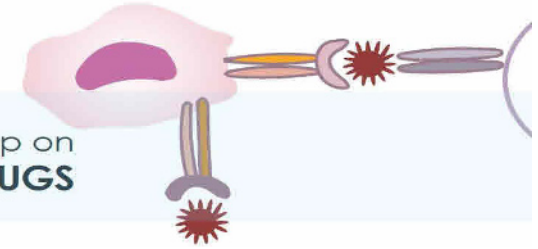


Professor Jacques Rottembourg, MD, France

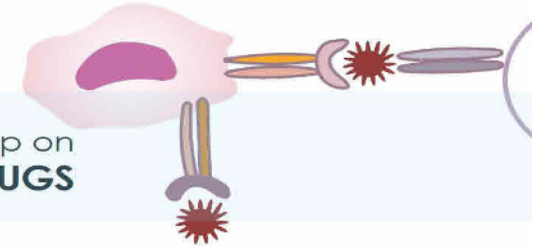
- Professor of Nephrology
- Department of Nephrology, Hôpital de la Pitié, Paris, France
- **Conflict of Interest : Honorarium from Amgen, Fresenius, Vifor , Pharmacosmos for presentations at different meetings**



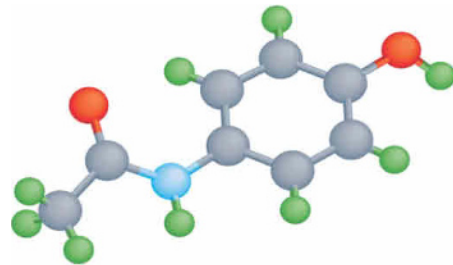
Substitution: clinical observations of differences in efficacy and efficiency (input versus output)

Professor Jacques Rottembourg, MD
Department of Nephrology, Hôpital de la Pitié,
Paris-France

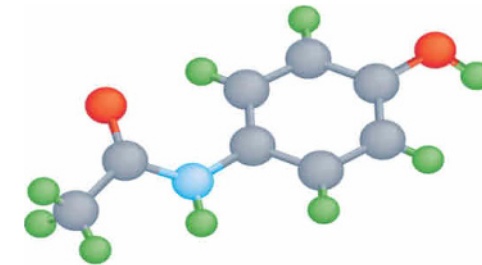
8 October 2013



Why the generic paradigm does not apply to iron sucrose preparations



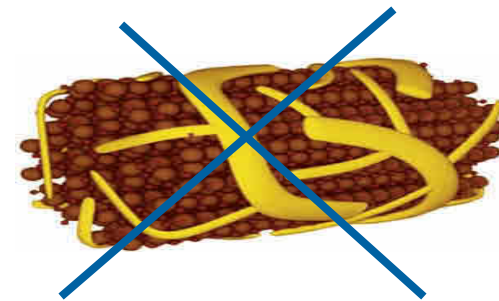
Simple molecule



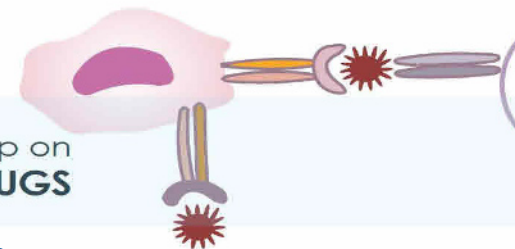
“Generic” (identical copy)



Complex molecule



“Similar” (non identical copy)



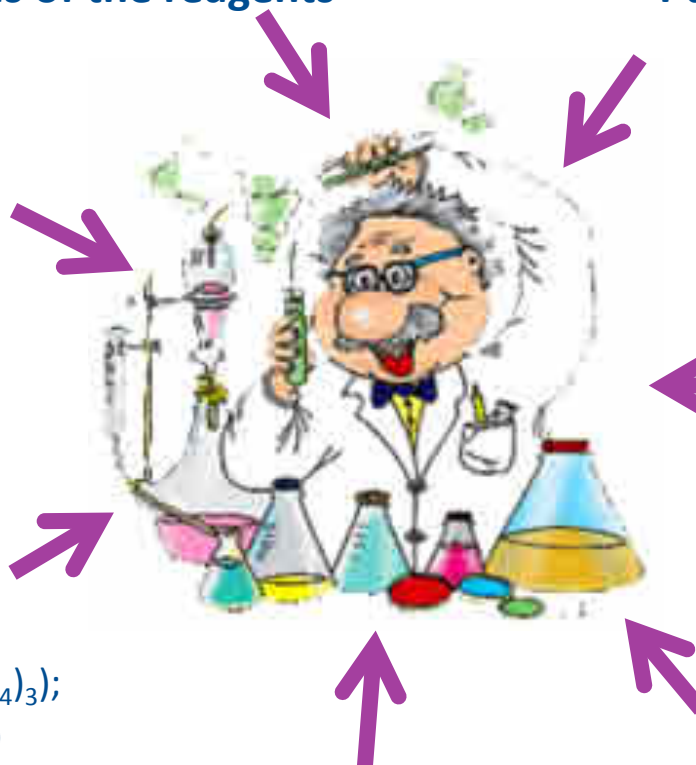
Parameters that influence the manufacturing process of iron sucrose

