

*12th International Conference on Thalassaemia & the Haemoglobinopathies, Antalya, Turkey:
11-14 May 2011*

Medical Panel Overview/Summary and Q&A

Chelation therapy in Thalassemia: 2010

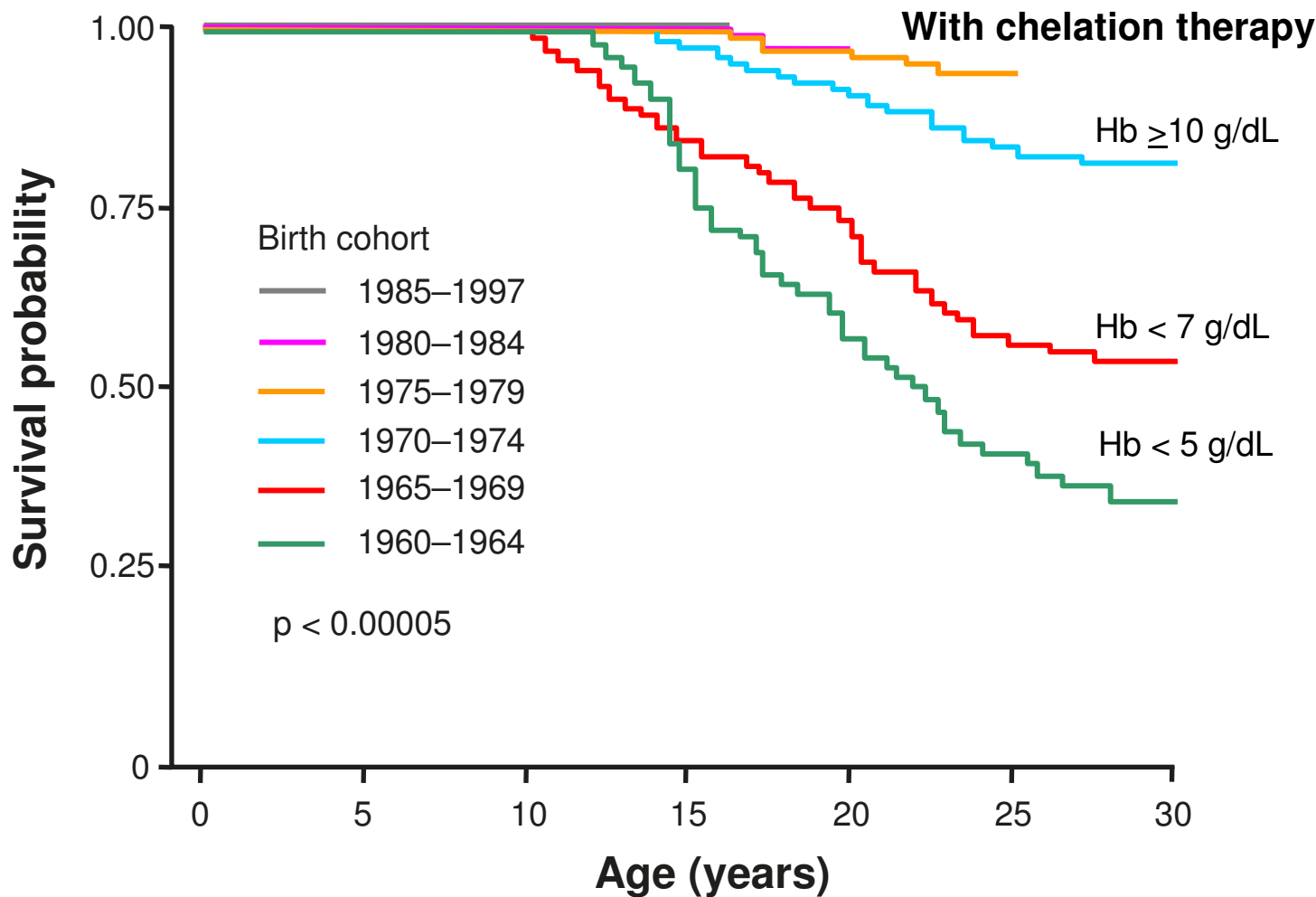


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Outline:

