There is approximately a 1% incidence of agranulocytosis associated with the use of Ferriprox. As a result, this patient must have their neutrophil count measured weekly.

If neutrophil counts are below the level of  $1.5 \times 10^9/L$  then Ferriprox should be discontinued and the patient should be monitored and treated accordingly until neutrophil counts return to normal.

If you have any questions please feel free to contact Medical Information at ApoPharma by email at [ferriprox@apotex.com](mailto:ferriprox@apotex.com)

### Monitoring Your White Blood Cell Count with Ferriprox

Ferriprox offers patients benefits when used properly. In order to minimize the impact of side effects it is important to read and follow the instructions listed.

There is a 1% chance that you may develop agranulocytosis (very low white blood cell count) while taking Ferriprox, which may lead to a serious infection.

Even though agranulocytosis is uncommon, it is important to monitor your blood on a regular basis.

#### Make sure you do the following:

1. Have your blood monitored on a weekly basis.
2. Contact your doctor immediately if you develop a fever, sore throat or flu like symptoms.
3. Carry this card with you and provide it to your healthcare provider if you have symptoms they should be aware of.

## Number of Agranulocytoses with Fatal Outcomes Prior to and After Implementation of Educational Program

Time Period	Estimated Exposure in Patient-years	N Agran.	Rate Agran. per 100 Patient-years	N Fatal Cases
1999 to 2006*	15,272	45	0.30	11
2007 to 2010	18,771	49	0.26	2

\*3 cases in 2003; 4 cases in 2005; 4 cases in 2006.

## Safety Summary: Clinical Trials

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- Safety profile based on 23 years of clinical use
- Most common AEs irrespective of causality were transient and mild/moderate in severity
  - Gastrointestinal upset
  - Respiratory infections
  - Pyrexia
  - Arthropathies
- Agranulocytosis is the most serious adverse event, in 1.7% of patients; occurring mostly in the 1st year

# Historical Question: Liver Fibrosis

<b>Publication</b>	<b>N Patients Studied</b>	<b>Time on Deferiprone</b>	<b>Authors' Conclusion of Liver Fibrosis</b>
Olivieri et al, 1998	14	2.3 years	Yes

# Historical Question: Liver Fibrosis

<b>Publication</b>	<b>N Patients Studied</b>	<b>Time on Deferiprone</b>	<b>Authors' Conclusion of Liver Fibrosis</b>
Olivieri et al, 1998	14	2.3 years	Yes
Callea, 1998	14	2.3 years	No
Stella et al., 1998	10	2 ± 1 years	No
Piga et al., 1998	16	2 ± 0.5 years	No
Hoffbrand et al., 1998	17	2-4 years	No
Töndury et al., 1998,	11	6-12 years	No
Galanello et al., 1999	18	1-2.4 years	No
Berdoukas et al., 1999	14	1 year	No
Maggio et al., 2002	21	2.5 ± 0.2 years	No
Wanless et al., 2002	56	2.5 years	No
Peng et al., 2003	11	3 years	No
Francis et al., 2003	11	2 years	No
Taher et al., 2004	12	5 years	No
Chen et al., 2006	45	2-5 years	No
Wu et al., 2006	17	3.3 years	No
Aydinok et al., 2007	12	1 year	No

# Safety Summary: Post-marketing

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1999 - 2010:

- No new serious events identified
- Changes to product label
  - Headache
  - Fatigue
  - Diarrhea
  - Chronic overdose

# Risk Management Plan (I)

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## ■ Main Objective

- Mitigate risks associated with agranulocytosis
  - Weekly monitoring of the neutrophil count
  - Interruption of therapy at neutropenia or infection
  - Educational program for healthcare professionals and patients

## Risk Management Plan (II)

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### ■ Action Plan

- Single Central Pharmacy Distribution
- Register Health-Care Professionals (HCP) & patients to facilitate education
- Medication Guide provided to HCP & patient prior to drug dispensing
- Quarterly Communication Plan to reinforce adherence to the program

## Risk Management Plan (III)

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- Safety study in patients with SCD
- Active Drug-Surveillance Program for patients with conditions other than thalassemia

## Clinical Perspective

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Dr. Renzo Galanello

Professor of Pediatrics, University Hospital Cagliari  
Sardinia, Italy

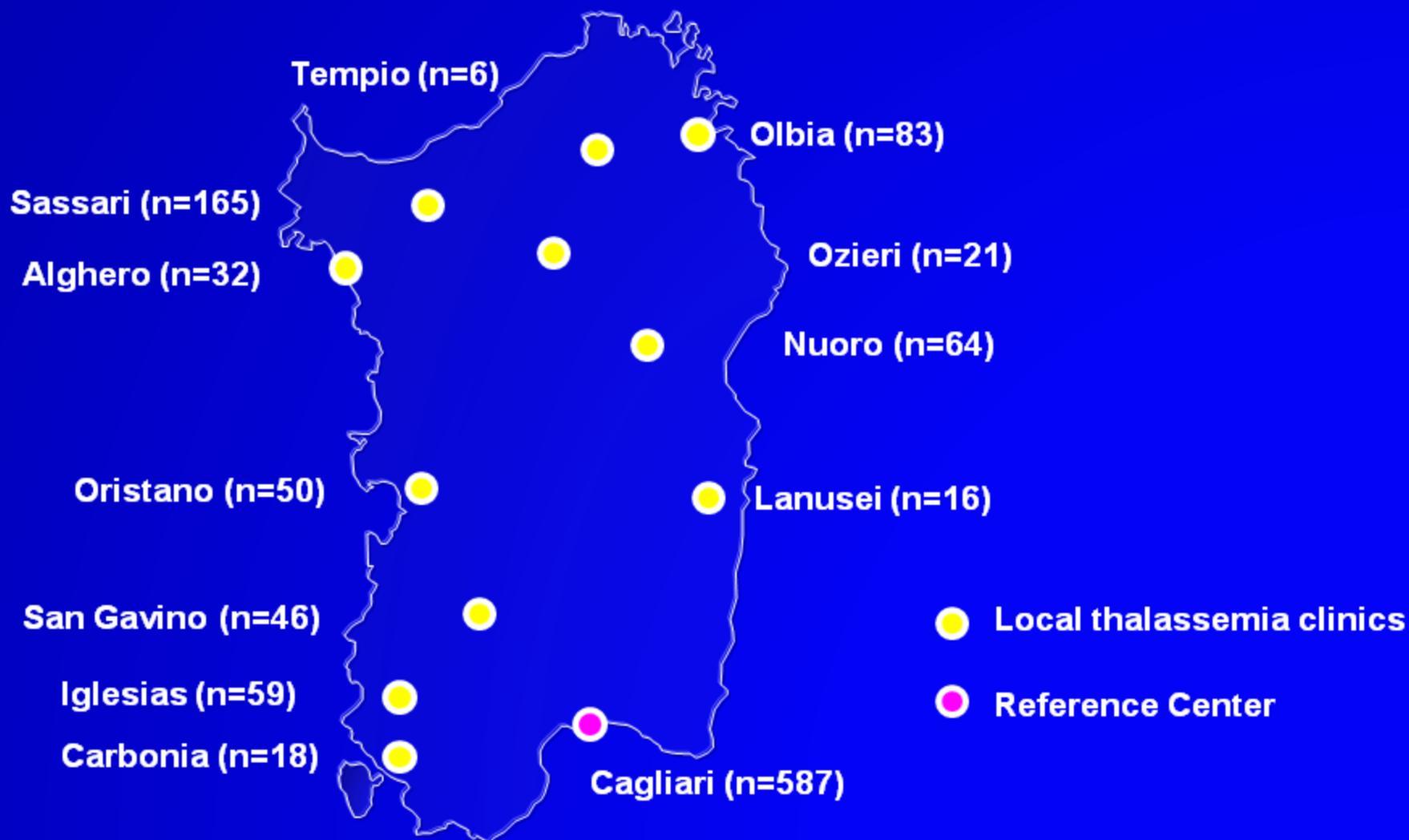
Head of Pediatric Clinic and Thalassemia Unit

