Iron management: new strategies currently under investigation

Iain Macdougall
King's College Hospital, London, UK

Disclosure of Interests

Consultancy, honoraria, research grant income:-

- Vifor Pharma
- Vifor FMC Renal Pharma
- Pharmacosmos
- Takeda
- AMAG
- FibroGen
- Astellas
- Glaxo Smith Kline
- Bayer
- Rockwell
- Keryx
- Noxxon
- Pieris
- Amgen
- Janssen Cilag
- Roche

(No employment, stock ownership, legal expert witness)

Outline of lecture

- **PIVOTAL Trial**
- **Intra-dialytic soluble ferric pyrophosphate (SFP)**
  Ray Pratt, Rockwell
- **Ferric citrate**
  Amit Sharma, Keryx
- **Hepcidin modulators**
- **HIF stabilisers (PHI's)**
  Peony Yu, Lynda Szczech, Anatole Besarab (FibroGen)

PIVOTAL

Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

- **UK multicentre prospective open-label 2-arm RCT of IV iron therapy in incident HD patients**
  - Lead investigator: Iain Macdougall
  - Clinical Trial Manager: Claire White
  - No of sites: >40
  - No. of patients: 2080
  - Trial oversight: Glasgow Clinical Trials Unit
  - Funder : Kidney Research UK

This investigator-led clinical trial is supported through an unrestricted grant from
Vifor Fresenius Medical Care Renal Pharma
www.kidneyresearchuk.org
University of Glasgow
NHS Greater Glasgow and Clyde
THE RENAL ASSOCIATION founded 1950
UK Kidney Research Consortium : Renal Anaemia CSG
Registered Charity No: 252892 Registered Scottish Charity No. SC039245
Kidney Research UK
Funding research to save lives

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
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Incident new HD patients (0-12 mths)

R

On ESA

KDIGO

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NHS Foundation Trust

Inclusion Criteria

- Age ≥18 years
- Patients established on a chronic haemodialysis programme for end-stage renal failure
- Clinically stable (principal investigator's judgement)
- 0–12 months since commencing haemodialysis
- Ferritin < 400 µg/L
- TSAT < 30%
- On ESA therapy
- Written informed consent

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Proactive IV irOn Therapy in haemodiALysis patients

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NHS Foundation Trust

Exclusion Criteria

- **Life expectancy < 12 months (principal investigator's judgement)**
- **Living-donor transplant scheduled within the next 12 months**
- **CRP > 50 mg/L**
- **Active infection**
- **Current active malignancy (with exception of basal cell or squamous cell carcinoma of the skin, and cervical intraepithelial neoplasia)**
- **Known HIV or active hepatitis B or C**
- **Chronic liver disease and/or screening ALT or AST above 3 times the upper limit of the normal range**

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Exclusion Criteria *(cont'd)*

- Advanced heart failure (NYHA IV)
- Pregnancy or breast feeding
- History of acquired iron overload
- Previous severe hypersensitivity reactions to IV iron sucrose (Venofer®)
- Subject has any disorder that compromises their ability to give written informed consent and/or to comply with study procedures

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Primary endpoint

- Time to all-cause death or a composite of non-fatal cardiovascular events (myocardial infarction, stroke, and hospitalisation for heart failure) adjudicated by a blinded Endpoint Adjudication Committee.

Secondary endpoints

- Incidence of all-cause death and a composite of myocardial infarction, stroke, and hospitalisation for heart failure as recurrent events.
- Time to (and incidence of) all-cause death
- Time to (and incidence of) composite cardiovascular event
- Time to (and incidence of) myocardial infarction
- Time to (and incidence of) stroke
- Time to (and incidence of) hospitalisation for heart failure
- ESA dose requirements
- Transfusion requirements
- EQ-5D QOL and KDQOL
- Vascular access thrombosis
- All-cause hospitalisation
- Hospitalisation for infection

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Proactive IV irOn Therapy in haemodiALysis patients

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PIVOTAL *Trial*

Steering Committee

- Iain Macdougall, London
- Phil Kalra, Manchester
- Chris Winearls, Oxford
- Ken Farrington, Stevenage
- Sunil Bhandari, Hull
- David Wheeler, London
- Charlie Tomson, Bristol
- John McMurray, Glasgow
- Stefan Anker, Norwich
- Ian Ford *(Statistician)*

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Proactive IV irOn Therapy in haemodiALysis patients

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- **Endpoint Adjudication Committee**
  – chair, Prof John McMurray *(Glasgow)*
- **Data Safety Monitoring Board**
  – chair, Prof Alan Jardine *(Glasgow)*

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PIVOTAL

Proactive IV irOn Therapy in haemodiAlysis patients

Network of Sites

King's College Hospital NHS
NHS Foundation Trust

England

Queen Elizabeth Hospital, Birmingham; Heartlands Hospital, Birmingham; Royal Free, London, King's College Hospital, London; Guy's & St Thomas', London; St Helier, Surrey; St George's, London; Royal Liverpool Hospital, University Hospital Aintree; Sheffield Teaching Hospital; Lister Hospital, Stevenage; Salford Royal Hospital, Manchester; Manchester Royal Hospital; Queen Alexandra Hospital, Portsmouth; Kent & Canterbury Hospital, Leicester General Hospital, Hull Royal Infirmary; Freeman Hospital, Newcastle; Churchill Hospital, Oxford; University Hospital of North Staffordshire, Stoke-on-Trent; Southmead Hospital, Bristol; Royal Cornwall Hospital; Nottingham City Hospital; Norfolk & Norwich Hospital; New Cross Hospital, Wolverhampton; Royal London Hospital; Wirral University Teaching Hospital; Royal Shrewsbury Hospital, Royal Devon & Exeter Hospital, Royal Preston Hospital, St James' Hospital, Leeds; Hammersmith Hospital, London

Wales

Morriston Hospital, Swansea; University Hospital, Cardiff

Scotland

Western Infirmary, Glasgow; Victoria Hospital, Kirkcaldy; Ninewells Hospital, Dundee; Dumfries (PI tbc), Edinburgh (PI tbc)

N. Ireland

Belfast City Hospital

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PIVOTAL

Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS

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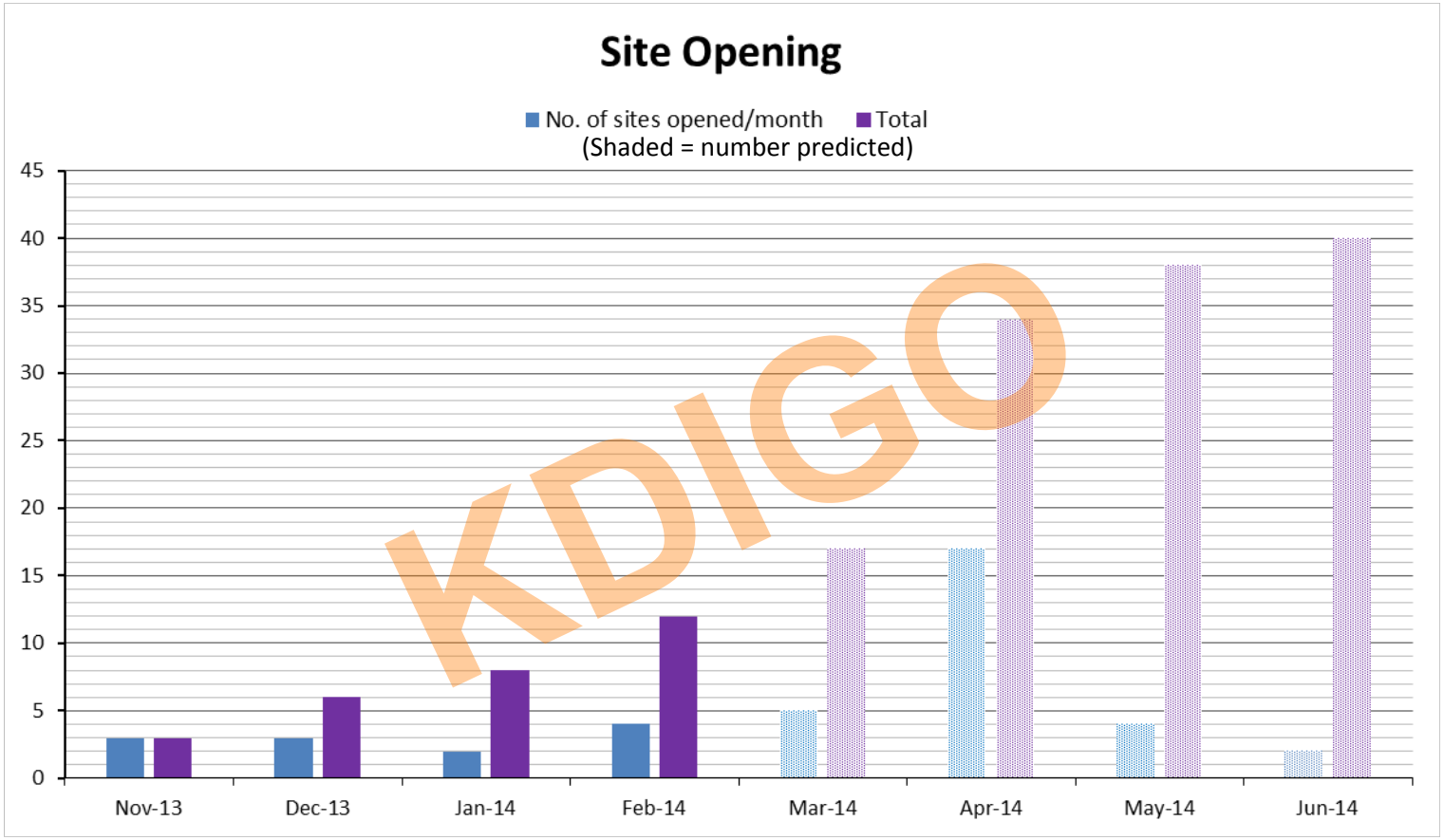

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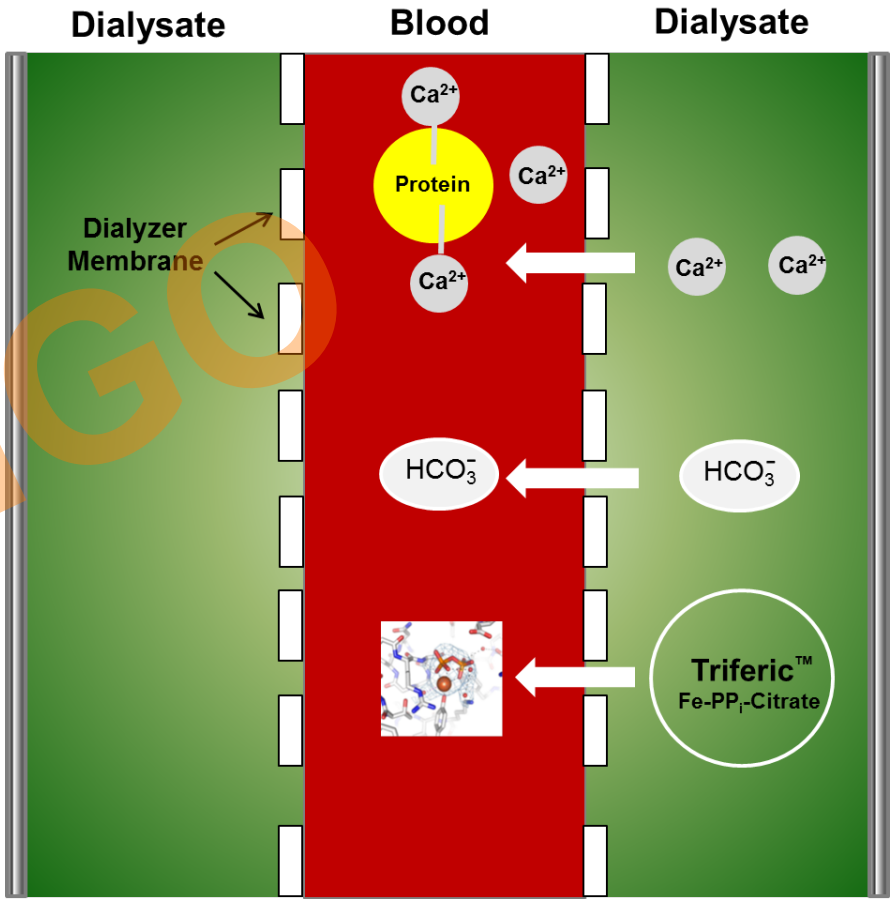
Iron management: new strategies currently under investigation