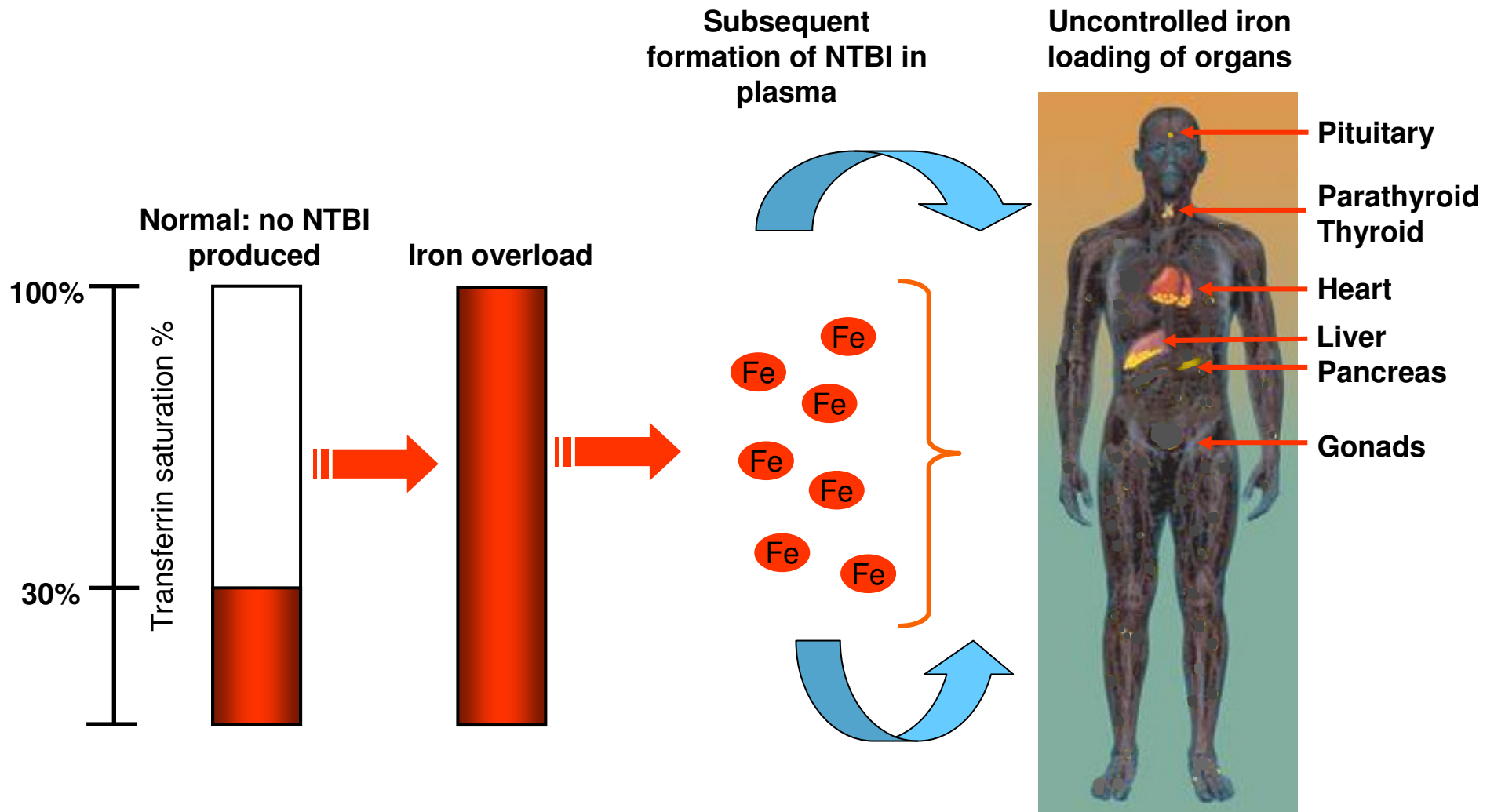
- ❑ Practical management of iron overload in thalassemia
 - DFO
 - Deferiprone
 - Deferasirox
 - Combination therapy
- ❑ Optimal chelation therapy: what to consider?