Concentrations of the reagents

Purification procedures

Synthetic procedure

(Isolation of core then addition of sucrose ligand; production of core in the presence of ligand)



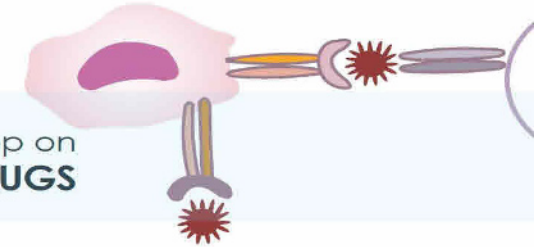
pH of the reaction mixture at different stages of the synthesis

Starting materials

(Iron source (e.g. FeCl_3 or $\text{Fe}_2(\text{SO}_4)_3$);
Base (e.g. NaOH , Na_2CO_3 or NH_3))

Reaction temperature

Reaction time

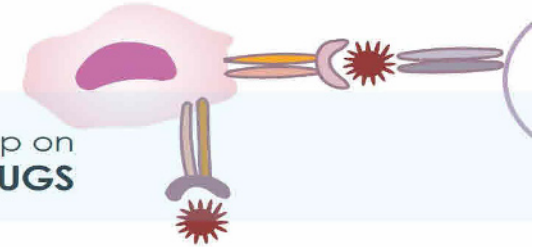


The “European ISS Study”

Venofer[®] versus 4 European ISS Preparations

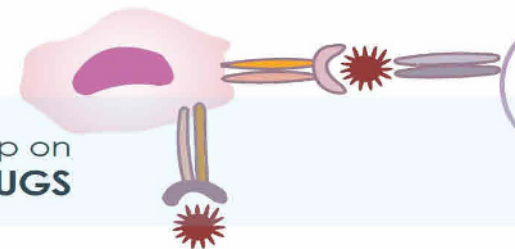
Brand (Country)	ISS Preparations	Manufacturer
Ferroven[®] (Turkey)	ISS ₁	Santa Farma, Istanbul, Turkey
Fer Mylan (France)	ISS ₂	Help SA Pharmaceuticals, Athens, Greece
Ferrovin (Greece)	ISS ₃	Rafarm Pharmaceuticals, Athens, Greece
FerMed[®] (Germany, Austria)	ISS ₄	Medice Arzneimittel GmbH Pütter Iserlohn, Germany

Venofer[®]	IS	Vifor International, St Gallen, Switzerland
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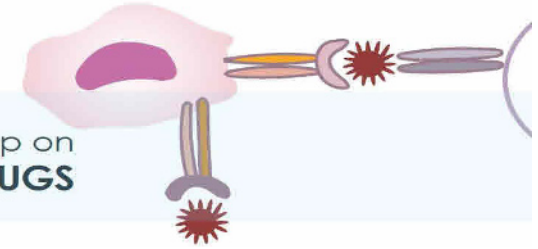
Context

- Patients with Chronic Renal Failure treated by dialysis frequently present anaemia related to deficit of Iron and Erythropoietin.
- Control of anaemia requires ESA and Iron treatment.
- Two iron-complexes are available in France: Venofer[®], Cosmofer[®].
- From 2003 up to 2009, the exclusive use of Venofer[®] in the dialysis unit resulted in good control of anaemia together with Aranesp[®] (ESA) administered once every week then once every two weeks.