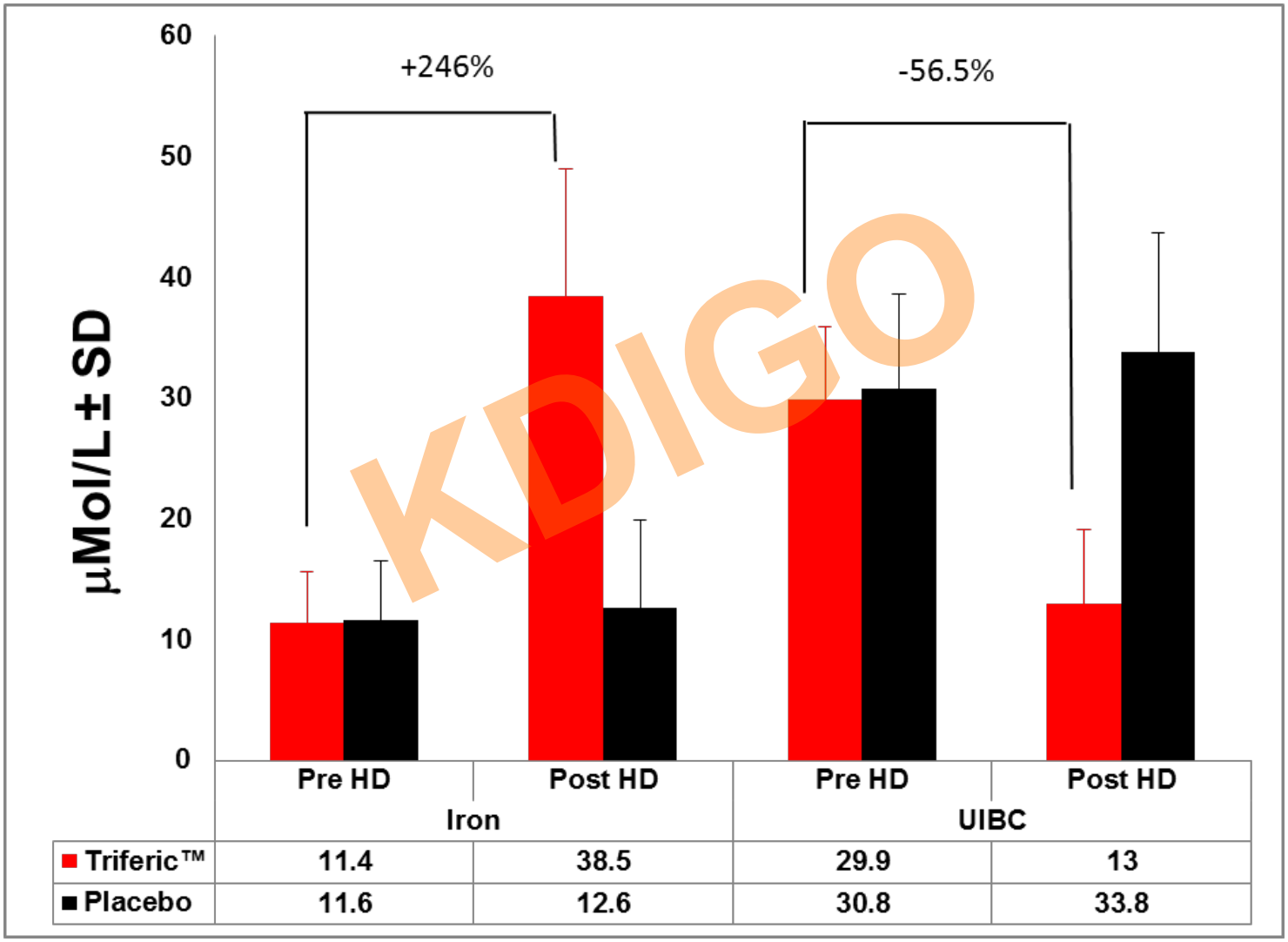
- PIVOTAL Trial
- Intra-dialytic soluble ferric pyrophosphate (SFP)
- Ferric citrate
- Hepcidin modulators
- HIF stabilisers (PHI‘s)

Iron delivered via dialysate

- Soluble and non-colloidal iron salt, not conjugated with a sugar moiety
- Iron- citrate- pyrophosphate
- MW ~1000 Da, similar to vitamin B_{12}
- Added to bicarbonate concentrate
- Crosses the dialyzer during the hemodialysis treatment and binds immediately to apotransferrin, largely bypassing the RE system
- Replaces the 5-7 mg iron/treatment lost by trapping of blood in dialysis circuit, bleeding and blood draws
- Dialysate iron concentration of 2 µMol (110 µg/L) maintains iron balance without overloading iron stores



Iron parameters during a single HD



	Iron		UIBC	
	Pre HD	Post HD	Pre HD	Post HD
■ Triferic™	11.4	38.5	29.9	13
■ Placebo	11.6	12.6	30.8	33.8

A new way of administering iron to HD patients?

Kidney International, Vol. 55 (1999), pp. 1891–1898

Dialysate iron therapy: Infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis

AJAY GUPTA, NEETA B. AMIN, ANATOLE BESARAB, SUSAN E. VOGEL, GEORGE W. DIVINE, JERRY YEE, and J. V. ANANDAN

Division of Nephrology, Department of Pharmacy Services, and Department of Biostatistics, Henry Ford Hospital, Detroit, Michigan, USA

Dialysate iron therapy: Infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis.

Background. Soluble iron salts are toxic for parenteral administration because free iron catalyzes free radical generation. Pyrophosphate strongly complexes iron and enhances iron transport between transferrin, ferritin, and tissues. Hemodialysis patients need iron to replenish ongoing losses. We evaluated the short-term safety and efficacy of infusing soluble ferric pyrophosphate by dialysate.

Methods. Maintenance hemodialysis patients receiving erythropoietin were stabilized on regular doses of intravenous

with prematurity and low birth weight during pregnancy, defects in cognitive and psychomotor development during childhood, and impaired work capacity in adulthood [3–8]. Oral iron supplementation programs have failed primarily because of noncompliance in addition to gastrointestinal adverse effects [9]. As an adjunct or alternative to the oral route, iron has been administered parenterally for more than 100 years [10]. Soluble iron compounds are considered too toxic for parenteral ad-

12 years later!!.....

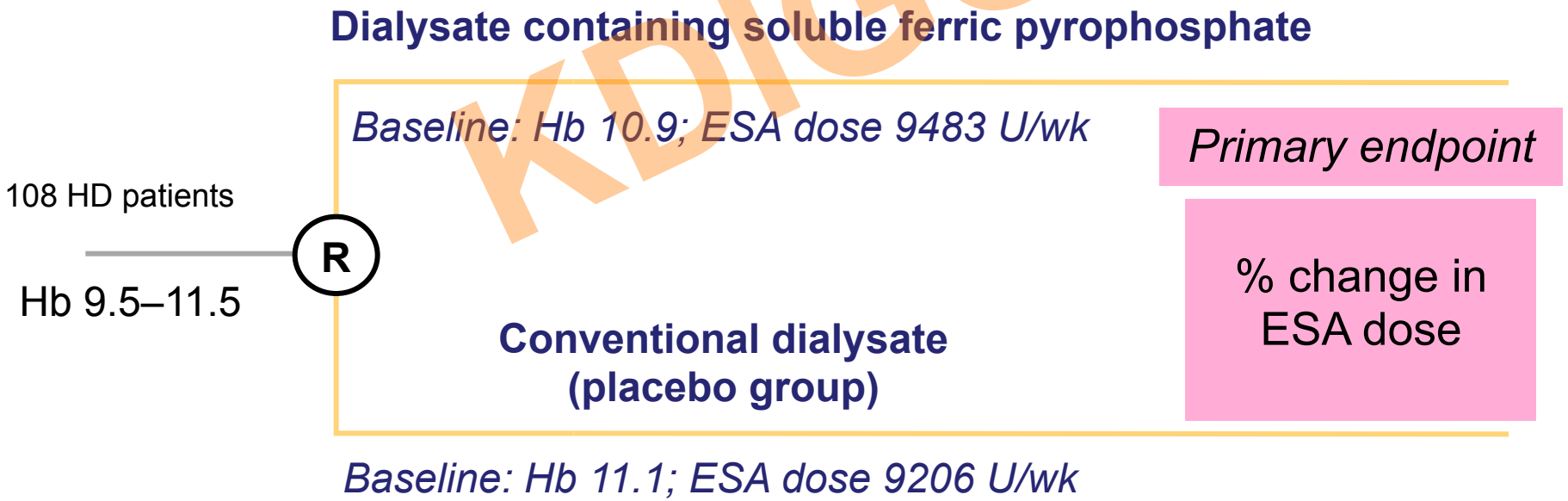
CONTINUOUS DELIVERY OF SOLUBLE FERRIC PYROPHOSPHATE (SFP) VIA THE DIALYSATE MAINTAINS IRON BALANCE IN CHRONIC HEMODIALYSIS PATIENTS: A PHASE II CLINICAL TRIAL

ROCKWELL

Ajay Gupta[1], Richard Yocum[2], Carrie Cuss[1], Steven Fishbane[3], and Anatole Besarab[4]
[1]Rockwell Medical, Wixom, MI, USA; [2]Hillsthrop-University Hospital, Long Island, NY, USA; [3]Henry Ford Hospital, Detroit, MI, USA

PRIME study

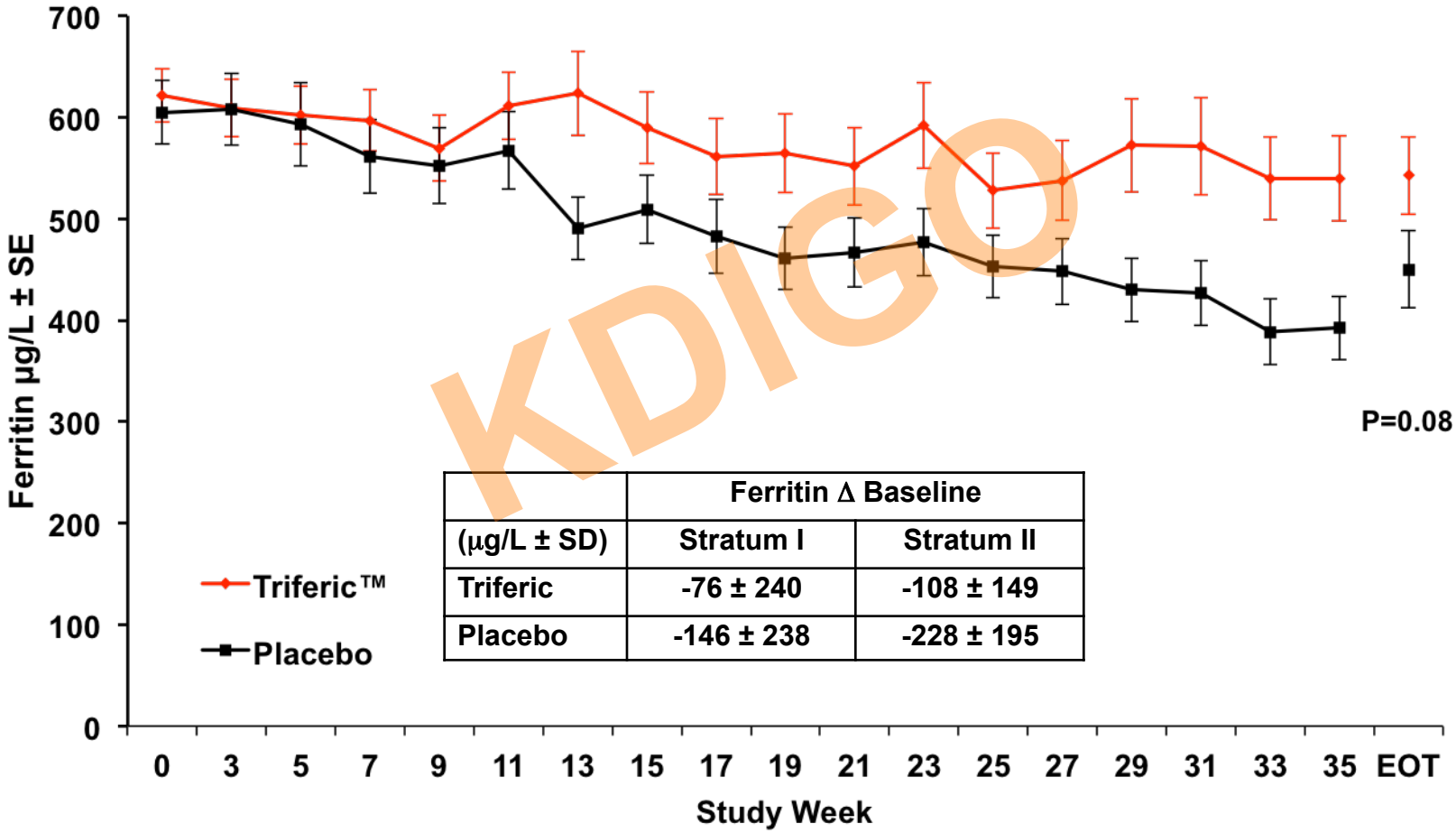
- Prospective, randomised, placebo-controlled, double-blind trial
- Study duration = 9 months