# Thalassemia Regional Hospital (Sardinia): Patient Distribution

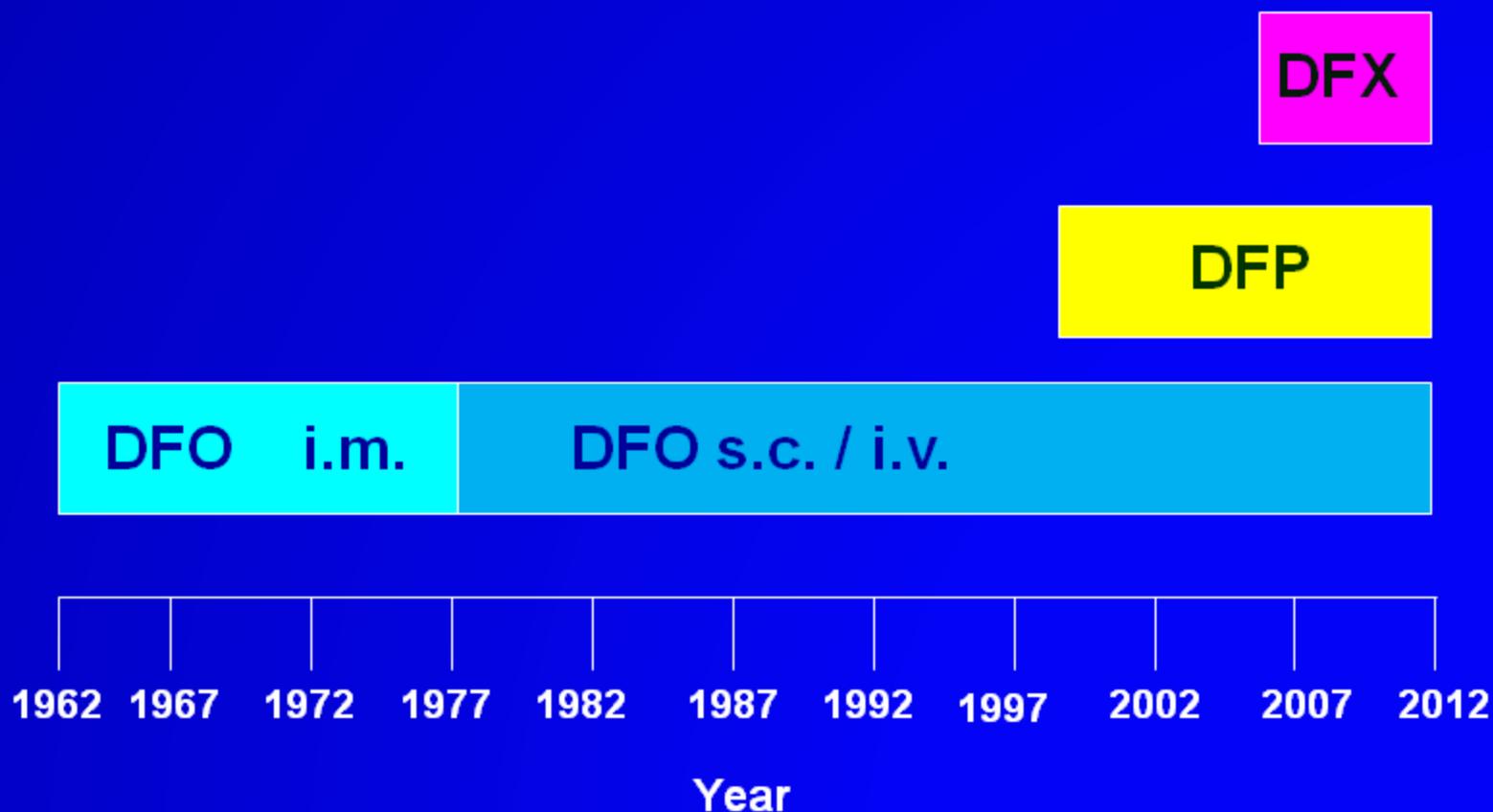


<b>Thalassemia Major</b>	<b>476</b>
<b>Thalassemia Intermedia</b>	<b>111</b>
<b>Hemoglobin H Disease</b>	<b>270</b>
<b>Sickle Cell Syndromes</b>	<b>12</b>

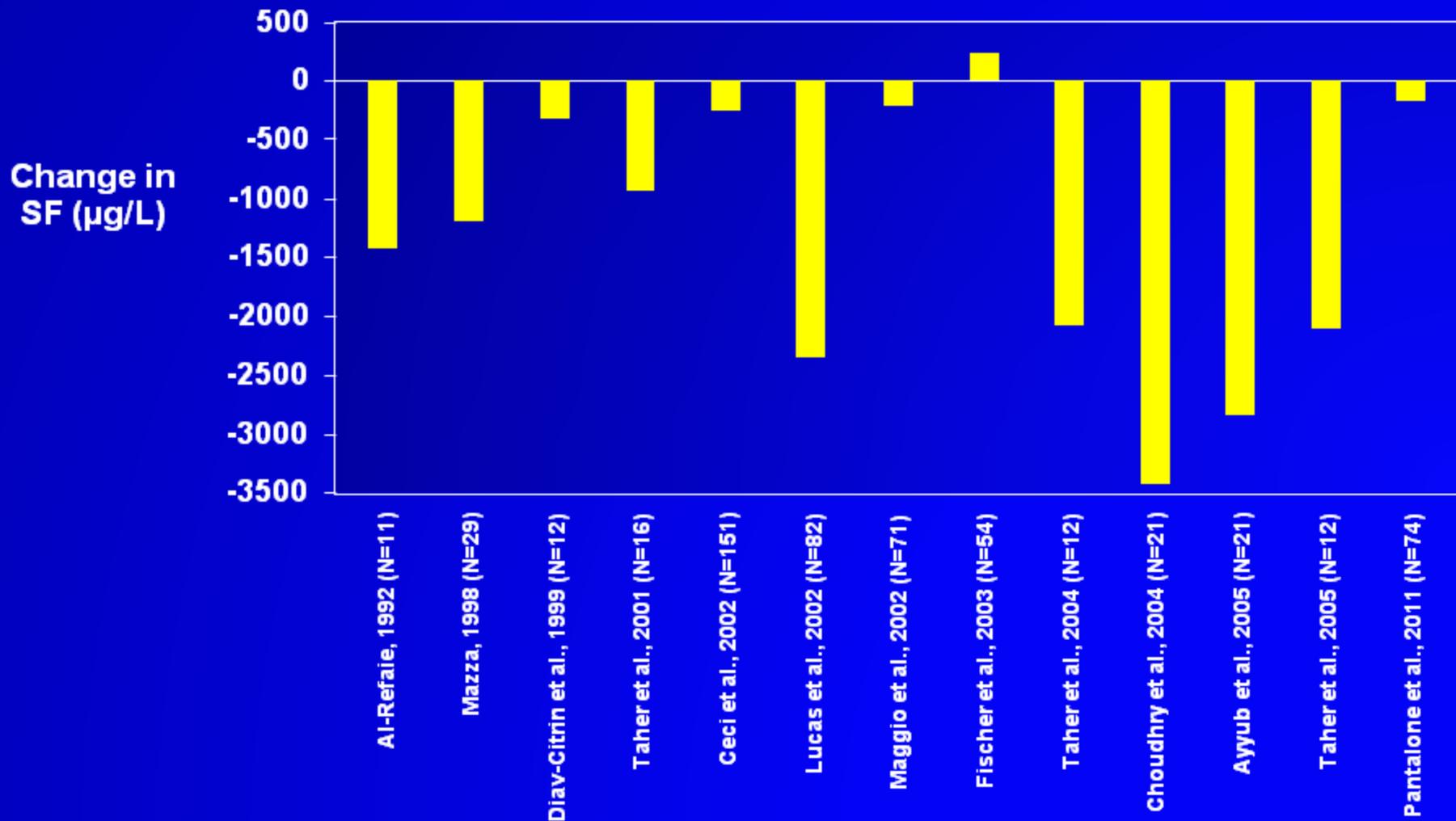
# Distribution of $\beta$ -thalassemia Patients Within Sardinia



# Availability of Iron Chelators in Europe



# Change in Serum Ferritin with Deferiprone Reported in Literature



# Cardiac Iron Load in Thalassemia Patients Treated Long-term with Deferoxamine

	Iron Overload T2* < 20 ms		No Iron Overload T2* ≥ 20 ms	
	n	%	n	%
London (n=146) <sup>1</sup>	82	56%	64	44%
Cagliari (n=167) <sup>2</sup>	107	64%	60	36%
Los Angeles (n=165) <sup>3</sup>	61	37%	104	63%
Torino (n=63) <sup>4</sup>	37	59%	26	41%