Transfusion management significantly improves survival in patients with thalassaemia major



200–250 mg iron:
Whole blood:
0.47 mg iron/mL 'Pure' red cells:
1.16 mg iron/mL

Iron overload leads to formation of NTBI and organ loading



NTBI, non-transferrin-bound iron.

Goals of iron chelation therapy

- Maintain iron balance with “safe” tissue iron levels
 - **PREVENTION: SF \geq 1000 ng/ml**
 - match transfused iron with chelated (excreted) iron
 - prevent iron from reaching levels at which tissue damage occurs
 - **RESCUE: SF \geq 2500 ng/ml**
 - remove excess iron – slow process – finite pools
 - reverse dysfunction

Compliance to DFO chelation therapy is the key

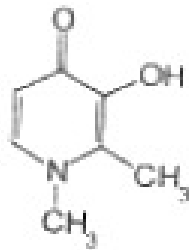


Limitation of the “Gold standard”

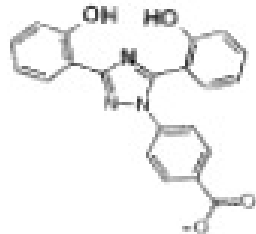
- Local complications
- Painful therapy
- Oto-neurotoxicity
- Allergy to the drug (< 0.5%)
- Regular subcutaneous infusion not effective in the rapid removal iron from the heart



Oral Chelation Therapy



Deferiprone (L1)



Deferasirox (ICL670)

Preclinical investigation:

FBS 0701 (desferrithiocin)

HBED (hexadentate phenolic aminocarboxylate)

Pyridoxal isonicotinoyl hydrazone PCIH

40SD02 (Starch deferoxamine)

Deferiprone

(Kelfer[®], Ferriprox[®], GPO-L-ONE[®])