35% ESA dose reduction vs. placebo

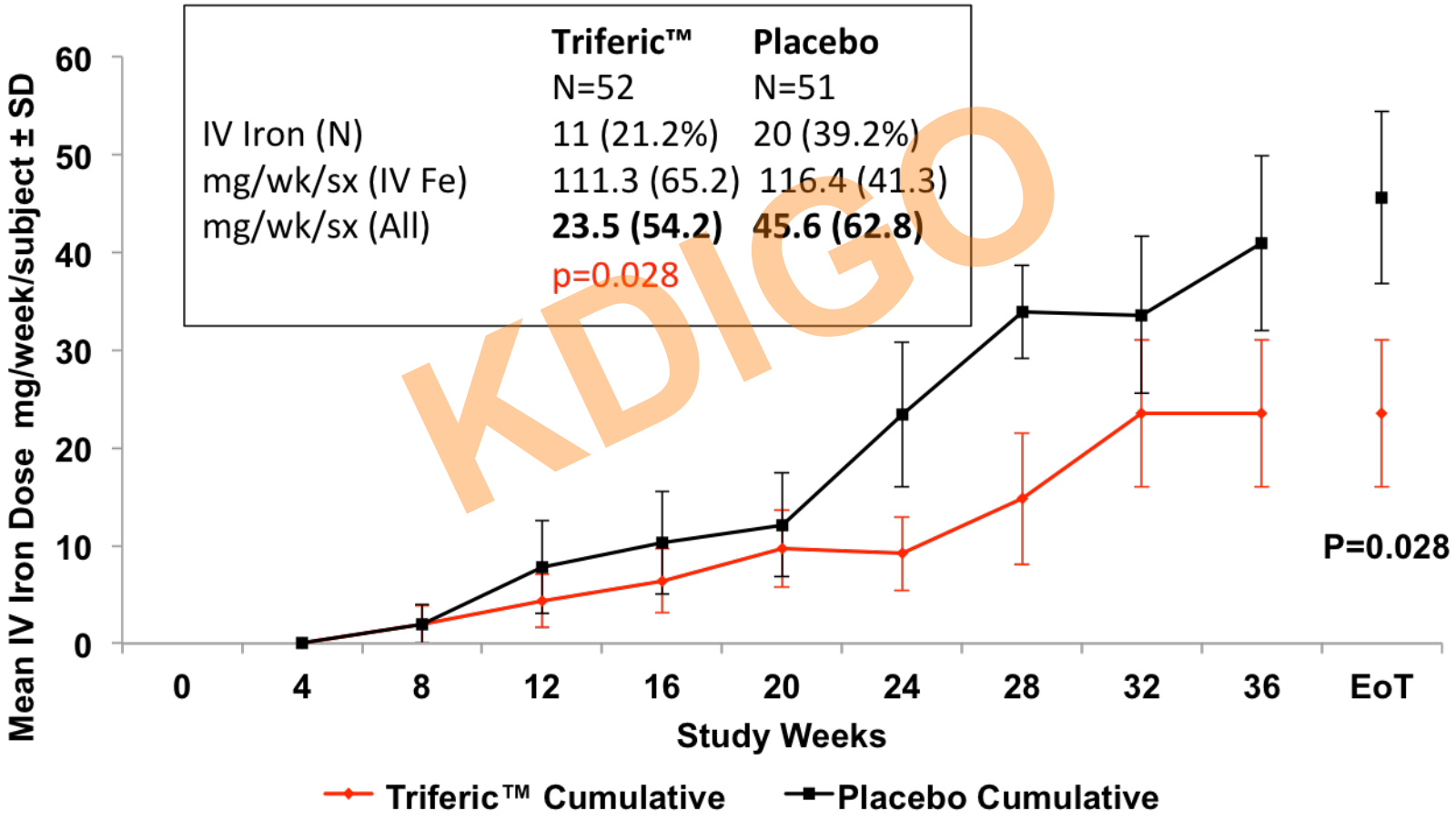
	Triferic N=52		Placebo N=51	
	U/wk (SD)	**% Change from Baseline**	**U/wk (SD)**	**% Change from Baseline**
Hgb g/dL Baseline	11.0		11.1	
Hgb g/dL EoT	10.4	-5.1	10.5	-5.8
Prescribed ESA Dose U/wk (SD) Baseline	9483 (5414)		9206 (5500)	
Prescribed ESA Dose U/wk (SD) EoT	9871 (7523)	7.3 (67.66)	12,628 (13,967)	37.3 (106.9)
LS mean (SE) % Change from Baseline	4.9 (12.1)		39.8 (12.2)	
95% CI LS mean	-19.1, 28.8		15.7, 64.0	
LS mean difference from Placebo	**-35.0 (17.20)**			
95% CI LS mean difference	**-69.1, -0.8**			
P-value	**0.045**			

Triferic Does Not Increase Iron Stores



	Ferritin Δ Baseline	
(µg/L ± SD)	Stratum I	Stratum II
Triferic	-76 ± 240	-108 ± 149
Placebo	-146 ± 238	-228 ± 195

Triferic reduces IV iron requirement by 48%



Iron management: new strategies currently under investigation

- PIVOTAL Trial
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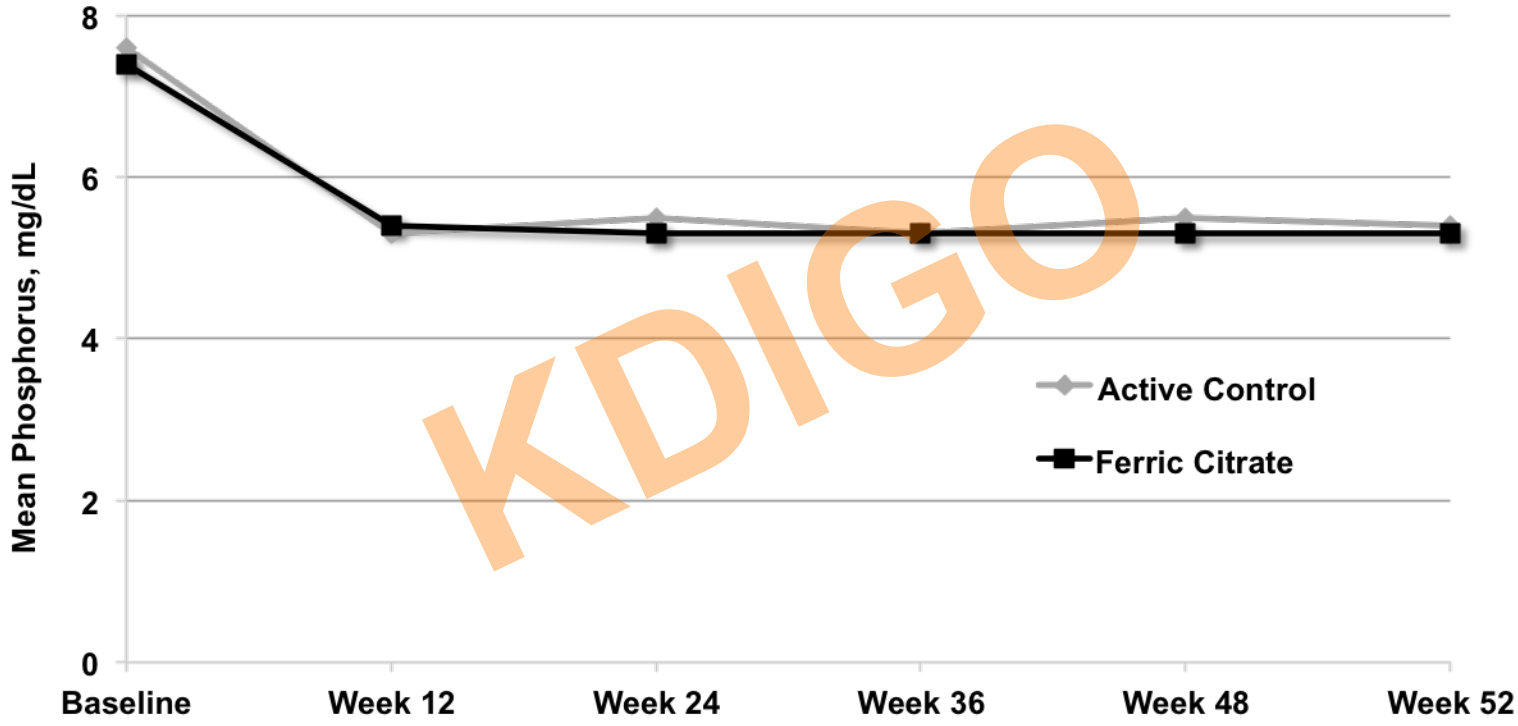
- Ferric citrate
- Hepcidin modulators
- HIF stabilisers (PHI‘s)