<sup>1</sup>Pennell, personal communication

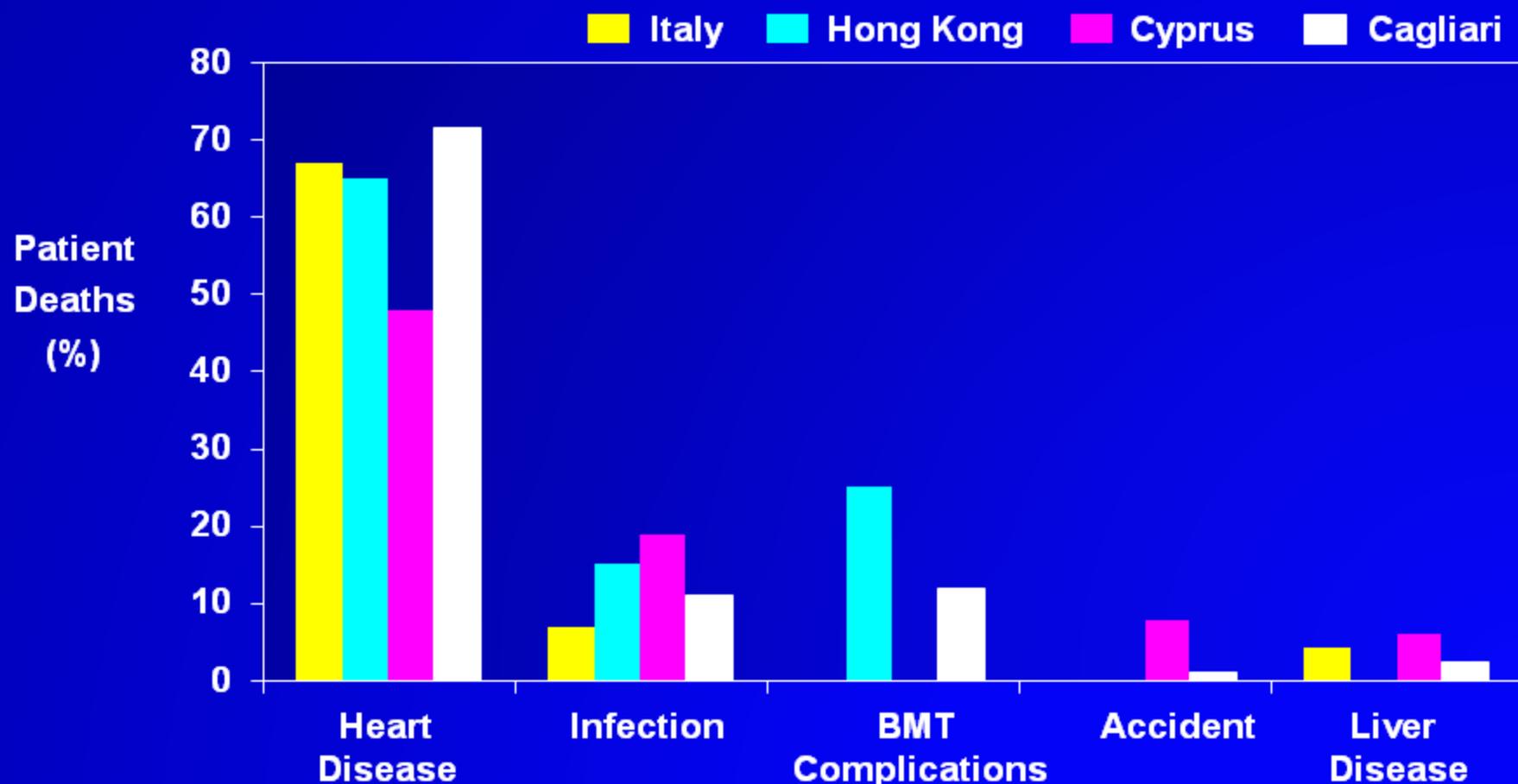
<sup>2</sup>Tanner, 2007

<sup>3</sup>Wood, personal communication

<sup>4</sup>Piga, personal communication

# Causes of Death in Patients with $\beta$ -thalassemia

## Major Prior to 1999 (EU Availability of Deferiprone)



Italy: C. Borgna-Pignatti, 2004

Hong Kong: CK Li, 2002

Cyprus: P. Telfer, 2006

BMT = bone marrow transplantation

# Incidence of Cardiac Events Higher with Deferoxamine than Deferiprone

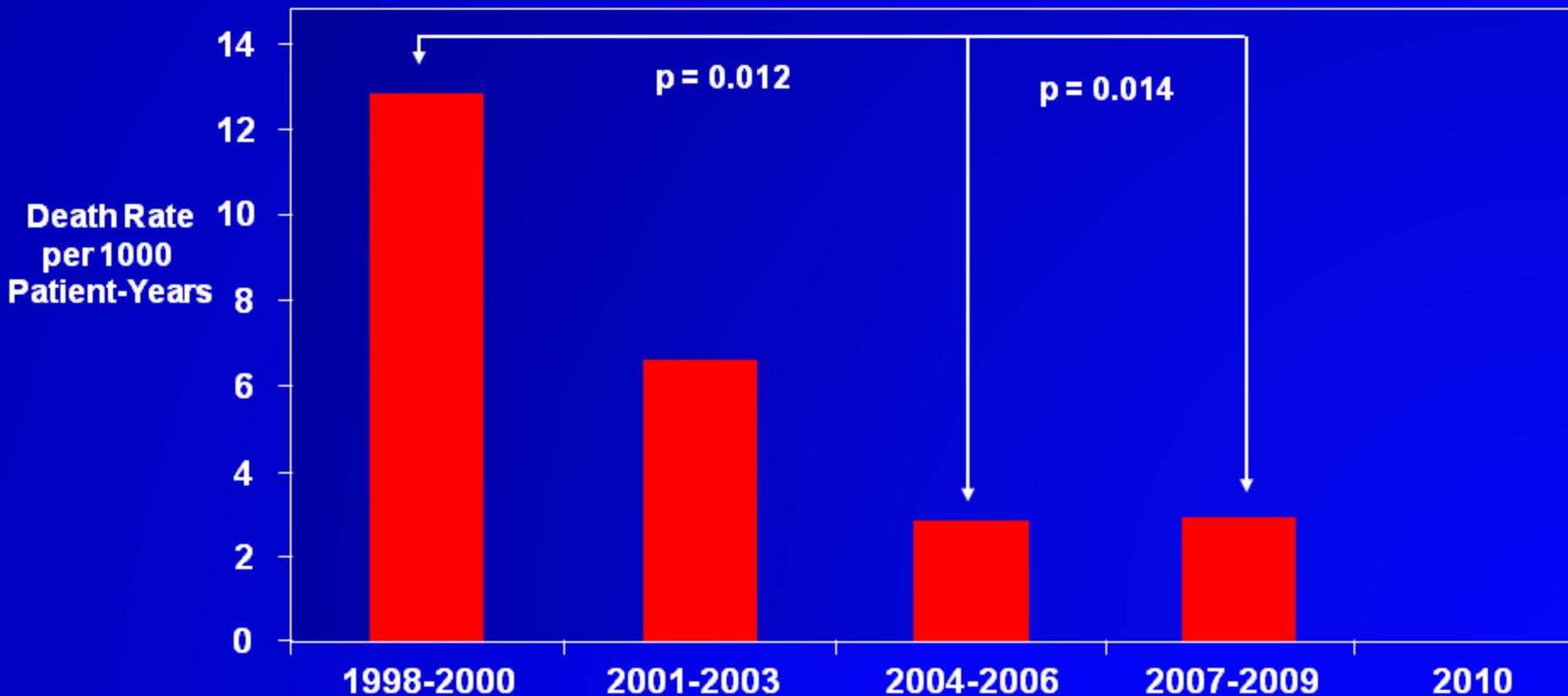
Year**	Deferoxamine			Deferiprone		
	Patients at Risk	Cardiac Events*	Percentage (95%CI)	Patients at Risk	Cardiac Events*	Percentage (95%CI)***
1995	516	3	0.58 (0.12, 1.69)	0	0	---
1996	444	11	2.48 (1.24, 4.39)	63	0	0 (0, 5.69)
1997	420	4	0.95 (0.26, 2.42)	75	0	0 (0, 4.80)
1998	398	5	1.26 (0.41, 2.91)	93	0	0 (0, 3.85)
1999	396	3	0.76 (0.16, 2.20)	89	0	0 (0, 4.06)
2000	393	4	1.02 (0.28, 2.59)	87	0	0 (0, 4.15)
2001	387	6	1.55 (0.57, 3.34)	89	0	0 (0, 4.06)
2002	374	4	1.07 (0.29, 2.72)	88	0	0 (0, 4.30)
2003	358	12	3.35 (1.74, 5.78)	92	0	0 (0, 3.93)

\* Cardiac events were defined as cardiac failure or arrhythmias requiring use of inotropic or antiarrhythmic drugs.

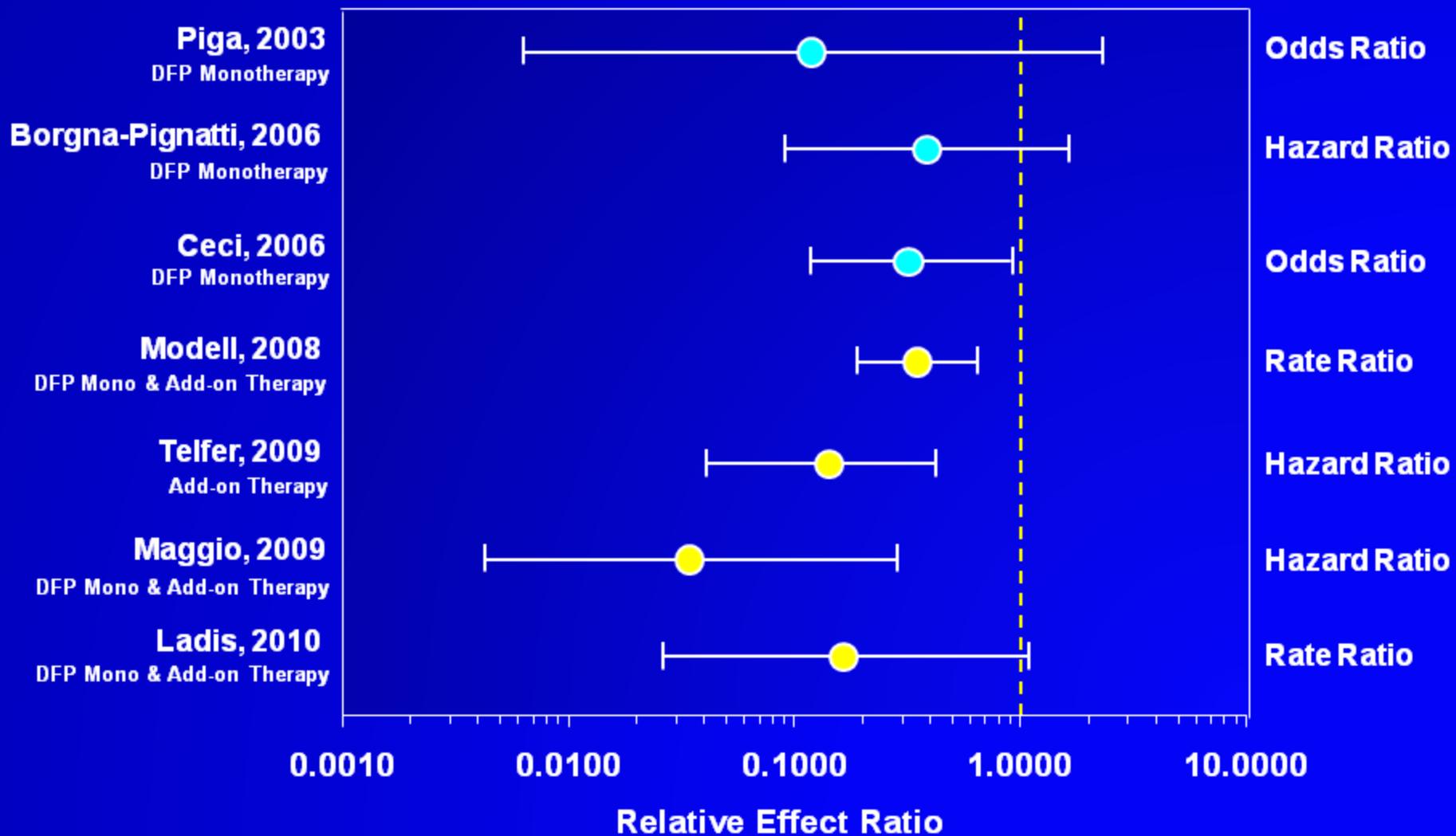
\*\*Each subject is included once in each year, based on the treatment received on January 1 of that year.

\*\*\*One-sided 97.5% confidence interval.