2 USD

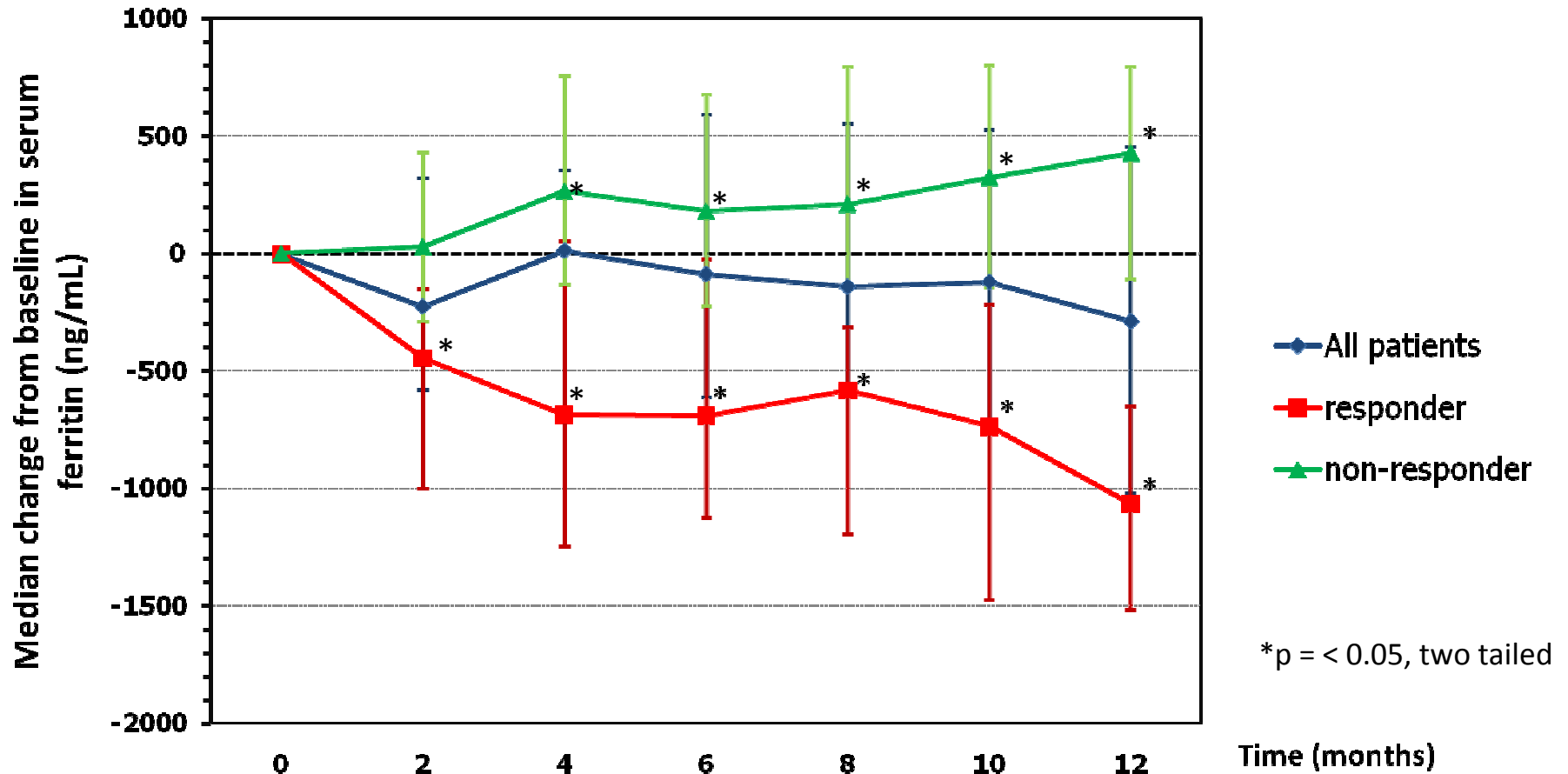


1 USD



0.2 USD

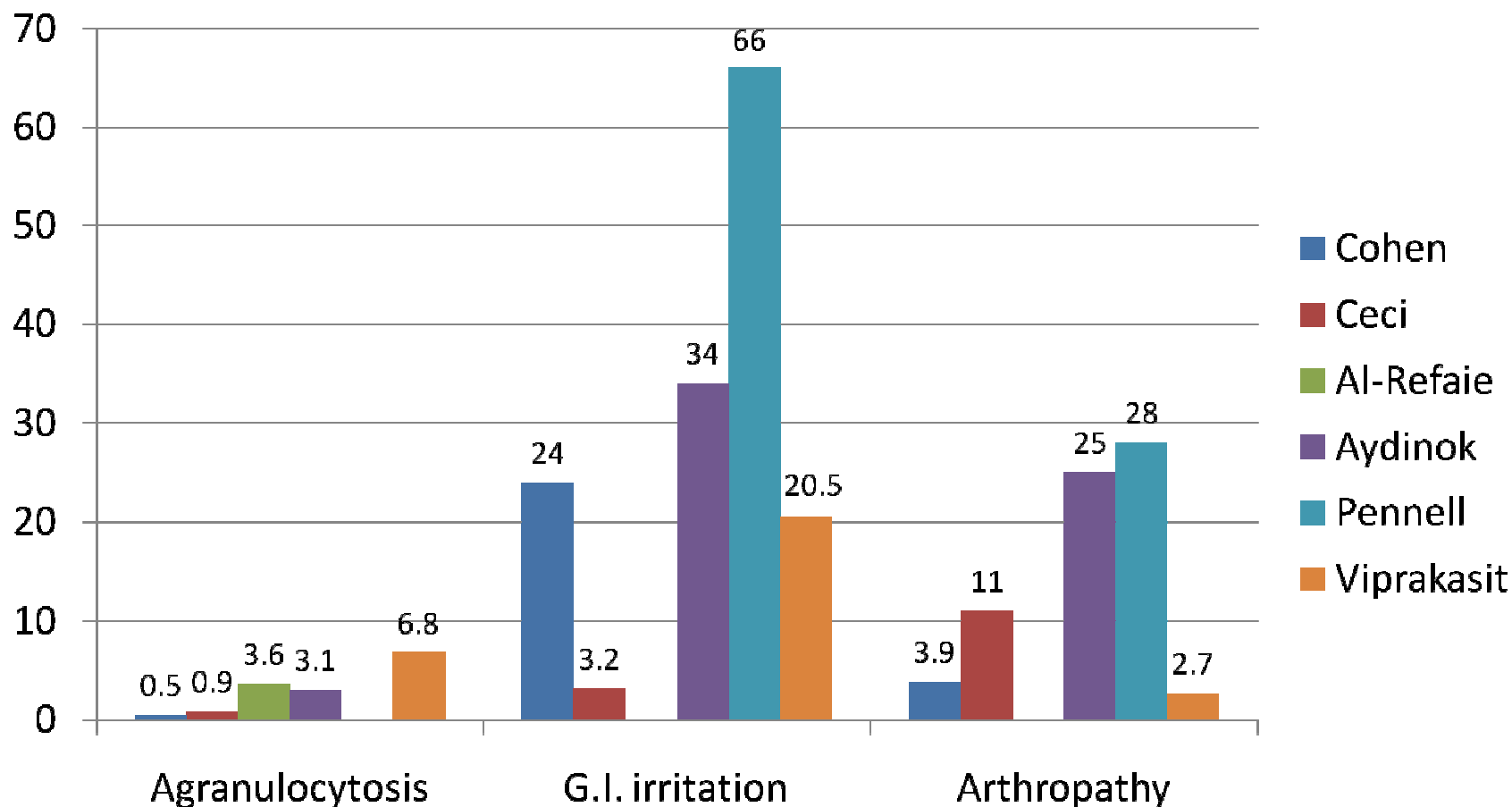
Median serum ferritin change from baseline in a sub-analysis based on clinical criteria



Responder = reduction of serum ferritin $\geq 15\%$ from baseline value at EOS (N=33, 45.2%)

Non-responder = increase or reduction of serum ferritin $< 15\%$ from baseline value at EOS (N=40, 54.8%)