Serum phosphorus control over 52 weeks



Treatment Difference at Week 52 ANCOVA, *p*=0.8

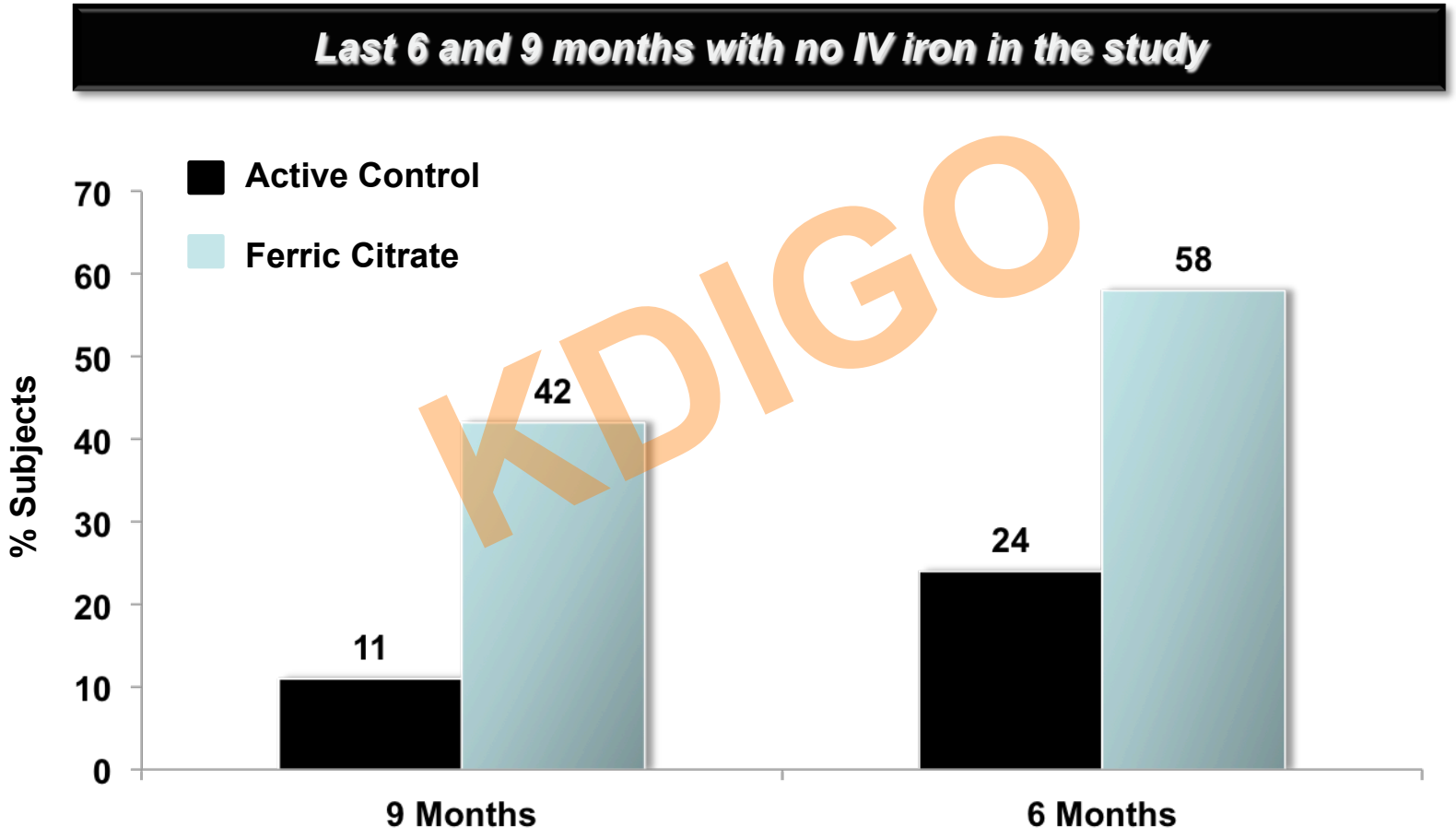
Effect of phosphate-binders on ferritin

Mean Ferritin (ng/mL)	Active Control (n=135)	Ferric Citrate (n=252)
Baseline (Day 0)	609	593
Week 12	649	751
Week 24	652	846
Week 36	631	862
Week 48	619	881
Week 52	624	898
Change from Baseline at Week 52 *% Change from Baseline*	15 *2.5%*	305 *51.4%*
Least Squares Mean Difference at Week 52 P-value		285 <0.0001

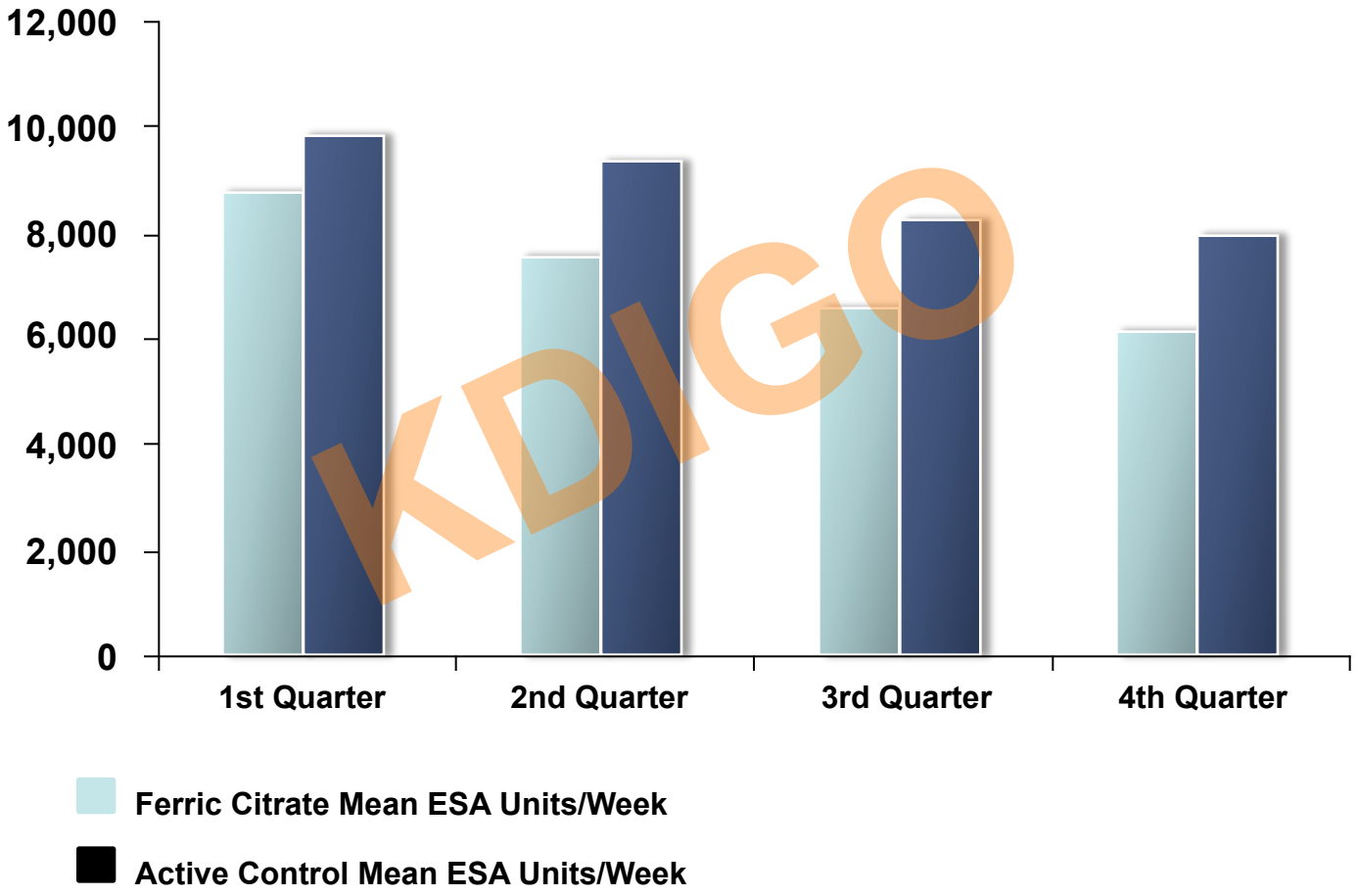
Effect of phosphate-binders on TSAT

Mean TSAT (%)	Active Control (n=135)	Ferric Citrate (n=252)
Baseline (Day 0)	31	31
Week 12	31	40
Week 24	31	40
Week 36	31	40
Week 48	29	41
Week 52	30	39
Change from Baseline at Week 52 *% Change from Baseline*	-1 *-3.2%*	8 *25.8%*
Least Squares Mean Difference at Week 52 P-value		9 <0.0001

Effect of phosphate-binders on IV iron use



Effect of phosphate-binders on ESA dose



Iron management: new strategies currently under investigation

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- Ferric citrate
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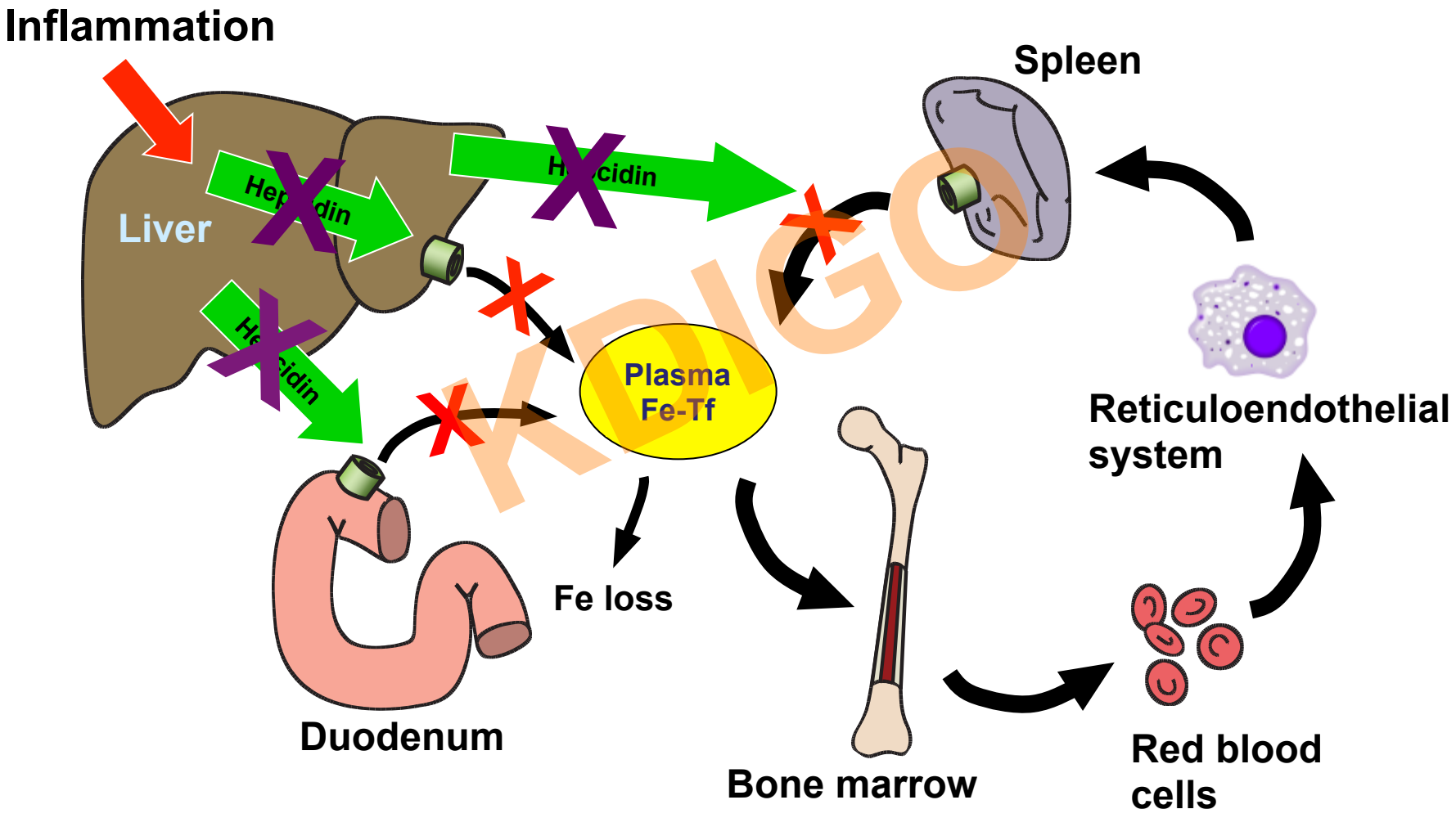
- HIF stabilisers (PHI‘s)

Regulation of iron availability in CKD



Hepcidin – a potential target for future anaemia therapies ?