# Decline in Cardiac Mortality Over Past 10 Years at Thalassemia Unit Cagliari

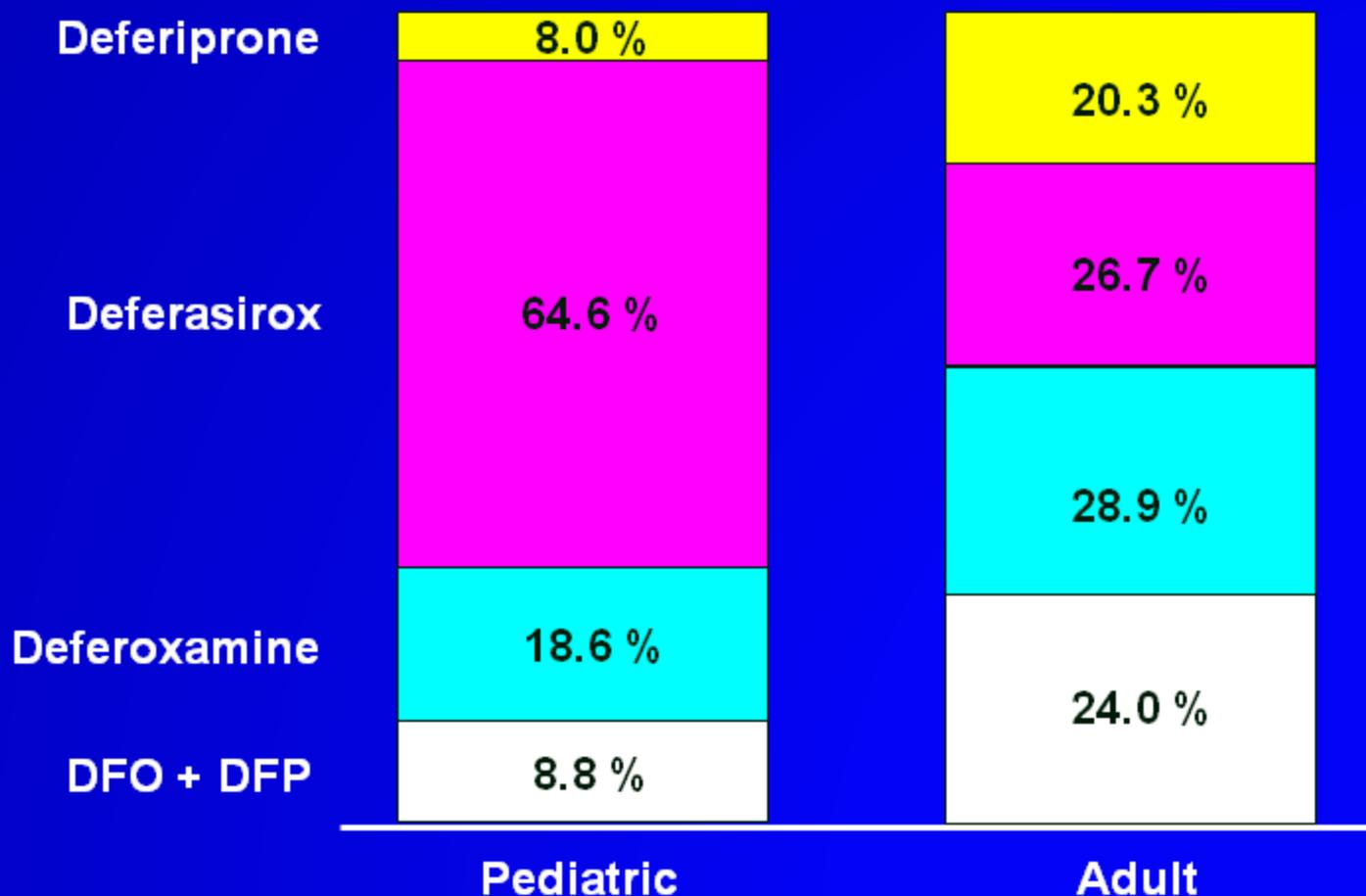


# Heart Disease in Patients Treated with Deferiprone or Deferoxamine



# Iron Chelation Treatment in the Pediatric and Adult Population in Italy

(981 patients from 15 Thalassemia Centers)



## Conclusions – My Clinical Perspective

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- Deferiprone significantly reduces serum ferritin
- Natural history studies showed less cardiac disease with deferiprone than deferoxamine
- Deferiprone is an important part of iron chelation treatment

## Conclusion

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Michael Spino, PharmD  
President, ApoPharma Inc.

## Conclusion

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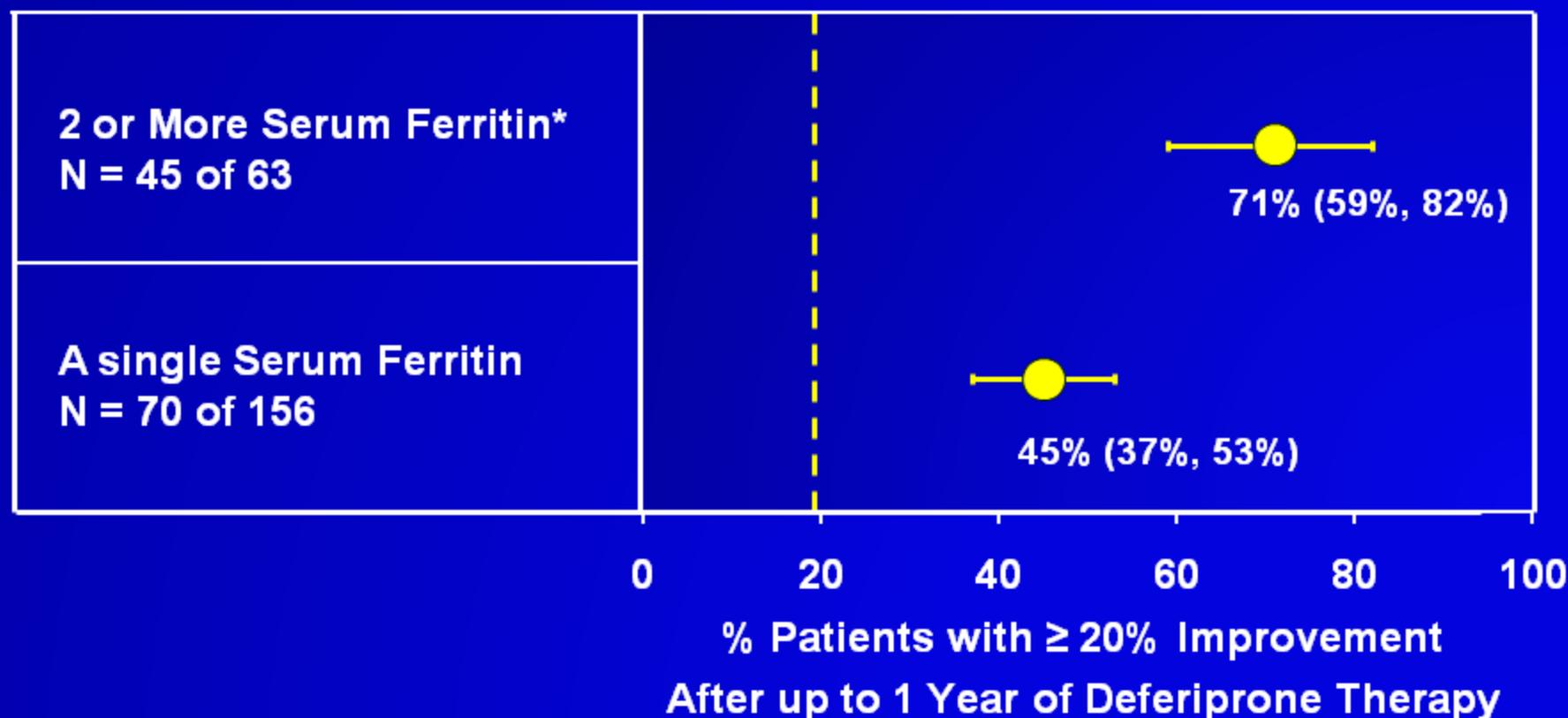
- Deferiprone met the success criteria for reducing iron load in patients who failed previous therapy
- Superior to deferoxamine in reducing cardiac iron
- Most serious adverse event is agranulocytosis
- Benefits outweigh potential risks in the proposed indication

# LA36 - Success Rate for Serum Ferritin

ST-21

## Patients with 2 or more Pre-Deferiprone Serum Ferritin Values vs a Single Serum Ferritin Value

Success Rate with 95% Confidence Interval



\* Patients for whom 2 of the 2, 2 of the 3, 3 of the 4, or 3 of the 5 serum ferritin values obtained prior to starting deferiprone were > 2500 µg/L

## LA36 - Knowledge of Chelator Prior to Selection

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- The Independent Committee received a dataset named PC (previous chelation)
- The data were compiled from the patient case report forms or datasets, where information regarding previous chelation therapy was available