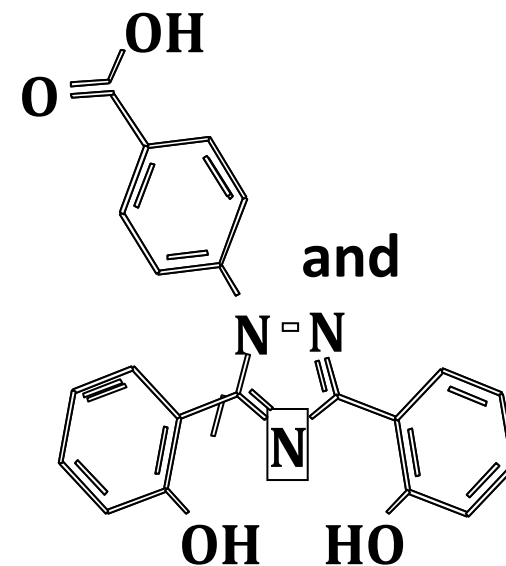
Comparison of common adverse events reported from deferiprone trials



Ceci A et al. Br J Haematol 2002;118:330–336; Cohen AR et al. Br J Haematol 2000;108:305–312; Aydinok Y et al. Blood 2006;108(11):abstract 557; Pennell DJ et al. Blood 2006;107:3738–3741