RED CELLS, IRON, AND ERYTHROPOIESIS

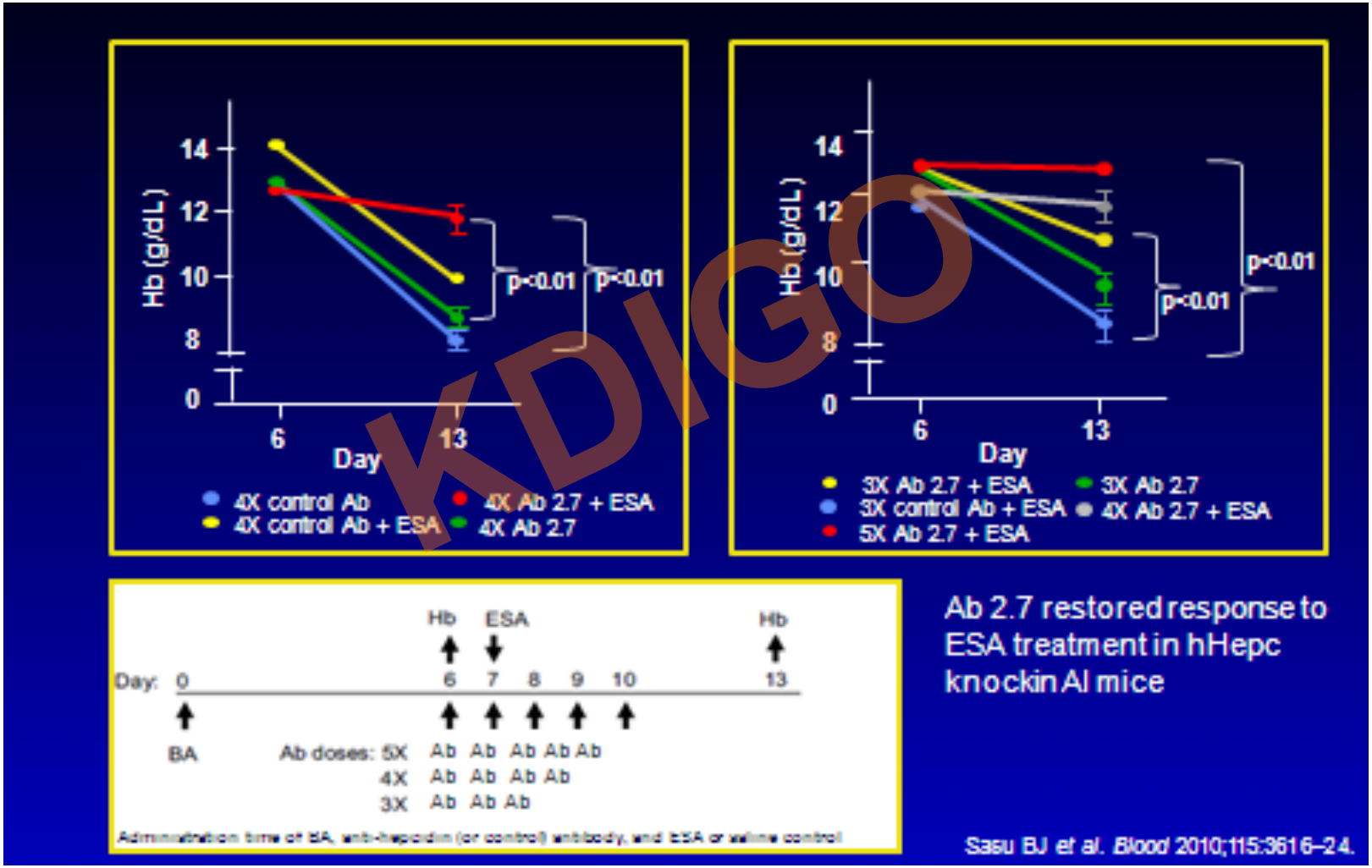
Antihepcidin antibody treatment modulates iron metabolism and is effective in a mouse model of inflammation-induced anemia

Barbra J. Sasu,[1] Keegan S. Cooke,[1] Tara L. Arvedson,[1] Cherylene Plewa,[2] Aaron R. Ellison,[2] Jackie Sheng,[2] Aaron Winters,[2] Todd Juan,[2] Hongyan Li,[3] C. Glenn Begley,[1] and Graham Molineux[1]

Departments of [1]Hematology/Oncology, [2]Protein Sciences, and [3]Pharmacokinetics and Drug Metabolism, Amgen Inc, Thousand Oaks, CA

Iron maldistribution has been implicated in multiple diseases, including the anemia of inflammation (AI), atherosclerosis, diabetes, and neurodegenerative disorders. Iron metabolism is controlled by hepcidin, a 25-amino acid peptide. Hepcidin is induced by inflammation, causes iron to be sequestered, and thus, potentially contributes to AI. Human hepcidin (hHepc) overexpression in mice caused an iron-deficient phenotype, including stunted growth, hair loss, and iron-deficient erythropoiesis. It also caused resistance to supraphysiologic levels of erythropoiesis-stimulating agent, supporting the hypothesis that hepcidin may influence response to treatment in AI. To explore the role of hepcidin in inflammatory anemia, a mouse AI model was developed with heat-killed *Brucella abortus* treatment. Suppression of hepcidin mRNA was a successful anemia treatment in this model. High-affinity antibodies specific for hHepc were generated, and hHepc knock-in mice were produced to enable antibody testing. Antibody treatment neutralized hHepc in vitro and in vivo and facilitated anemia treatment in hHepc knock-in mice with AI. These data indicate that antihepcidin antibodies may be an effective treatment for patients with inflammatory anemia. The ability to manipulate iron metabolism in vivo may also allow investigation of the role of iron in a number of other pathologic conditions. (*Blood*. 2010;115(17):3616-3624)

MAb against hepcidin effective in mouse-model of inflammation-induced anaemia



Targeting the hepcidin–ferroportin axis to develop new treatment strategies for anemia of chronic disease and anemia of inflammation

Chia Chi Sun,[1] Valentina Vaja,[1,2] Jodie L. Babitt,[1] and Herbert Y. Lin[1]*

Anemia of chronic disease (ACD) or anemia of inflammation is prevalent in patients with chronic infection, autoimmune disease, cancer, and chronic kidney disease. ACD is associated with poor prognosis and lower quality of life. Management of ACD using intravenous iron and erythropoiesis stimulating agents are ineffective for some patients and are not without adverse effects, driving the need for new alternative therapies. Recent advances in our understanding of the molecular mechanisms of iron regulation reveal that increased hepcidin, the iron regulatory hormone, is a key factor in the development of ACD. In this review, we will summarize the role of hepcidin in iron homeostasis, its contribution to the pathophysiology of ACD, and novel strategies that modulate hepcidin and its target ferroportin for the treatment of ACD. Am. J. Hematol. 00:000–000, 2012.

Introduction

Anemia of chronic disease (ACD), also known as anemia of inflammation, is the most prevalent anemia in hospitalized patients worldwide. It occurs in patients with acute or chronic inflammatory conditions including infections, cancer, rheumatoid arthritis, and chronic kidney disease [1]. ACD is a heterogenous disorder that is typically characterized by a normocytic anemia, changes in erythropoietic responses, low serum iron, and low transferrin saturation, but unlike in true dietary iron deficiency, iron is retained in the macrophages and there may be an increase in total body iron [2,3]. Until recently, the molecular mechanisms and pathogenesis of the iron distribution abnormalities in ACD were unknown. It is now clear that inflammatory cytokines

the body's iron stores. Intracellular iron can be exported from the hepatocytes when needed [15].

Hepcidin—The Central Regulator of Iron Homeostasis

Hepcidin is the key regulatory protein that controls intestinal iron absorption and distribution of iron from body stores including reticuloendothelial macrophages [14]. Hepcidin is a 25 amino acid secreted peptide hormone that is produced in the liver in response to a number of signals including iron levels. Hepcidin functions by binding to and initiating the degradation of ferroportin, the only known iron exporter. Ferroportin is present on the cell surface of duodenal enterocytes, macrophages, and hepatocytes. Thus, downregulating ferroportin will inhibit the transfer of cellular iron into the plasma from these cell types [9,15,16].

Strategies for modulating hepcidin

- Anti-hepcidin antibodies
- Short interference RNA and anti-sense oligonucleotides
- Hepcidin-binding proteins
- Hepcidin-binding spiegelmeyers
- Hepcidin production inhibitors
- BMP6-HJV-SMAD pathway inhibitors
- IL-6 inhibitors
- Vitamin D
- Ferroportin agonists / stabilisers

NOXXON
PHARMA AG

You are here: home ▸ pipeline ▸ NOX-H94

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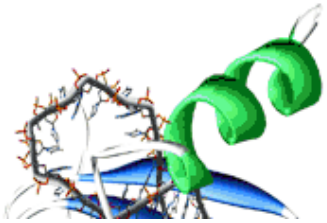


NOX-H94

Target	**Hepcidin**
Compound	44-nucleotide L-RNA oligonucleotide linked to 40 KDa PEG
Stage of Development	Pre-clinical
Administration	i.v. and s.c.
Pharmacokinetics	Similar to other Spiegelmers in development
Pharmacodynamics	Inhibition of IL-6 induced anemia in monkeys
Target Indications	Anemia of inflammation
Licensing Status	Un-partnered

About the target

Hepcidin is the master regulator of iron homeostasis via its effect on ferroportin, the only known iron export protein. Cytokine-induced synthesis of hepcidin plays a crucial role in macrophage iron retention, which underlies the anemia of inflammation by limiting the availability of iron for erythroid progenitor cells. Patients with anemia of inflammation display an impaired response to erythropoietin (EPO).

RED CELLS, IRON, AND ERYTHROPOIESIS

The effects of the anti-hepcidin Spiegelmer NOX-H94 on inflammation-induced anemia in cynomolgus monkeys

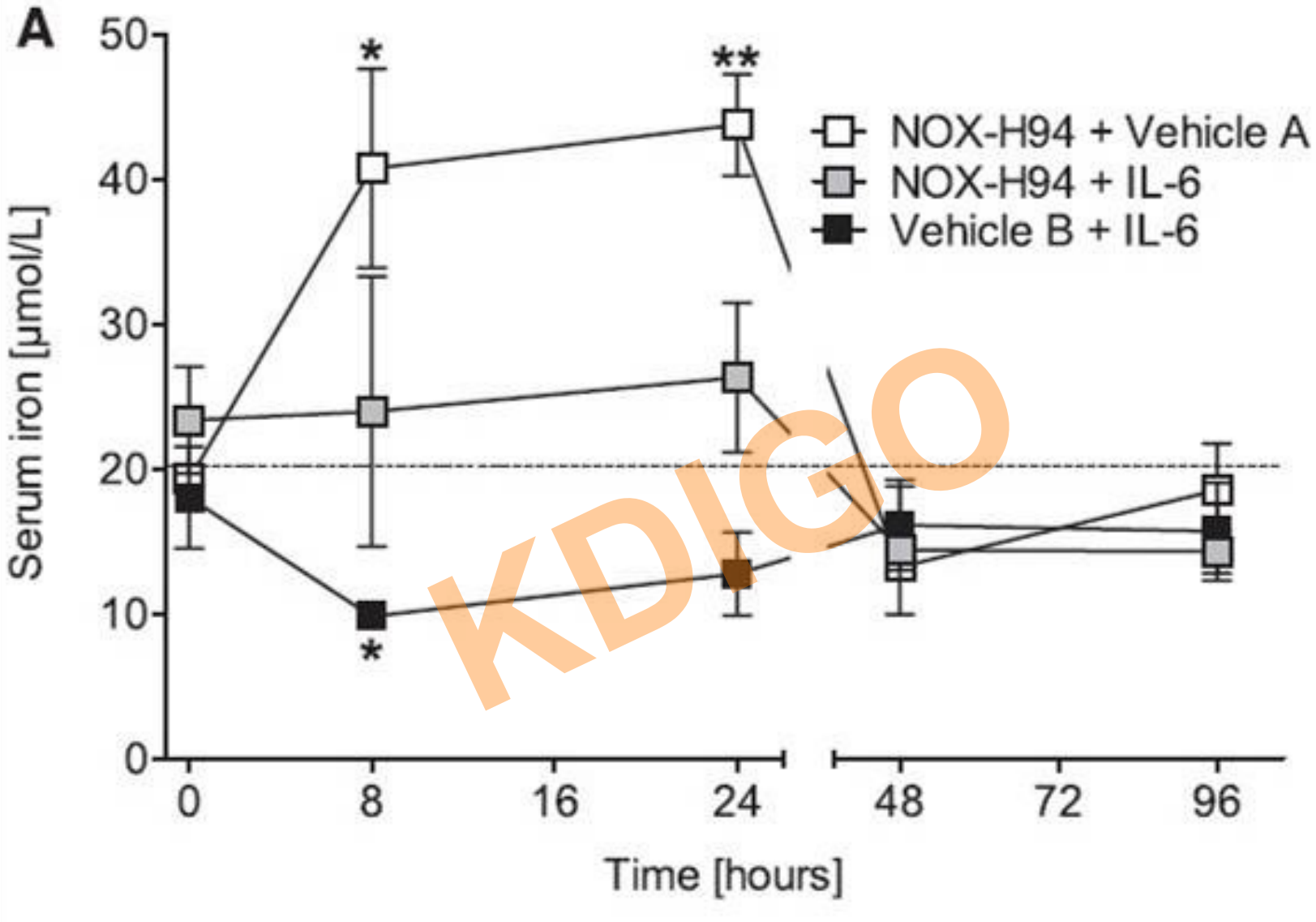
Frank Schwoebel,[1] Lucas T. van Eijk,[2] Dirk Zboralski,[1] Simone Sell,[1] Klaus Buchner,[1] Christian Maasch,[1] Werner G. Purschke,[1] Martin Humphrey,[3] Stefan Zöllner,[1] Dirk Eulberg,[1] Frank Morich,[4] Peter Pickkers,[2] and Sven Klussmann[1]

[1]NOXXON Pharma AG, Berlin, Germany; [2]Department of Intensive Care Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [3]Drug Development Consultancy & Services, Rheinfelden, Germany; and [4]Takeda Pharmaceutical Company Limited, Tokyo, Japan

Key Points

- The hepcidin inhibitor NOX-H94, a structured mirror-image RNA oligonucleotide, and its in vitro and in vivo characterization are described.
- First published hepcidin inhibitor that entered clinical trials for the treatment of

Anemia of chronic inflammation is the most prevalent form of anemia in hospitalized patients. A hallmark of this disease is the intracellular sequestration of iron. This is a consequence of hepcidin-induced internalization and subsequent degradation of ferroportin, the hepcidin receptor and only known iron-export protein. This study describes the characterization of novel anti-hepcidin compound NOX-H94, a structured L-oligoribonucleotide that binds human hepcidin with high affinity (K_d = 0.65 ± 0.06 nmol/L). In J774A.1 macrophages, NOX-H94 blocked hepcidin-induced ferroportin degradation and ferritin expression (half maximal inhibitory concentration = 19.8 ± 4.6 nmol/L). In an acute cynomolgus monkey model of interleukin 6 (IL-6)–induced hypoferremia, NOX-H94 inhibited serum iron reduction completely. In a subchronic model of IL-6–induced anemia, NOX-H94 inhibited the decrease in hemoglobin



Schwoebel et al, Blood, March 2013.