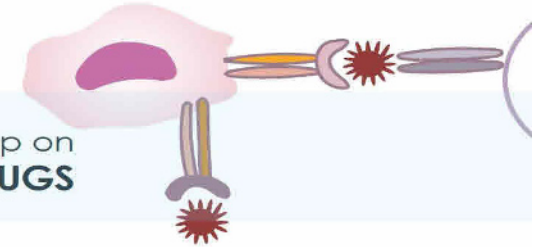
Long-Term satisfactory Clinical Situation with Venofer®

Year	Nb Sessions per year	Mean Hb g/dL	Consumption Aranesp® µg/year	Consumption Venofer® ampoules
2006	13846	11,72	171630	2600
2007	14218	11,88	178860	2650
2008	14596	11,82	167880	2700



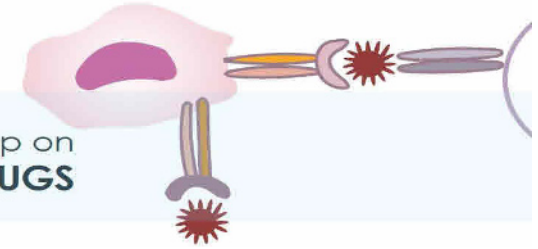
Context

- Patients with Chronic Renal Failure treated by dialysis frequently present with anaemia related to deficit of Iron and Erythropoietin. Control of anaemia requires ESA and Iron treatment
- Two iron-saccharose complexes are available in France: Venofer® and Cosmofer®
- From 2003 up to 2008, the exclusive use of Venofer® in the dialysis unit resulted in good control of anaemia together with Aranesp® (ESA) administered once every week then once every two weeks
- Due to a recent modification of supply, by the Pharmacy of all hospitals in Paris, without any knowledge of this change, Fer Mylan® was substituted for Venofer® in all dialysis units and specially in our (Centre Suzanne Levy Paris).
- Following the switch the physician in the unit noted that there was a rapid change in anaemia parameters.



Objectives of the study

- **Main objective:**
 - To describe and compare the impact of the switch from Venofer[®] to Fer Mylan[®] on anaemia and iron parameters in HD patients.
- **Secondary objectives:**
 - To describe the level of drug consumption for two periods (i.e. before and after the switch).
 - To document biological parameters that are routinely collected in this setting.
 - To estimate an anaemia drug expenditure for the two periods.



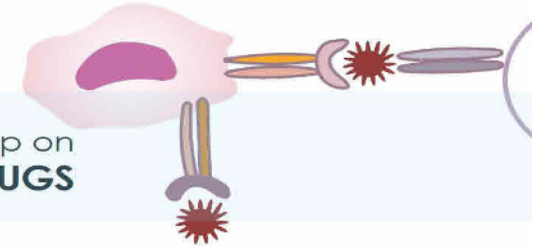
Material and methods

- **Observational, non-interventional phase IV study.**
- **Open-label, retrospective and prospective comparison of Venofer[®] and Fer Mylan[®] based on routinely collected data.**
- **Patient population consisted of HD patients receiving regular dialysis follow-up at the centre.**
- **Comparison of two 27-week periods:**
 - **P1: 01 December 08 → 07 June 09 (Venofer[®])**
 - **P2: 29 June 09 → 03 January 10 (Fer Mylan[®])**
 - **Data for part of June were excluded because the two products were simultaneously available.**

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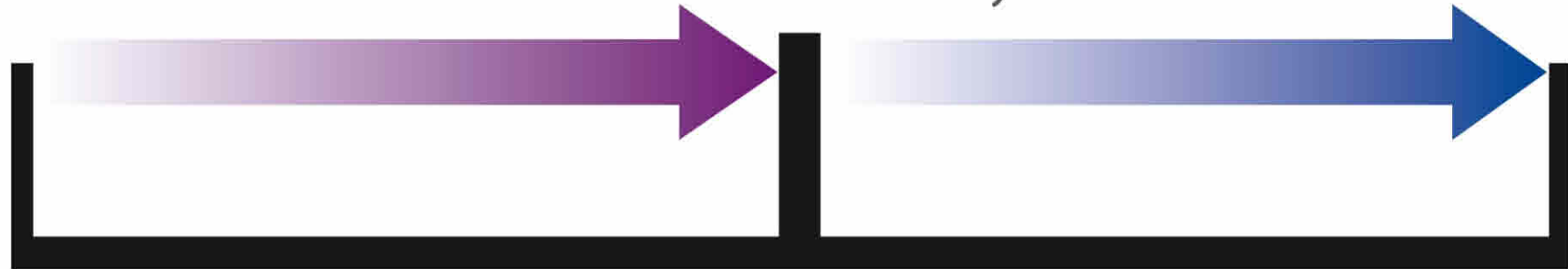
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Study design