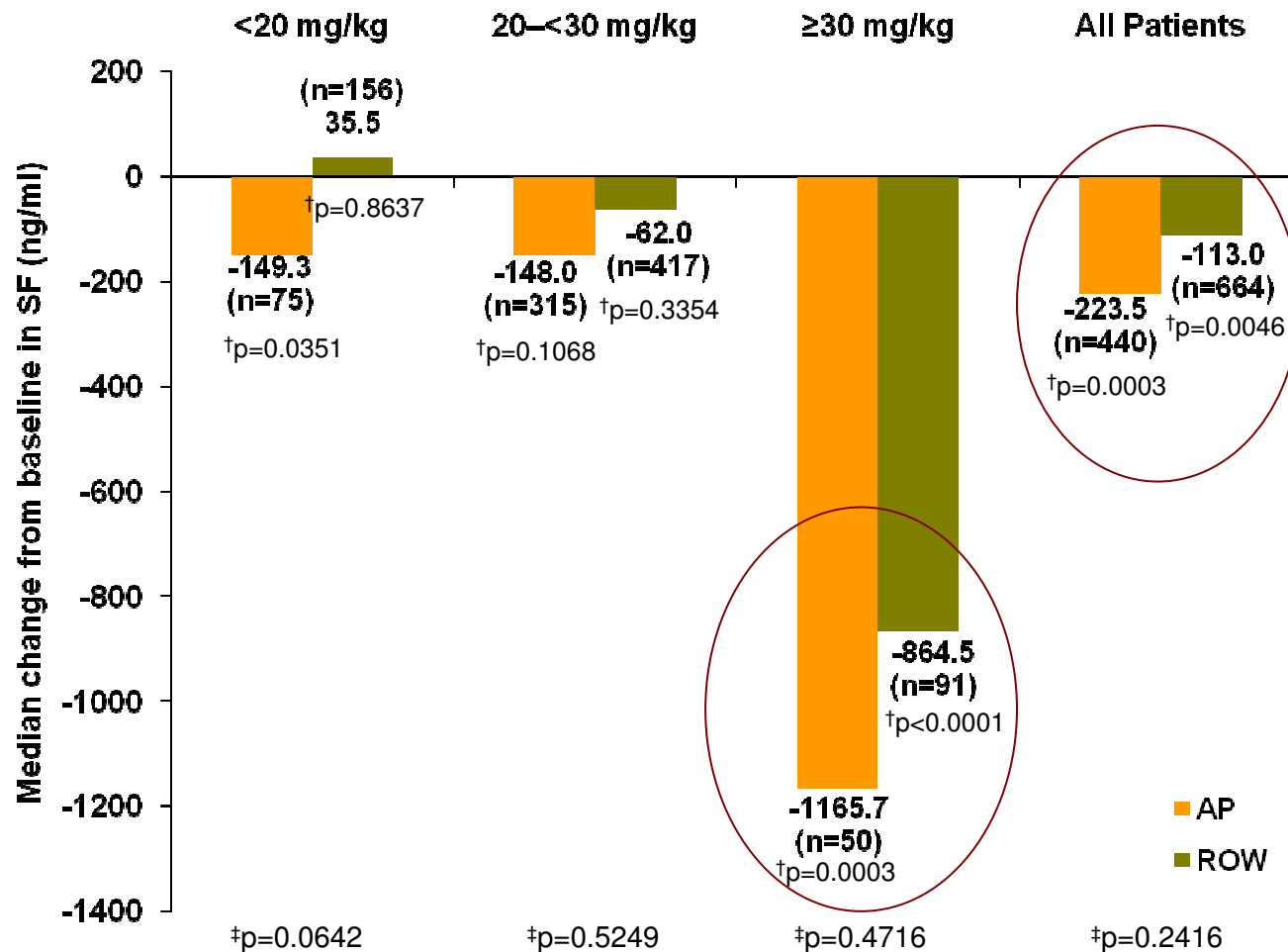
Deferasirox (ICL670)

- Tridentate iron chelator
- Available use since 2005 in adult children > 2 yo
- Long plasma half-life (8-16 hr)
- Primarily excreted in faeces
 - 27% of drug eliminated in iron-bound form
- Dose range : 20-30 mg/kg/day
- Given as once-daily drink



EXJADE [Package Insert]. East Hanover, NJ:Novartis Pharmaceuticals 2007

Median change from baseline in SF at the end of study by dose category in AP and non-AP



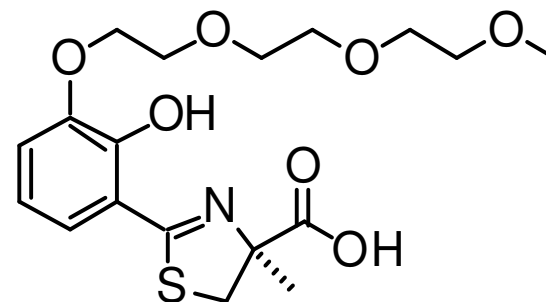
† p-value for change from baseline in SF at the EOS.