Single and Repeated Dose First-in-Human Study with the Anti-Hepcidin Spiegelmer® NOX-H94

ASH 2012, Atlanta
Session 504, Abstract #2342

K Riecke[1], S Zöllner[1], M Boyce[2], S Vauléon[1], DW Swinkels[3], T Dümmler[1], L Summo[1], CM Laarakkers[3], F Schwoebel[1], F Fliegert[1]

1: NOXXON Pharma AG, Berlin, Germany; 2: Hammersmith Medicines Research, London, United Kingdom; 3: Laboratory Medicine and Hepcidinanalysis.com (830), Radboud Univ. Medical Centre, Nijmegen, the Netherlands

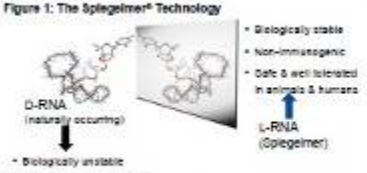
Background

NOX-H94, the first-in-class hepcidin inhibitor in development for treatment of anemia of chronic disease (ACD), is a PEGylated anti-hepcidin L-RNA oligonucleotide (Figure 1).

ACD is caused by iron sequestration in the reticulo-endothelial macrophages with subsequent iron restricted erythropoiesis due to high hepcidin production and subsequent ferroportin degradation.

The treatment of ACD is challenging: a significant number of ACD patients do not respond to erythropoiesis stimulating agents (ESAs), while repeated intravenous iron administrations bear a risk of iron overload. Targeting hepcidin may provide more efficacious and well tolerated treatment alternatives.

Figure 1: The Spiegelmer® Technology



Methods

This First-in-Human study investigated the safety and tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of escalating single and repeated doses of intravenous (i.v.) NOX-H94 in healthy men and women.

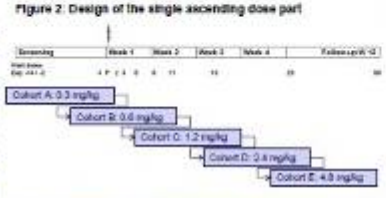
The study protocol (ClinicalTrials.gov NCT01372137) was approved by an independent ethics committee and conducted in accordance with the Declaration of Helsinki.

Five successive cohorts of 8 healthy subjects with a balanced gender distribution were randomly assigned to i.v. doses of 0.3, 0.6, 1.2, 2.4, and 4.8 mg/kg of NOX-H94 (n=6) or placebo (n=2; Figure 2).

Similarly, 2 cohorts of 8 male subjects randomly received 5 doses of either 0.6 or 1.2 mg/kg NOX-H94 or placebo every other day (q2d; Figure 3).

Safety parameters, iron parameters, total hepcidin-25 and PK were assessed during treatment and follow-up periods of ≥3 weeks. Data are given as arithmetic means ± SD.

Figure 2: Design of the single ascending dose part



In each study cohort, subjects were randomized 6:2 for double-blind treatment with NOX-H94/Placebo.

Figure 3: Design of the repeated IV dose part

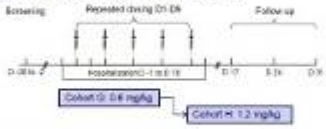


Figure 4: Kinetic profiles of NOX-H94 and hepcidin-25

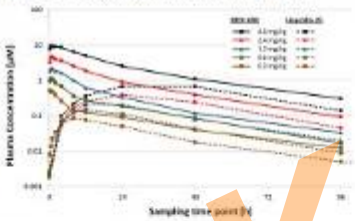
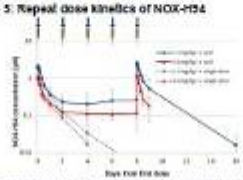


Table 1: Main pharmacokinetic parameters after single IV doses of NOX-H94

Dose [mg/kg]	n	C_{max} [µM]	AUC_{0-inf} [µM·h]	$t_{1/2}$ [h]	CL [L/h]
0.3	6	0.624 0.099	6.53 3.43	16.6 7.6	0.34 0.22
0.6	6	1.09 0.360	15.0 4.55	16.0 7.5	0.24 0.10
1.2	6	2.17 0.201	30.4 6.24	23.0 5.3	0.10 0.03
2.4	6	4.75 0.679	80.8 12.0	23.5 4.4	0.16 0.03
4.8	6	9.85 1.53	213 26.5	26.3 3.2	0.12 0.03

Figure 5: Repeat dose kinetics of NOX-H94



Full profiles at doses 1 and 5; predose (trough) concentrations prior doses 2, 3, 4.

Figure 6: Hepcidin-25 production rates

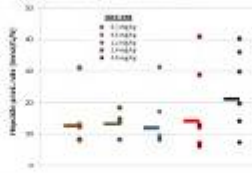


Figure 7: Serum iron kinetics after treatment with NOX-H94

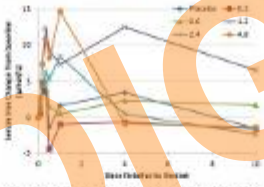
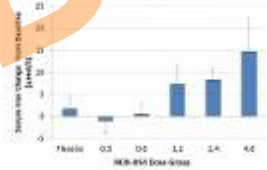


Figure 8: Serum iron at 24 h after NOX-H94 treatment



Results

All enrolled subjects with the exception of one man, assigned to 6 i.v. doses of 0.6 mg/kg, completed the study as scheduled.

Pharmacokinetics: After escalating single i.v. administrations of 0.3 to 4.8 mg/kg of NOX-H94, peak plasma concentrations of NOX-H94 (C_{max}) and systemic exposure (AUC) increased dose-proportionally. The elimination was bi-phasic with a terminal plasma half-life ($t_{1/2}$) in the range of 17 to 26 h. The systemic clearance (CL) was low (Figure 4, Table 1).

After repeated q2d i.v. administrations, no appreciable plasma accumulation was found based on C_{max} and AUC (Figure 5). No obvious gender-difference was observed.

Pharmacodynamics: The plasma concentration of total hepcidin-25 increased dose-dependently upon NOX-H94 treatment, without ever exceeding the plasma concentration of NOX-H94 (Figure 4). The rate of hepcidin-25 increase in plasma was largely constant over the dose range studied, suggesting that NOX-H94 does not induce plasma hepcidin (Figure 6). The PD effects were assessed by analysis of the area under the data time curve above baseline (AUD) of various iron parameters. Single and repeated doses of NOX-H94 up to 0.6 mg/kg had no effect on serum iron, serum ferritin, and transferrin saturation (TSAT) in the healthy subjects studied. At doses ≥1.2 mg/kg NOX-H94, serum iron, serum ferritin, and TSAT increased dose dependently (Figure 8, Table 2).

Safety: Treatment with NOX-H94 was generally safe and well tolerated. No serious adverse event occurred; headache and fatigue were the only treatment emergent signs and symptoms that occurred more than once (Tables 3, 4). Mild and transient increases in transaminases (<2 ULN) were noted in subjects treated with NOX H94 at single doses ≥2.4 mg/kg or with repeated doses of 1.2 mg/kg (4.2 mg/kg weekly).

Conclusions

Treatment with NOX-H94 was generally safe and well tolerated at all of the dose levels and schedules studied. PK analyses showed a dose-linear exposure. In these healthy subjects, only mild dose-dependent increases in iron parameters were observed which likely underestimate the effects that may be obtained in patients with iron-restricted anemia. No induction of hepcidin was observed after administration of increasing doses of NOX-H94. For subsequent phase II studies in patients, twice weekly i.v. doses of 1.2 mg/kg are recommended.

Table 2: Serum iron parameters after single dose treatment with NOX-H94 analyzed based on the area under the data time curve above baseline (mean±SD)

Dose	Serum Iron	Serum Ferritin	TSAT
[mg/kg]	h [µmol/L · h]	[ng/L · h]	[% · h]
Placebo	10 44.6 28.4	28.6 46.3	62.6 41.0
0.3	6 47.6 51.9	16.6 31.3	82.3 76.9
0.6	6 67.0 46.3	44.4 53.2	111 80.1
1.2	6 193 53.7	126 266	321 137
2.4	6 134 45.0	371 296	239 97.8
4.8	6 225 136	644 670	422 334

Table 3: Treatment emergent signs and symptoms (TESS) after single doses of NOX-H94

Adverse Event	Placebo IV	0.3 mg/kg	0.6 mg/kg	1.2 mg/kg	2.4 mg/kg	4.8 mg/kg
n=	10	6	6	6	6	6
Fatigue	1/1 (10%)	3/3 (50%)	-	-	1/1 (17%)	-
Somnolence	-	1/1 (17%)	-	-	-	-
Headache	-	-	-	-	1/1 (17%)	-
Migraine	-	-	-	-	1/1 (17%)	-
Palpitations	1/1 (10%)	-	1/1 (17%)	-	-	-
Dyspnea	-	1/1 (17%)	-	-	-	-
Gastro-oesophag. reflux disease	-	1/1 (17%)	-	-	-	-
Dyspepsia	1/1 (10%)	-	-	-	-	-
Cough	-	1/1 (16.7%)	-	-	-	-
No TESS	8 (80%)	2 (33%)	5 (83%)	6 (100%)	5 (83%)	6 (100%)
Sum of TESS	3/3 (30%)	7/6 (67%)	1/1 (17%)	0	3/3 (50%)	0

Table 4: Treatment emergent signs and symptoms (TESS) after repeated doses of NOX-H94

Preferred Term	No Placebo IV	4x0.6 mg/kg	4x1.2 mg/kg
n=	8	6	6
Headache	1/1 (25%)	0/2 (33%)	-
Insomnia	-	1/1 (17%)	-
Gastrointestinal hypermotility	-	1/1 (17%)	-
Abdominal pain	-	1/1 (17%)	-
Mouth ulceration	-	-	1/1 (17%)
Infusion site haemorrhage	-	-	1/1 (17%)
Ligament sprain	-	1/1 (17%)	-
Arthritis	-	1/1 (17%)	-
Dizziness	-	1/1 (17%)	-
No TESS	5 (63%)	2 (33%)	4 (67%)
Sum of TESS	1/1 (25%)	10/4 (67%)	2/2 (33%)