# LA36 - Success Rate for Serum Ferritin European vs Non-European

Subgroup of Geographic Region  
Analysis on Serum Ferritin

Success Rate with  
95% Confidence Interval

European Countries



Non-European Countries

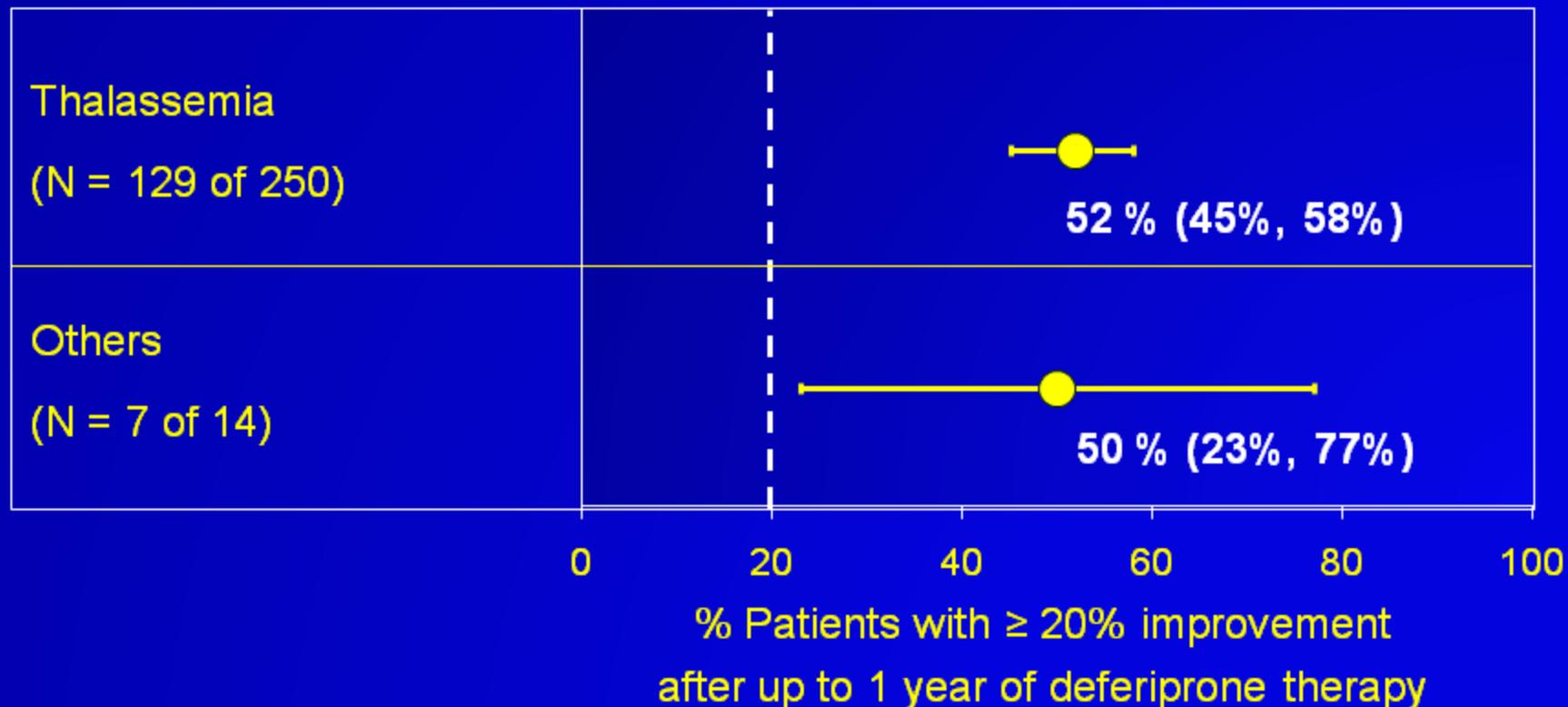


0 20 40 60 80 100

% Patients with  $\geq 20\%$  improvement  
after up to 1 year of deferiprone therapy

# LA36 - Success Rate for Serum Ferritin Thalassemia vs. Others

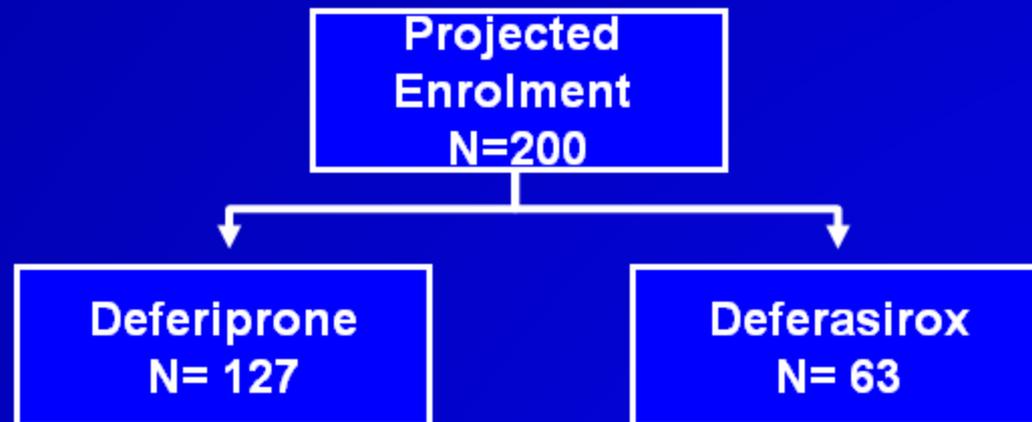
Success Rate with 95% Confidence Interval



Thalassemia: Thalassemia major (228), Hemoglobin e-thalassemia (21), Thalassemia intermedia (1)

Others: Myelodysplasia (7), Sickle cell disease (3), Congenital anaemia (1), Diamond-Blackfan anemia (1), Refractory anemia (2)

# 52 Week, Multi-centre, Randomized, Active controlled Study Comparing the Safety and Tolerability of Deferiprone vs. Deferasirox in Patients with Sickle cell disease



	<b>Serum Ferritin</b>	<b>Liver Iron Concentration</b>	<b>Safety Assessments*</b>
<b>Baseline</b>	✓	✓	✓
<b>Every 12 Weeks</b>	✓		
<b>Week 26</b>	✓		✓
<b>Week 52</b>	✓	✓	✓

\* Safety assessments: absolute neutrophil count, serum creatinine, liver enzymes, bilirubin, alkaline phosphatase and proteinuria, body weight, height, sexual development

# Importance of Measuring Iron Overload

No Iron Overload

Iron Overload



**Serum Ferritin**

**2,500  $\mu\text{g/L}$**

**Liver Iron  
Concentration**

**7 mg/g dw**

**15 mg/g dw**

**Cardiac MRI T2\***

**20 ms**

**12 ms**

■ Threshold for increased risk of iron induced toxicity

# Serum Ferritin Threshold Levels for Greater Risk of Cardiac Toxicity

<b>Serum Ferritin levels <math>\mu\text{g/L}</math></b>	<b>Total Number of Patients in the Study N = 97 (%)</b>	<b>15 year Cardiac disease-free survival N = 97<sup>1</sup></b>
<b>&lt;2,500 <math>\mu\text{g/L}</math></b>	<b>4 (4.1)</b>	<b>91 %</b>
<b>&gt;2,500 <math>\mu\text{g/L}</math></b>	<b>93 (95.9)</b>	<b>20 %</b>

<sup>1</sup>Olivieri et al., 1994,NEJM 331:574:578

# LA36 - Success Rate for Serum Ferritin by Different Success Criteria

Criterion for % reduction in Serum Ferritin after up to 1 year of Deferiprone therapy

% Patients with specified reduction  $\pm$  95% Confidence Interval

$\geq 20\%$  (N = 136 of 264)

52% (45%, 58%)

$\geq 30\%$  (N = 104 of 264)

39% (33%, 46%)

$\geq 40\%$  (N = 74 of 264)

28% (23%, 34%)



## Safety Comparison

### Patients eligible for LA36 (Serum Ferritin only) vs. the rest of the Pooled Safety Data Population

	DFP (All Doses)	
	LA36 eligible patients	Remaining Pooled Safety population
N Exposed	227	415
Total Exposure (years)	447.8	891.0
N (%) of patients reporting AEs	198(87.2)	340(82.0)
Rate AEs reported per 100 patient years	574.2	507.3
N (%) of patients reporting SAEs	48(21.1)	99(23.9)
Rate SAEs reported per 100 patient years	18.3	16.7

# Prevalence and Rate of Specific Adverse Events of Interest

## LA-36 (serum ferritin only) vs. Pooled Safety Data

	LA-36 eligible	Rest of pooled safety	LA-36 eligible	Rest of pooled safety
	Total number patients		Total exposure (pt years)	
	227	415	447.8	891.0
	N (%)		N events (rate per 100 patient-years)	
Agranulocytosis	3(1.3)	8(1.9)	3(0.67)	8(0.90)
Neutropenia	17(7.5)	26(6.3)	20(4.47)	29(3.25)
Neutrophil count ↓	21(9.3)	36(8.7)	26(5.81)	49(5.50)
ALT increased	19(8.4)	37(8.9)	29(6.48)	56(6.28)