‡ p-value for change in SF at the EOS comparing AP and ROW groups.

Most common drug-related adverse events (AE) due to deferasirox

AEs	Severity, n (%)						Total		p-value
	Mild		Moderate		Severe		AP	ROW	
	AP (n=444)	ROW (n=671)	AP (n=444)	ROW (n=671)	AP (n=444)	ROW (n=671)	AP (n=444)	ROW (n=671)	
Rash	51 (11.5)	27 (4.0)	25 (5.6)	19 (2.8)	4 (0.9)	3 (0.4)	80 (18.0)	49 (7.2)	<0.0001
Diarrhoea	39 (8.8)	40 (6.0)	2 (0.5)	6 (0.9)	–	–	41 (9.3)	46 (6.9)	0.1471
Increased serum Cr	24 (5.4)	27 (4.0)	6 (1.4)	7 (1.0)	–	–	30 (6.8)	34 (5.0)	0.2351
Abdominal pain	23 (5.2)	25 (3.7)	4 (0.9)	2 (0.3)	–	–	27 (6.1)	27 (4.0)	0.1170
Nausea	18 (4.1)	15 (2.2)	5 (1.1)	3 (0.4)	–	1 (0.1)	23 (5.2)	19 (2.7)	0.0438
Increased ALT	6 (1.4)	57 (8.5)	6 (1.4)	7 (1.0)	1 (0.2)	1 (0.1)	13 (3.0)	65 (9.6)	<0.0001
Increased AST	3 (0.7)	48 (7.2)	5 (1.1)	3 (0.4)	1 (0.2)	1 (0.1)	9 (2.0)	52 (7.7)	<0.0001

Cr – creatinine; ALT - alanine aminotransferase; AST - aspartate aminotransferase



- **Tridentate chelator**
- **Binds Fe(III) with very high affinity**
- **Preclinical toxicological studies**
 - **Higher no-observable-adverse-effect level (NOAEL) compared to deferasirox**
 - **Suggesting favorable clinical safety profile**