Disclosures, Funding

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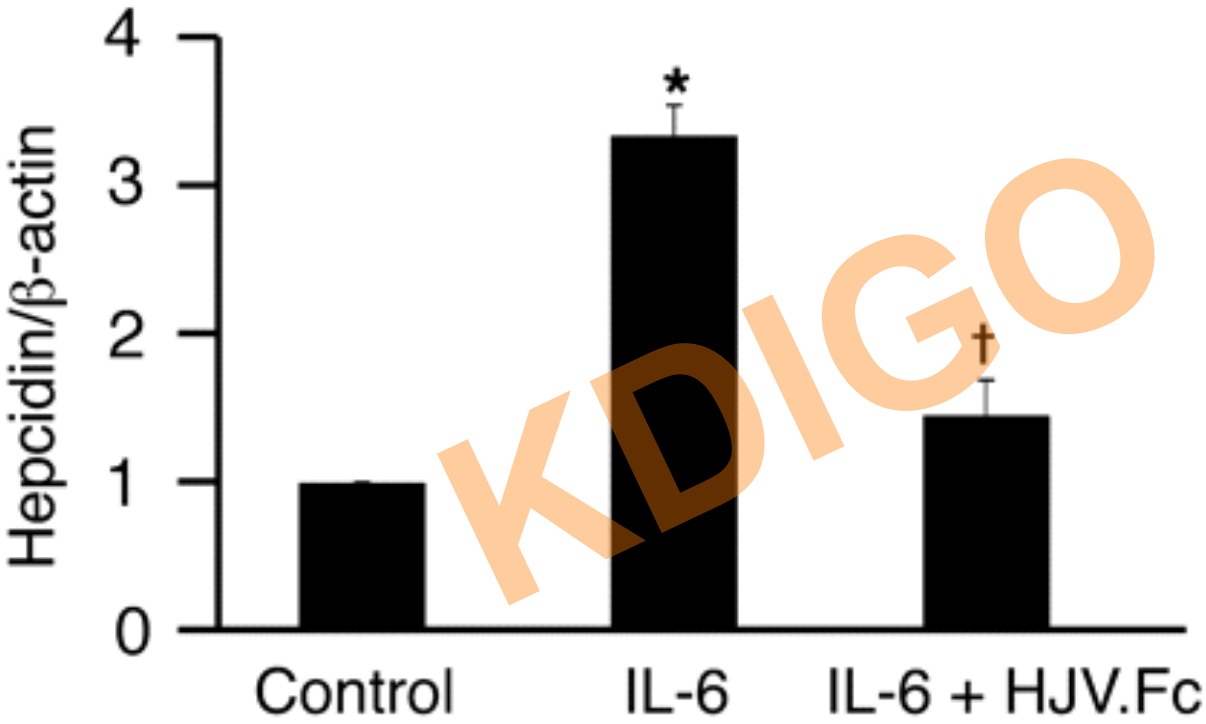
Soluble HJV.Fc inhibits IL-6 induction of hepcidin expression



Babitt et al *J. Clin. Invest.* **117**:1933-1939 (2007).

BASIC RESEARCH www.jasn.org

Suppression of Iron-Regulatory Hepcidin by Vitamin D

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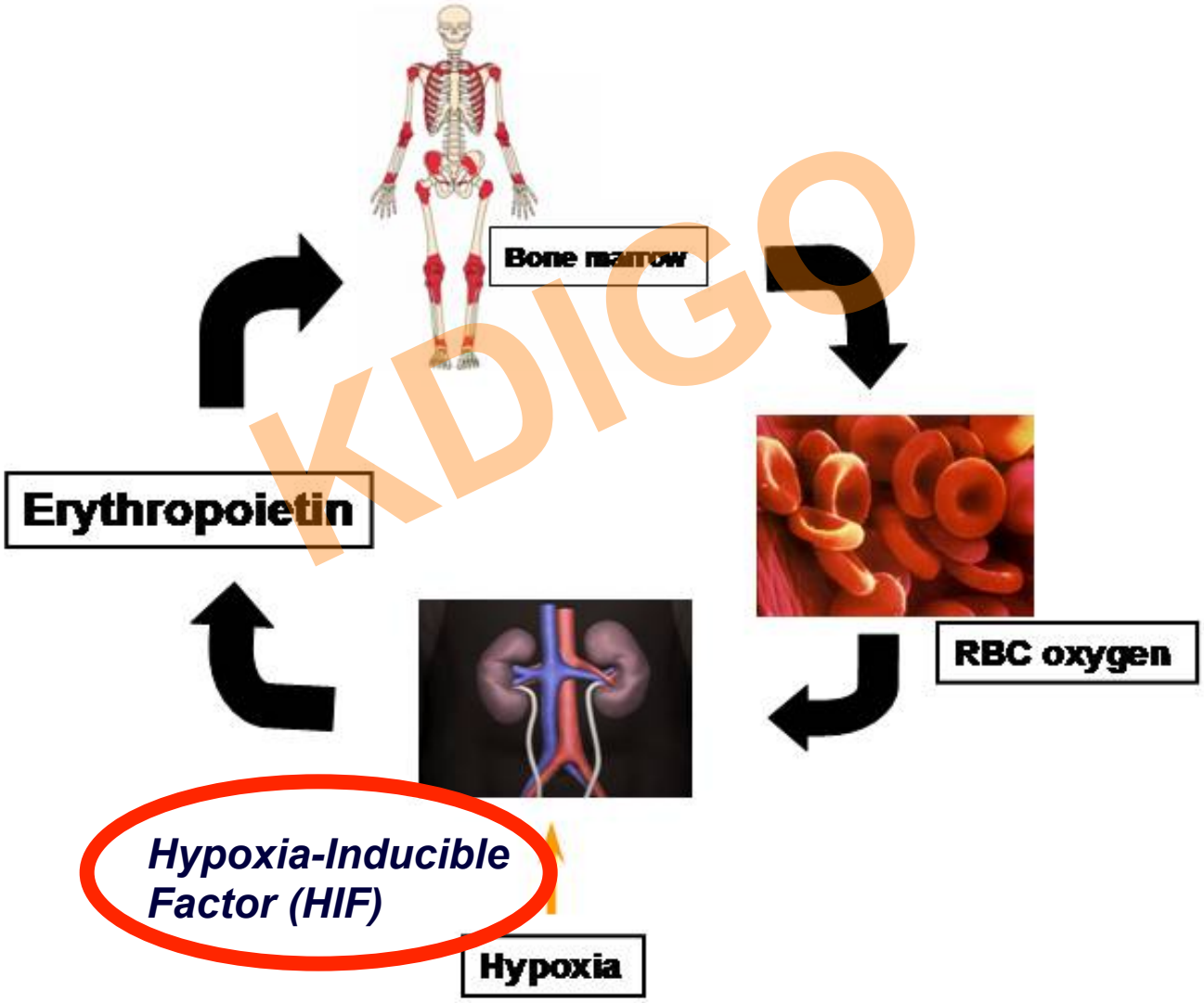
ABSTRACT

The antibacterial protein hepcidin regulates the absorption, tissue distribution, and extracellular concentration of iron by suppressing ferroportin-mediated export of cellular iron. In CKD, elevated hepcidin and vitamin D deficiency are associated with anemia. Therefore, we explored a possible role for vitamin D in iron homeostasis. Treatment of cultured hepatocytes or monocytes with prohormone 25-hydroxyvitamin D or active 1,25-dihydroxyvitamin D decreased expression of hepcidin mRNA by 0.5-fold, contrasting the stimulatory effect of

Iron management: new strategies currently under investigation

- PIVOTAL Trial
- Intra-dialytic soluble ferric pyrophosphate (SFP)
- Ferric citrate
- Hepcidin modulators
- HIF stabilisers (PHI‘s)

Regulation of erythropoietin



Identification of HIF

MOLECULAR AND CELLULAR BIOLOGY, Dec. 1992, p. 5447–5454
0270-7306/92/125447-08$02.00/0

Vol. 12, No. 12

A Nuclear Factor Induced by Hypoxia via De Novo Protein Synthesis Binds to the Human Erythropoietin Gene Enhancer at a Site Required for Transcriptional Activation

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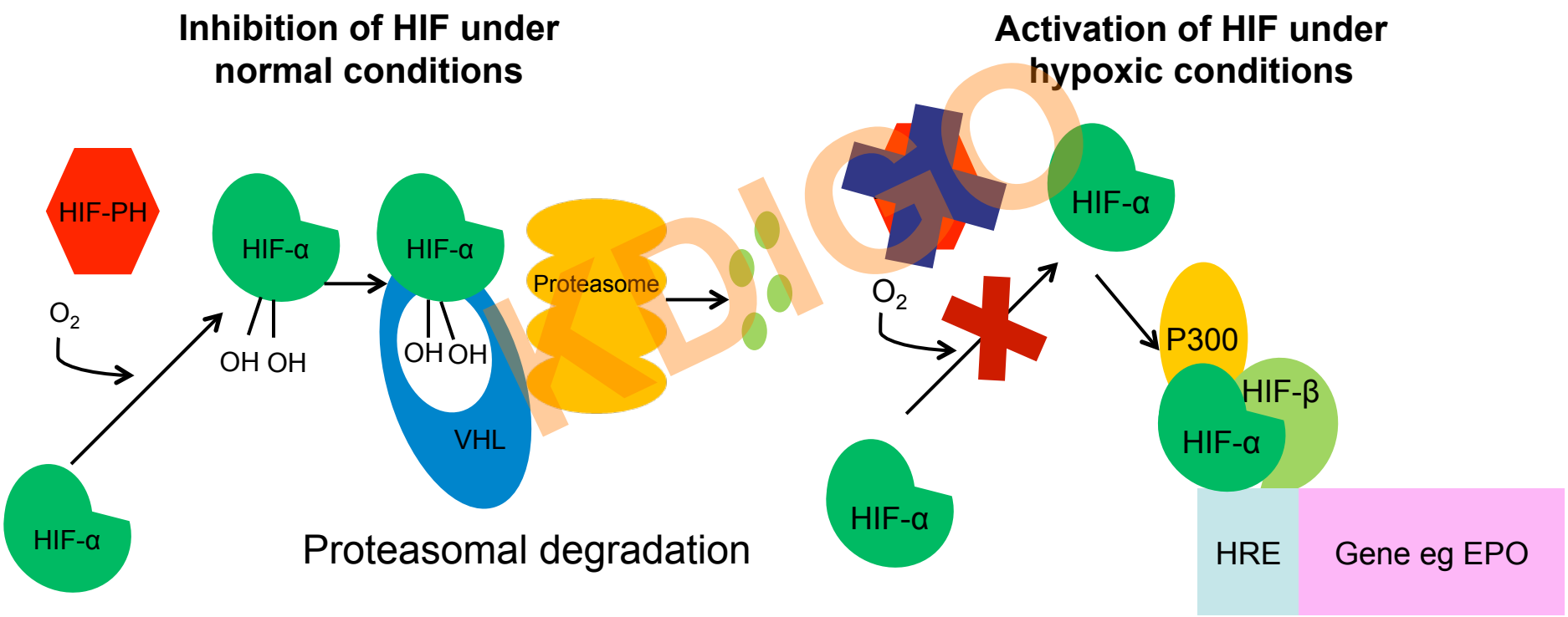
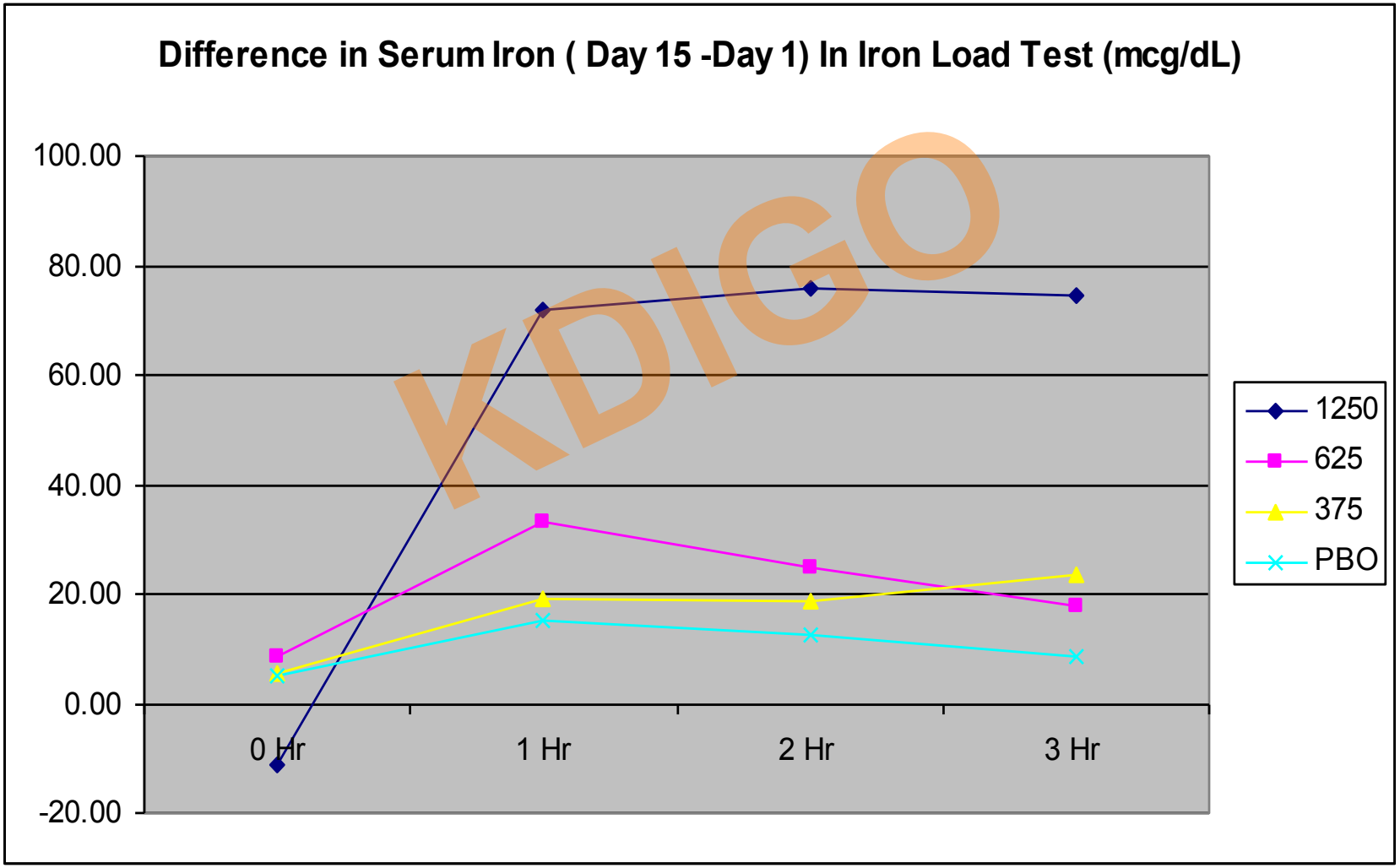
Received 17 July 1992/Returned for modification 25 August 1992/Accepted 2 September 1992