# LA-36 Number (%) of patients with last value<sup>€</sup> below the threshold for lower risk

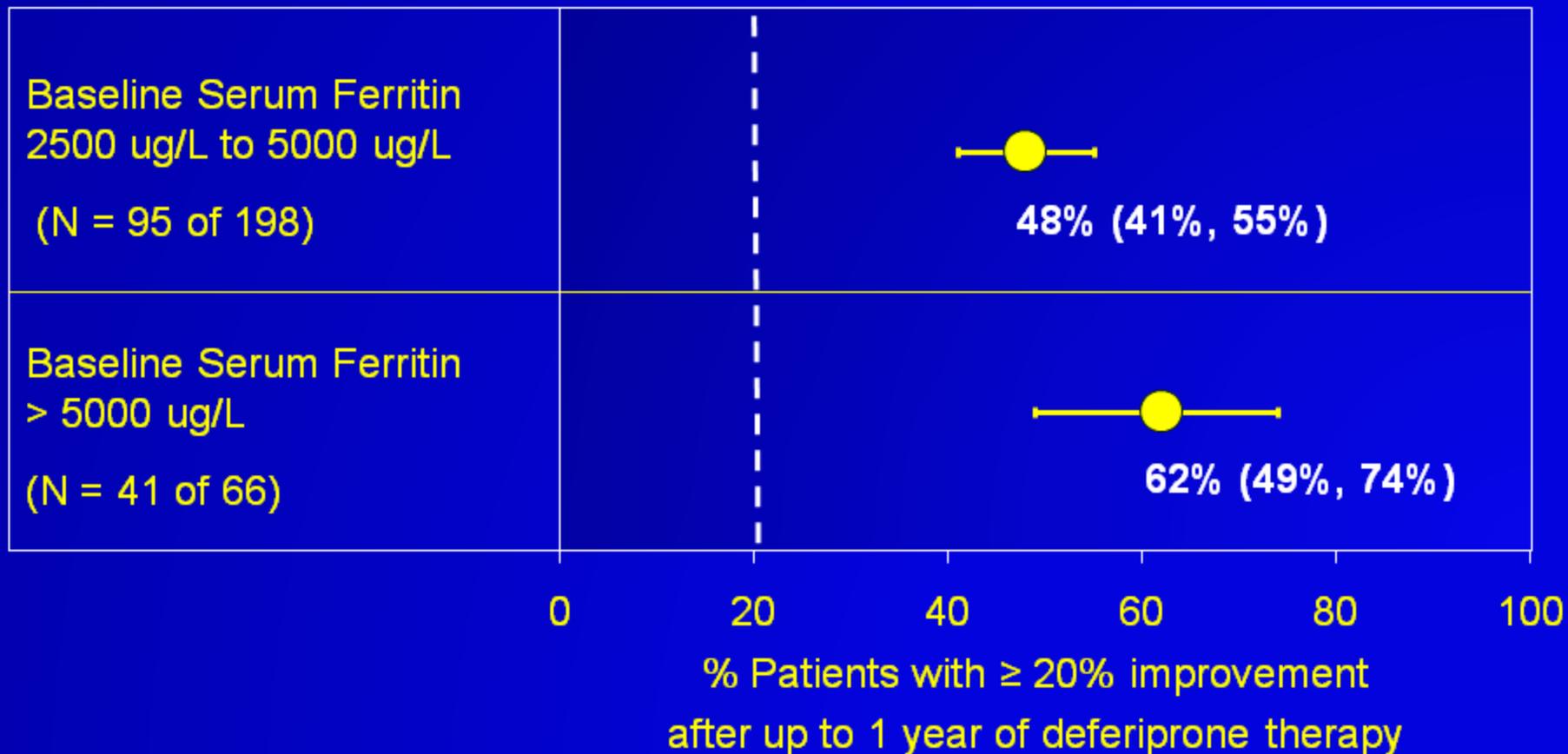
Baseline	Threshold for Lower Risk	N (%) of Patients
<b>Serum Ferritin</b> (N = 264) Range: 2505 – 16550	$\leq 2500 \mu\text{g/L}$	<b>97 (37%)</b>
<b>Liver Iron Concentration</b> (N = 117) Range: 7.1 – 66.6	$\leq 7 \text{ mg Fe/g liver dry weight}$	<b>15 (13%)</b>
<b>Cardiac MRI T2*</b> (N = 39) Range: 4.0 – 19.5	$\geq 20 \text{ ms}$	<b>9 (23%)</b>

€ Post baseline value closest to the 1 year assessment date

# LA36 - Success Rate for Serum Ferritin

## Baseline Serum Ferritin 5000 ug/L Threshold

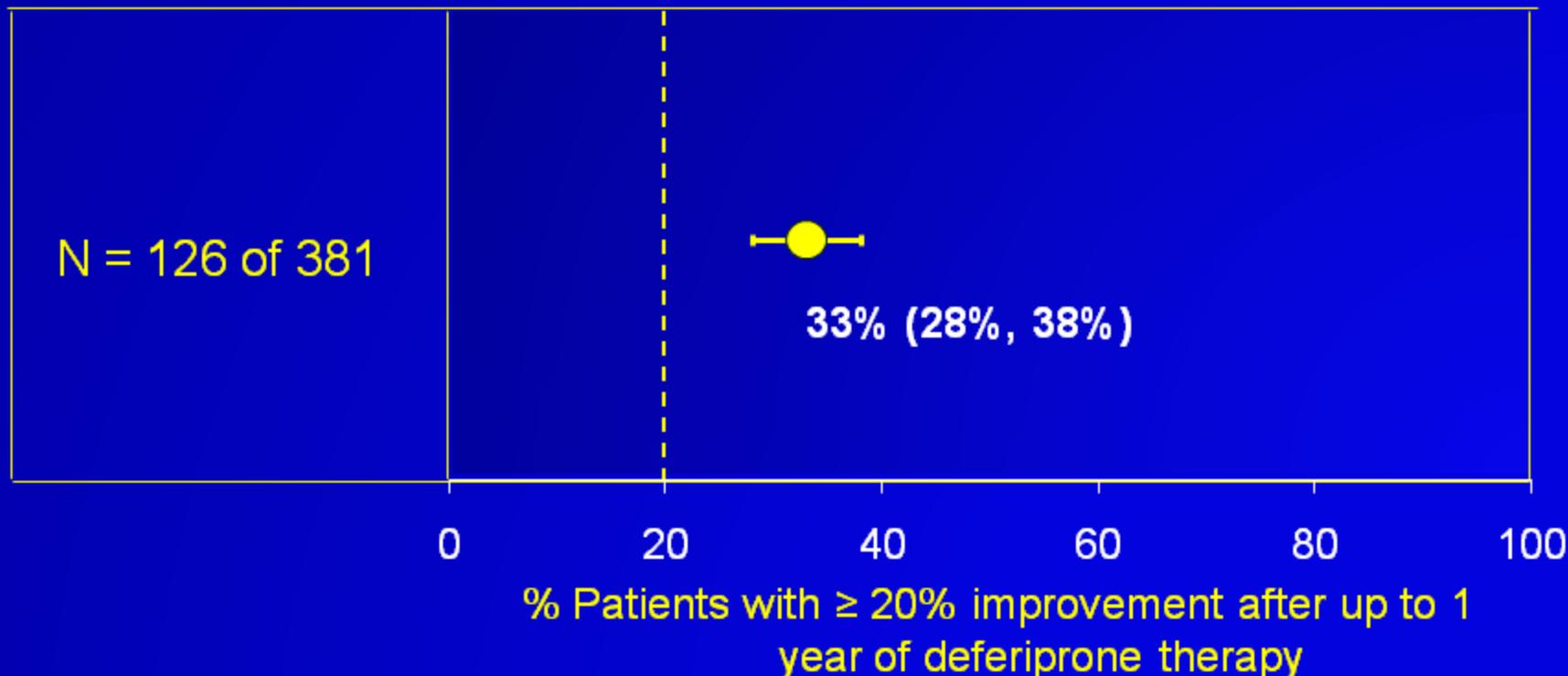
Success Rate with 95% Confidence Interval



# Success Rates for Serum Ferritin

Excluded patients due to their baseline SF  $\leq 2500$   $\mu\text{g/L}$

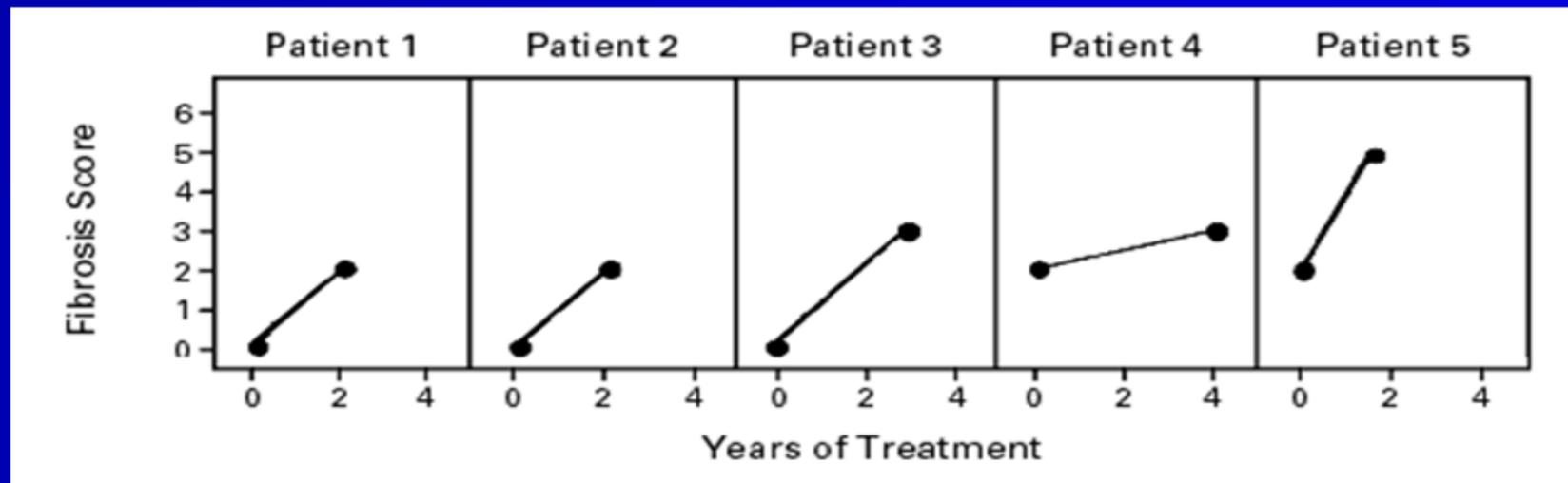
Success Rate with 95% Confidence Interval



Note: 414 patients were excluded due to their baseline SF  $\leq 2500$   $\mu\text{g/L}$  and of which 381 patients had a post baseline SF within 1 year + 3 months

# Is there a progression of liver fibrosis during deferiprone use?

Progression of liver fibrosis in 5/14 deferiprone and 0/12 deferoxamine evaluated patients<sup>1</sup>



(1) Olivieri et al. N Engl J Med. 1998;339(7):417-23

## Limitations Emphasized by the Author<sup>1</sup>

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- The study
  - retrospective
  - observational and not randomized
- Sample size is small
- Deferoxamine group did not constitute a true control population
- The effect of hepatic fibrosis was not confirmed by re-challenge after drug discontinuation
- “Relation between deferiprone and fibrosis cannot be considered definite or proved”

<sup>1</sup> Olivieri et al. N Engl J Med. 1998;339(7):417-23

## Confounding Factors Noted by Editorial <sup>1</sup>

- Fibrosis identical to that caused by iron overload
- Infectious hepatitis (4/5 patients HCV+)
- Older age
- Mean baseline of LIC significantly higher than in deferoxamine group (81 vs. 35  $\mu\text{mol/L}$ )
- Size of biopsy sample too small
- Lack of true control population