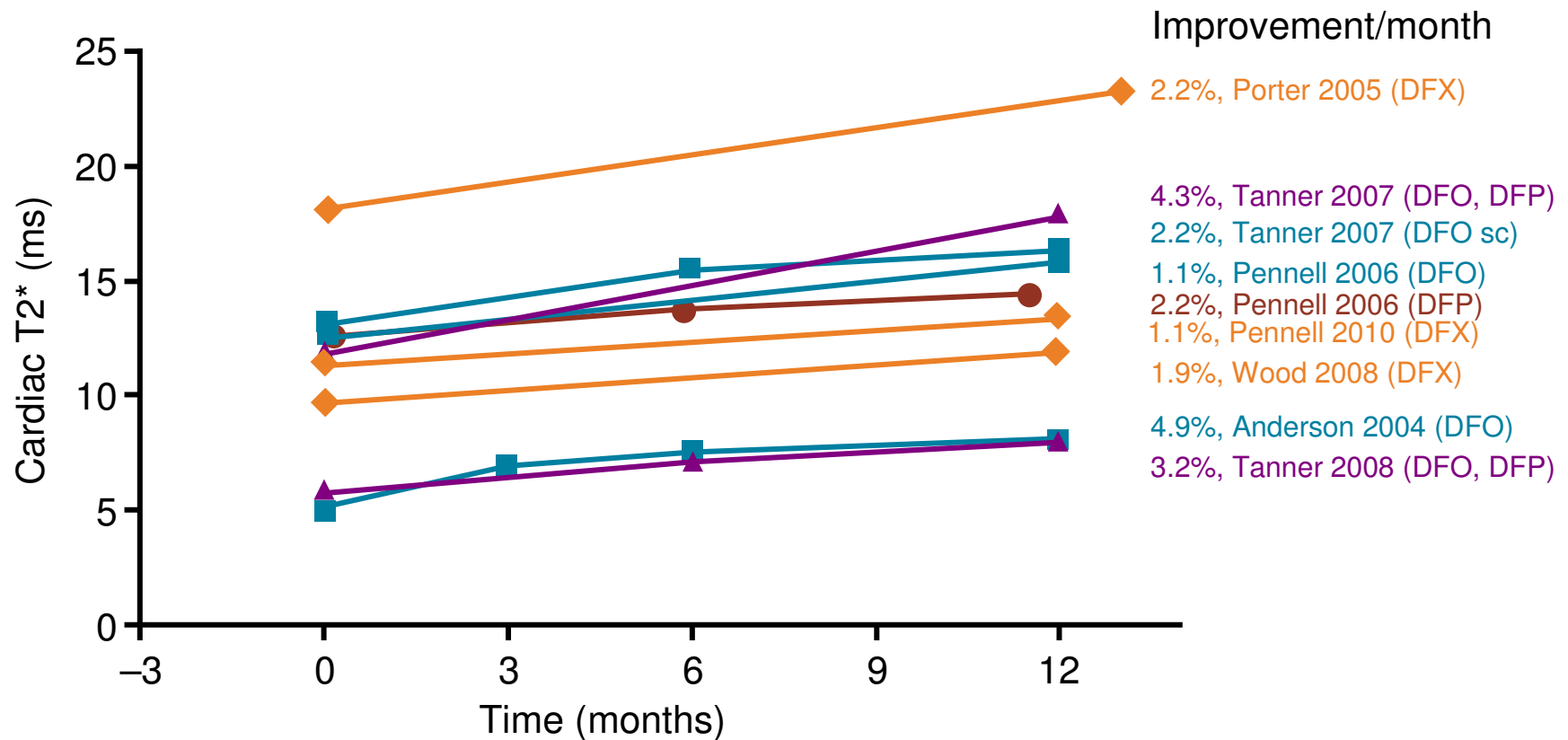


FBS0701

STUDY	SUMMARY	STATUS
FBS CTP-01	Phase 1 study to evaluate safety and pharmacokinetics of FBS0701 in healthy volunteers	Completed
FBS CTP-02	Phase 1 study to evaluate safety, pharmacokinetics and tolerability in iron overloaded patients	Completed
FBS CTP-03	Phase 1 study to evaluate safety and pharmacokinetics of FBS0701 after multiple doses in iron overloaded patients	Completed
FBS CTP-04	Phase 2 study to evaluate safety and iron-clearing activity of FBS0701 in iron overloaded patients	Ongoing

Ref : http://www.ferrokin.com/fbs0701_program.html

Overview of iron chelation therapy: effects on cardiac T2*



DFP, deferiprone; DFX, deferasirox

Anderson LJ *et al. Br J Haematol* 2004;127:348–355; Pennell DJ *et al. Blood* 2006;107:3738–3744; Pennell DJ *et al. Blood* 2010;115:2364–2371; Porter J *et al. Blood* 2005;106:abst 3600; Tanner MA *et al. Circulation* 2007;115:1876–1884; Tanner MA *et al. J Cardiovasc Magn Reson* 2008;10:12; Wood JC *et al. Blood* 2008;112(11):abst 3882

Summary: Take home message

- Iron chelation is critical for your health and its can make you live longer

- You have options for iron chelators: decision on which you should use depend on several factors

“People are different”

- If you have evidence of severe iron in the heart, combination of DFO & DFP seems to be the first option

- “A new kid on the block” is just around the corner

- The most important key of chelation success factor is;

Compliance, Compliance & Compliance