We have identified a 50-nucleotide enhancer from the human erythropoietin gene 3′-flanking sequence which can mediate a sevenfold transcriptional induction in response to hypoxia when cloned 3′ to a simian virus 40 promoter-chloramphenicol acetyltransferase reporter gene and transiently expressed in Hep3B cells. Nucleotides (nt) 1 to 33 of this sequence mediate sevenfold induction of reporter gene expression when present in two tandem copies compared with threefold induction when present in a single copy, suggesting that nt 34 to 50 bind a factor which amplifies the induction signal. DNase I footprinting demonstrated binding of a constitutive nuclear factor to nt 26 to 48. Mutagenesis studies revealed that nt 4 to 12 and 19 to 23 are essential for induction, as substitutions at either site eliminated hypoxia-induced expression. Electrophoretic mobility shift assays identified a nuclear factor which bound to a probe spanning nt 1 to 18 but not to a probe containing a

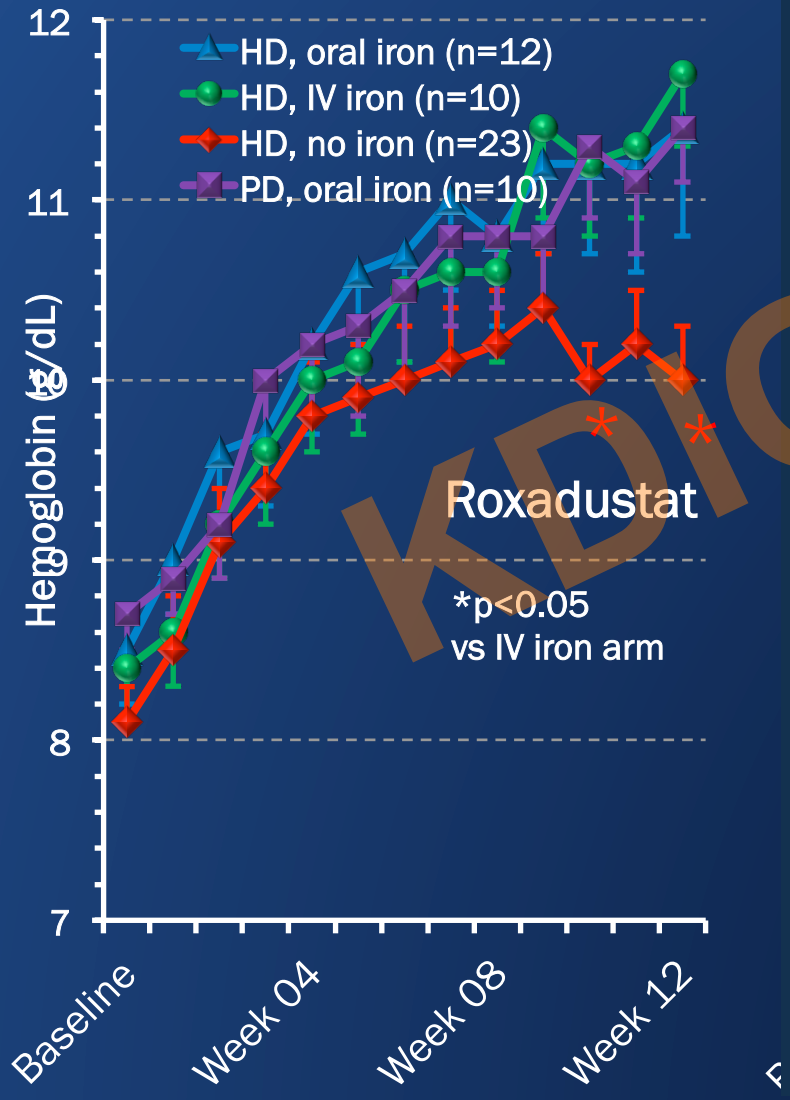
Regulation of HIF



FG-2216 enhances iron absorption

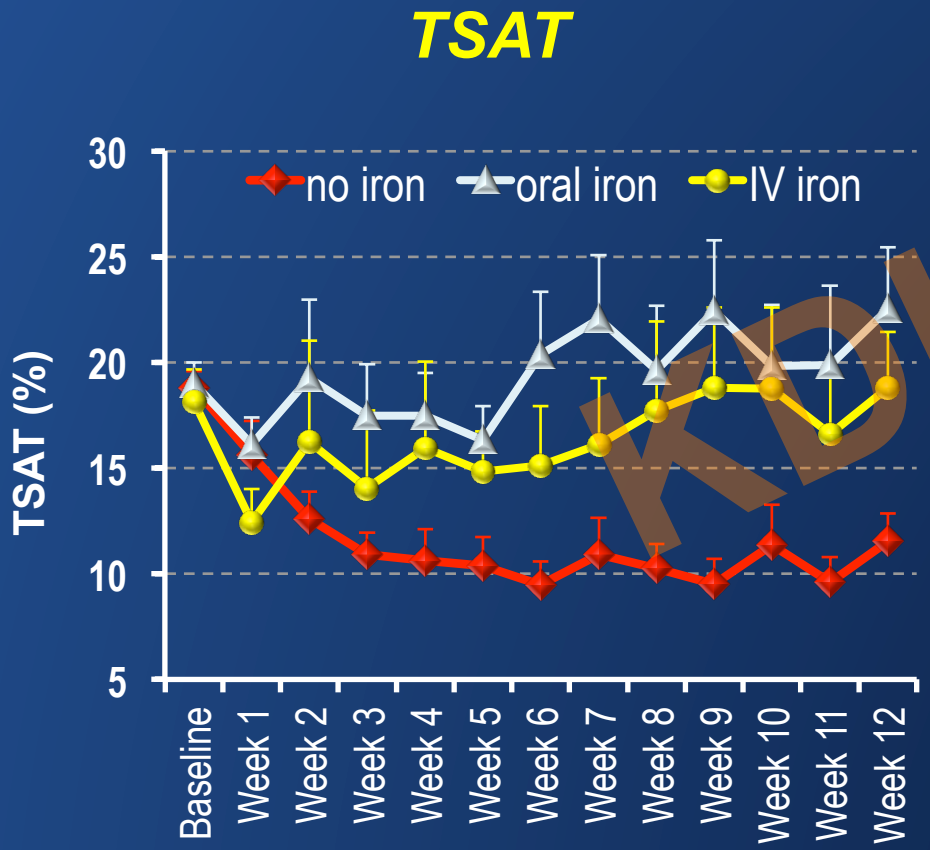


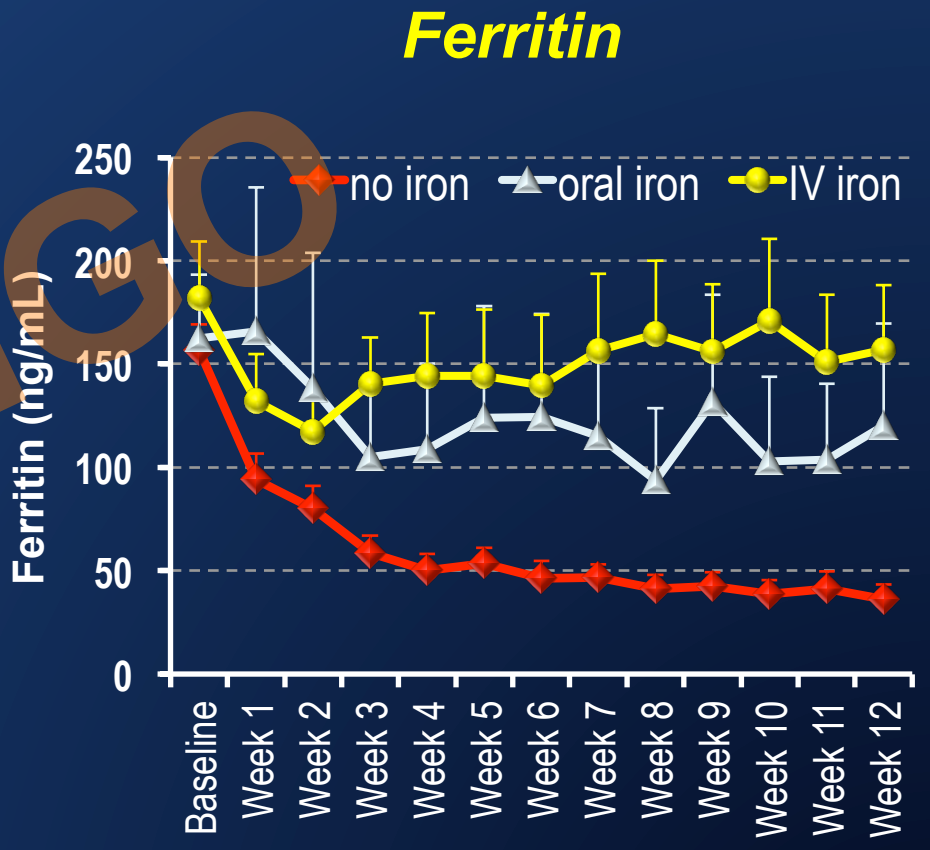
ESA-naïve incident HD patients



Besarab et al. 2012. J Am Soc Nephrol: 23:428A.

ESA-naïve incident HD patients





Conclusions

• The PIVOTAL Trial in the UK is a 2-arm RCT to investigate the long-term hard outcomes of a proactive more liberal approach to iron replacement *versus* a more conservative dosing regimen

-- currently recruiting, target 2080 patients in over 40 sites

• As with the ESAs, there are several new strategies for improving iron availability to the bone marrow

- *Intra-dialytic soluble ferric pyrophosphate*
- *Oral ferric citrate*
- *Hepcidin modulators*
- *HIF stabilisers*