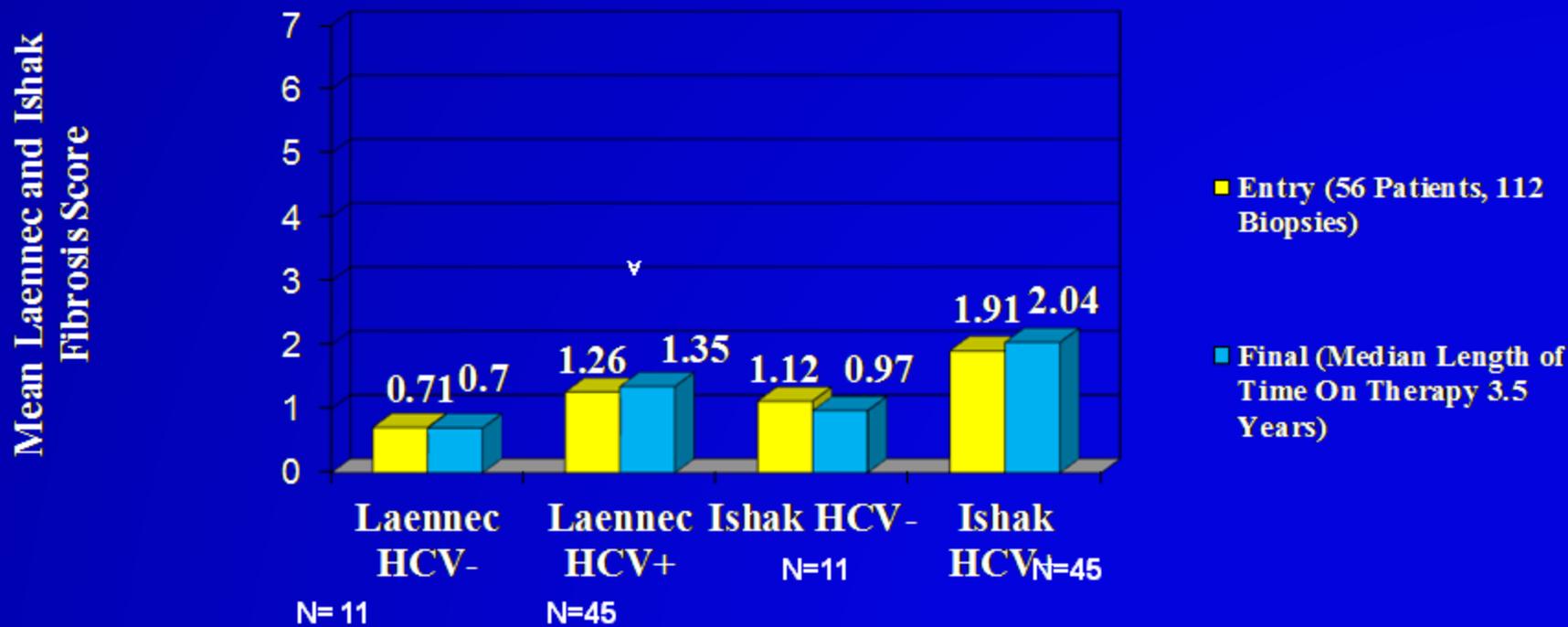
(1) Kowdley and Kaplan. N Engl J Med. 1998;339(7):468-9

# Historical Question:

## Is there progression of liver fibrosis on deferiprone?

Publication	N Patients Studied	Time on deferiprone	Authors conclusion of liver fibrosis progression
Olivieri et al, 1998	14	2.3 years	Yes
Callea, 1998	14	2.3 years	No
Stella et al., 1998	10	2 ± 1 years	No
Piga et al., 1998	16	2 ± 0.5 years	No
Hoffbrand et al., 1998	17	2-4 years	No
Töndury et al., 1998	11	6-12 years	No
Galanello et al., 1999	18	1-2.4 years	No
Berdoukas et al., 1999	14	1 year	No
Maggio et al., 2002	21	2.5 ± 0.2 years	No
Wanless et al., 2002	56	2.5 years	No
Peng et al., 2003	11	3 years	No
Francis et al., 2003	11	2 years	No
Taher et al., 2004	12	5 years	No
Chen et al., 2006	45	2-5 years	No
Wu et al., 2006	17	3.3 years	No
Aydinok et al., 2007	12	1 year	No

# Hepatic Fibrosis Score Prior and After Deferiprone Therapy Based on Hepatitis C Status (Wanless et al, 2002)



∇ This change represents an increase of 0.03 units of fibrosis per year, less than the published estimate of 0.1 for individuals with hepatitis C (Poynard et al. 1997; Ghany et al. 2003)

# Deferiprone vs Deferoxamine in Patients with Thalassaemia Major: a Randomized Clinical Trial (Maggio et al., 2002)

- Prospective, randomized study: 144 patients
- Duration of therapy
  - 30 months for deferiprone
  - 34 months for deferoxamine
- LIC and liver fibrosis examined by means of biopsy in 36 patients who
  - Consented to have liver biopsy before and after treatment

# Baseline and Follow-Up Values of Liver Fibrosis Score in Patients Treated with Deferiprone or Deferoxamine

Maggio et al., 2002

	<b>Deferiprone (n=21)</b>	<b>Deferoxamine (n=15)</b>	
<b>Mean fibrosis score before treatment</b>	<b>2.1±1.3</b>	<b>2.2±1.3</b>	<b>P=0.77</b>
<b>Mean fibrosis score after treatment</b>	<b>2.1± 1.5</b>	<b>2.2±1.2</b>	<b>P=0.84</b>
<b>N patients with increased fibrosis score during treatment</b>	<b>7/21 (33%)</b>	<b>4/15 (27%)</b>	
<b>N patients with increased fibrosis score during treatment and anti-HCV positive</b>	<b>6/7(86%)</b>	<b>4/4 (100%)</b>	

# Recommendation for Deferiprone Use in Patients with Myelodysplasia

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- ApoPharma recommends that deferiprone therapy in patients with myelodysplasia should not be initiated except as a last resort

# Exposure and Rates of AEs, SAEs Myelodysplasia and Myelofibrosis Patients Pooled Safety Data

	<b>MDS and Myelofibrosis patients N=19</b>
Exposure (years)	
Total	20.15
Mean $\pm$ SD	1.06 $\pm$ 1.8
Median (range)	0.64 (0.03, 7.81)
Rate of AEs per 100 patient years	580.65
Rate of SAEs per 100 patient years	89.33

\*Doses included 75 mg/kg/d (n=16), 100 mg/kg/d (n=1), combination therapy (n=1), 41 mg/kg/d (n=1)

# Agranulocytosis, irrespective of causality

## Thalassemia Major vs. Non Thalassemia Major

### Pooled Safety Data

	Thalassemia Major N=560	Non Thalassemia Major N=82
<b>No. Events</b>	8 (1.4%)	3* (3.7%)
<b>Time to Onset (days): Median Range</b>	161 65-3352	301 140-567
<b>Duration (days): Median Range</b>	9 3-18	19 16-85

\*1 event considered unrelated to deferiprone use and agranulocytosis has not recurred upon rechallenge and continued therapy for 7 years

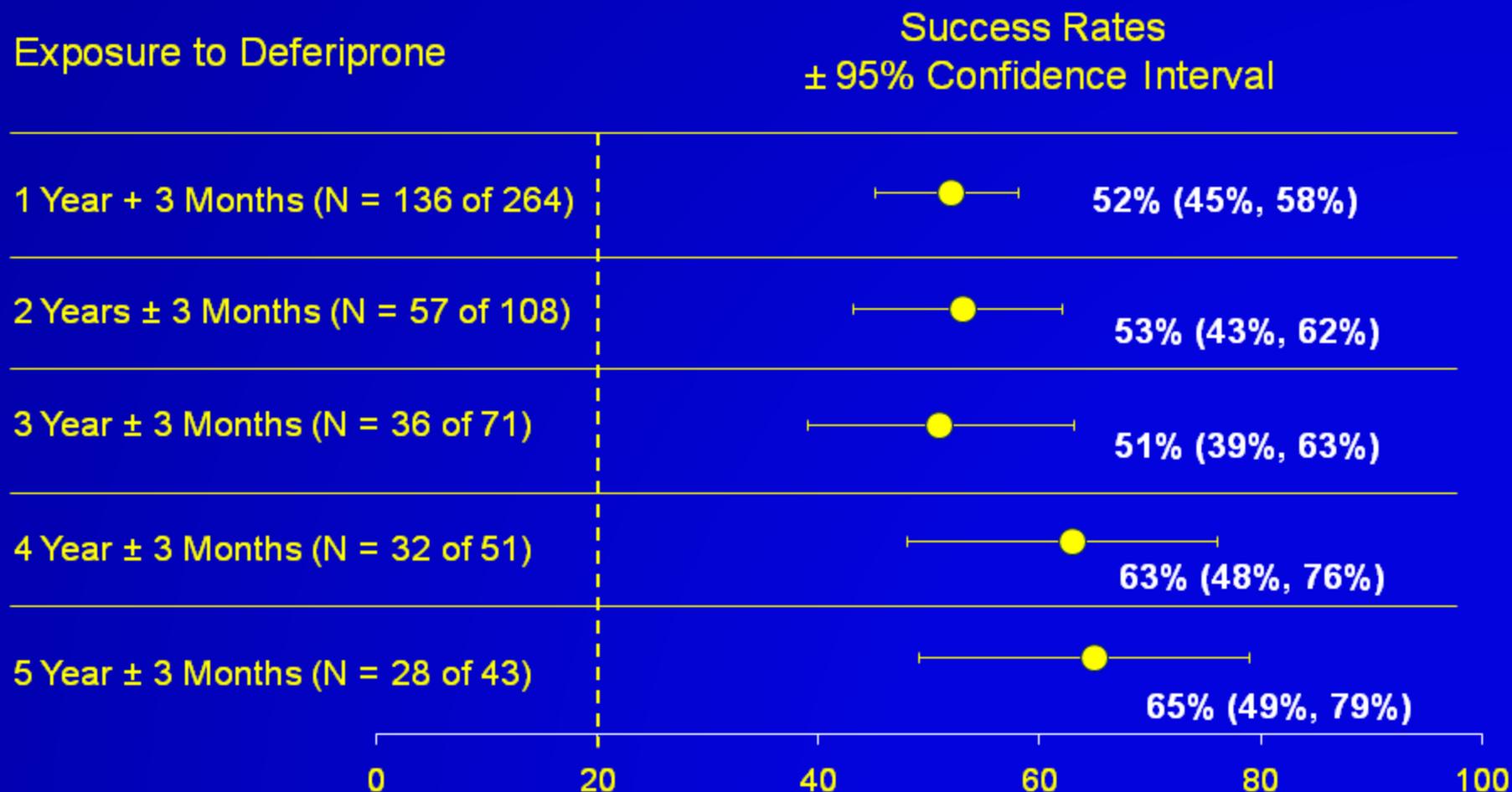
# Adverse Events, Irrespective of Causality Geriatric Patients ( $\geq 65$ years old) Pooled Safety Data