Venofer® 27 weeks

Fer Mylan® 27 weeks



Dec 2008

June 2009

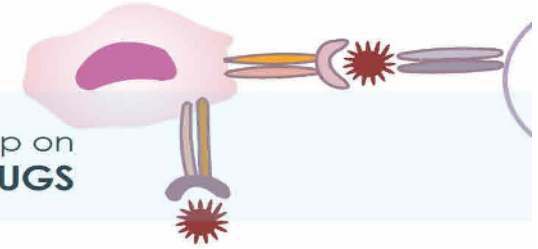
Sept 2009

Jan 2010



Retrospective

Prospective



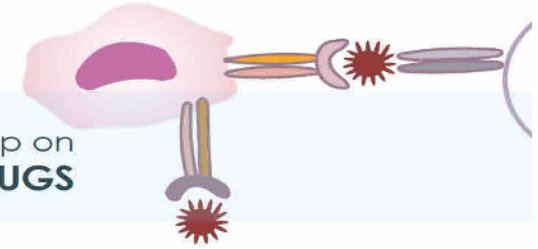
Iron and ESA treatments

I.V. iron treatments:

- Venofer[®] (5 mL ampoules of 100 mg iron) and Fer Mylan[®] (5 mL ampoules of 100 mg iron) prescribed according to local SmPC.
- I.V. iron was administered once a week during the second dialysis session at weekly dosages varying from 25-100 mg iron.

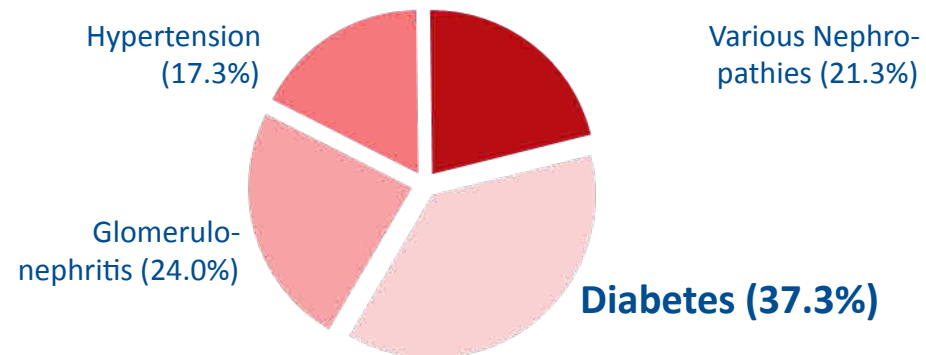
ESA:

- Aranesp[®] (Darbepoetin- α [DA], Amgen, Thousand Oaks, CA, USA).
- DA was injected intravenously once every two weeks (even weeks) on Monday or Tuesday.



Patient characteristics

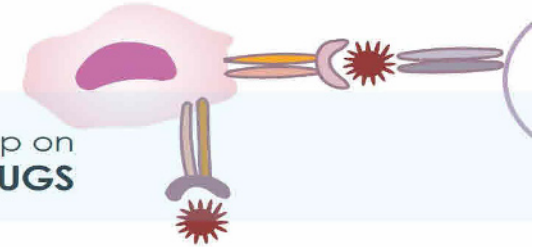
- Study population: **75 patients** included in the analysis: **same patients** in both periods.
- Gender: 31% female and 69% male.
- Age: 63.4 ± 15.2 y [mean ± SD].
61.8 (25.7 - 89.1) [median (min - max)].
- Number of dialysis sessions:
 - P1: 75.1 (5.1)
 - P2: 75.1 (6.3)
- Primary renal diseases:



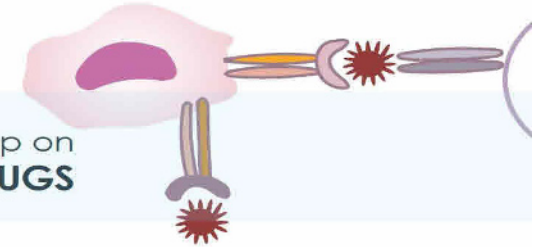
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Results: **Hemoglobin**
Iron
ESA
Biological Parameters