Preferred Term	ApoPharma Clinical Studies N=15 Exposed Patients	
	Number of Patients with AEs*	% (Out of 15 Patients Exposed)
Neutrophil Count Decreased	4	26.7
Atrial Fibrillation	2	13.3
Congestive Cardiac Failure	2	13.3
Diarrhea	2	13.3
Nausea	2	13.3
Hip Fracture	2	13.3

\*AEs in  $\geq 2$  geriatric patients shown

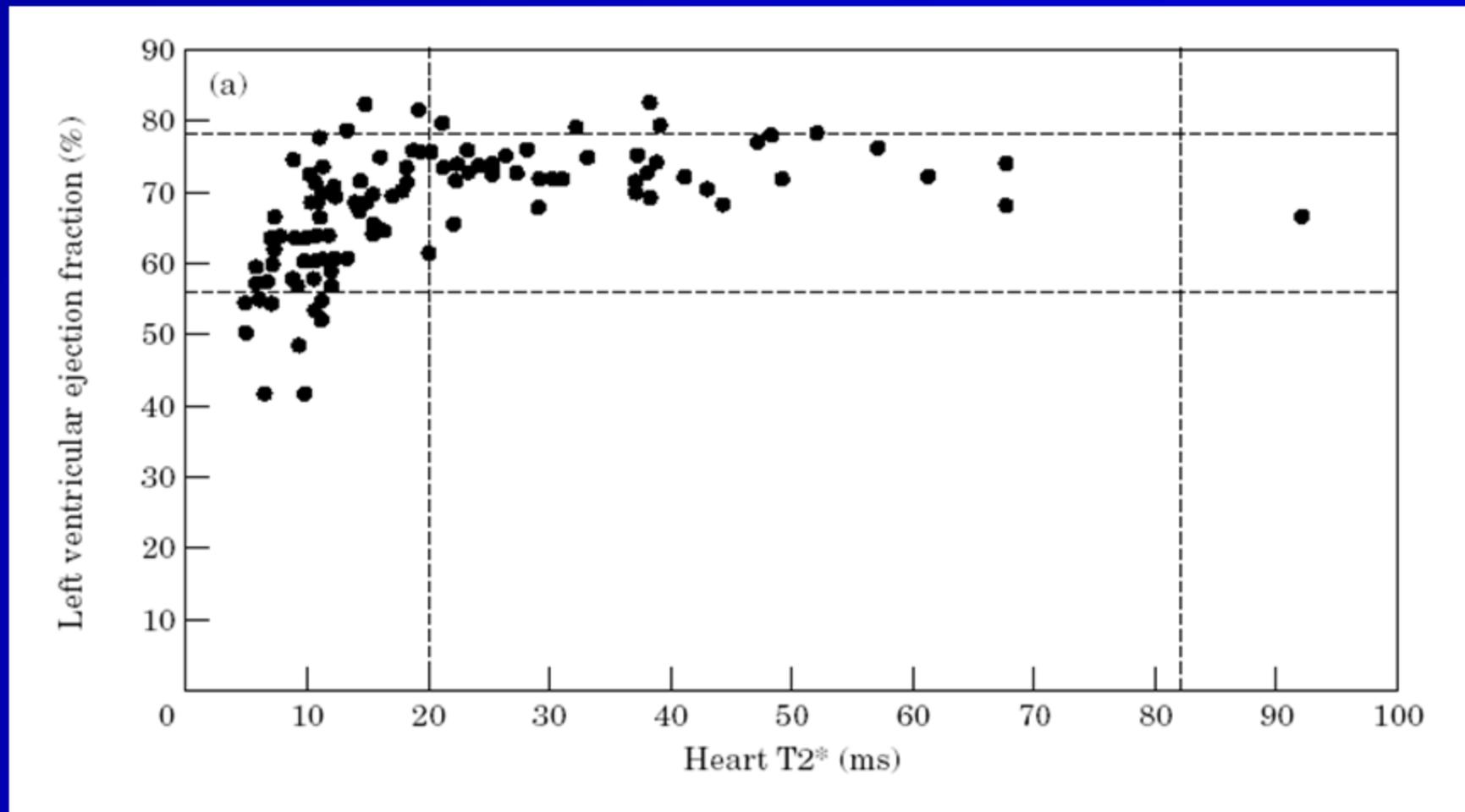
Primary Diagnosis of 15 Geriatric patients: Myelodysplasia (10), Myelofibrosis (3), Chronic lymphocytic leukemia (1), Refractory anemia (1)

# LA36 - Success Rate for Serum Ferritin by Different Duration of Exposure to Deferiprone

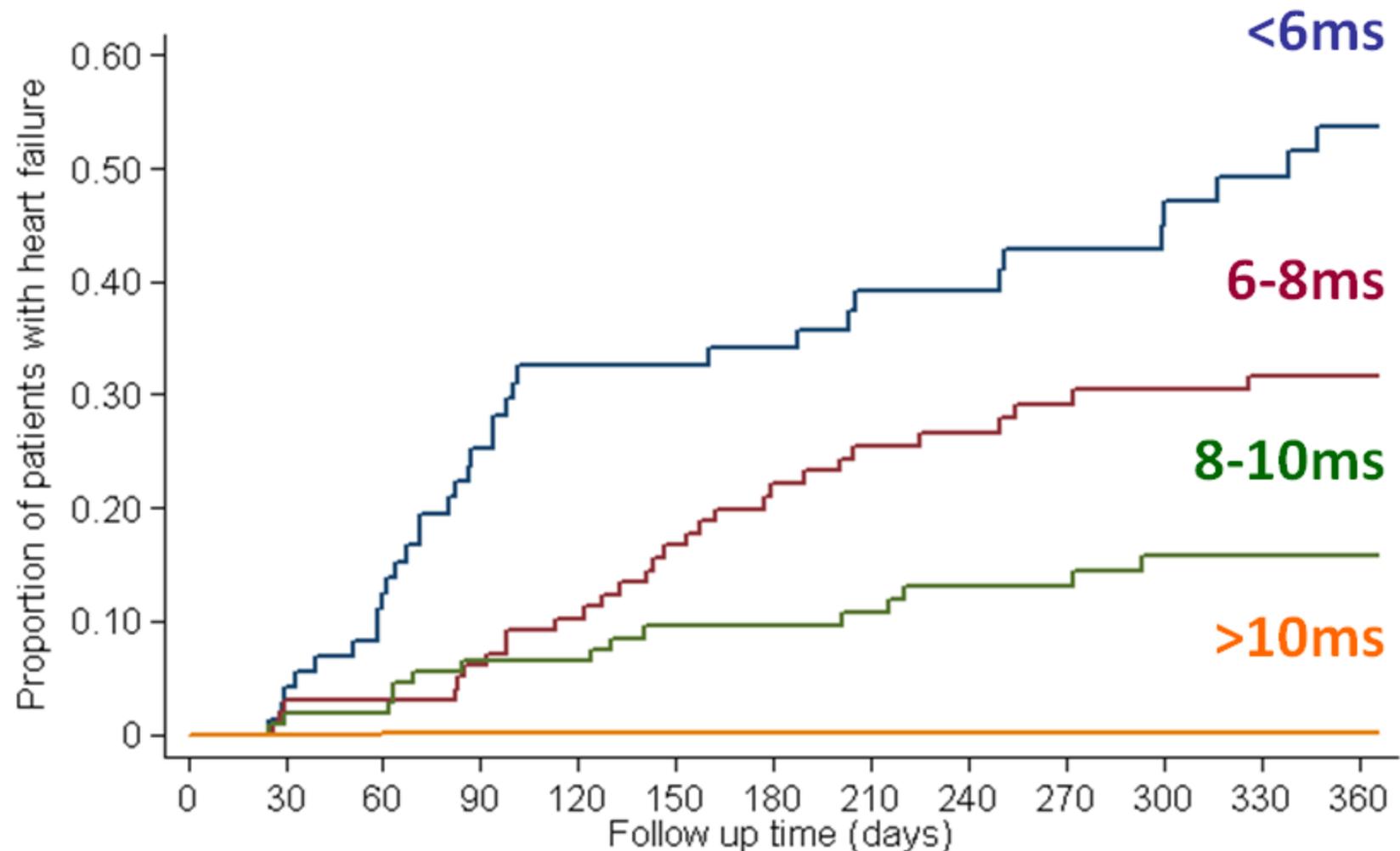


Note: Based on the serum ferritin value which was measured during the corresponding exposure to deferiprone.

# T2\* in Relation to Left Ventricular Function



# KM Curve for Occurrence of Heart Failure Over 1 Year According to Baseline Cardiac T2\*



# KM Curve for Occurrence of Arrhythmia Over 1 Year According to Baseline Cardiac T2\*