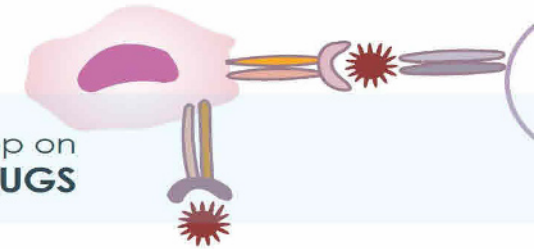


Haemoglobin analysis: overall study period

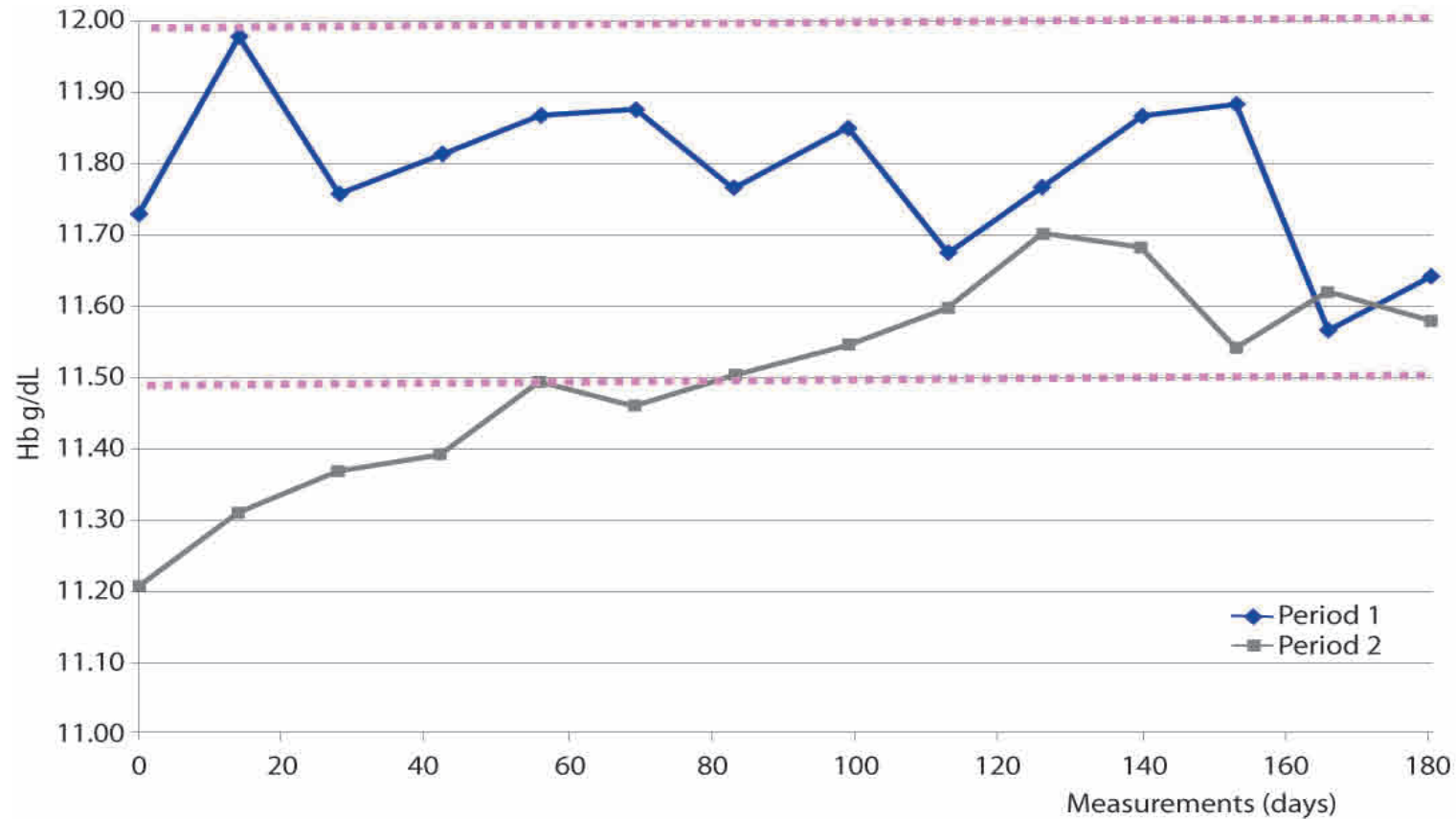
Hb (g/dL)	Period 1 n=75	Period 2 n=75	p
Mean (SD)	11.78 (0.99)	11.48 (0.98)	0.01*
Median (min-max)	11.80 (8.57-14.14)	11.47 (9.20-15.42)	0.01**

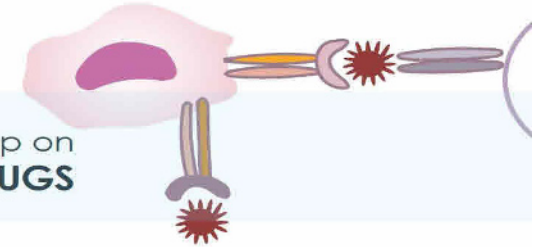
* Paired Student's t-test

** Median's t-test



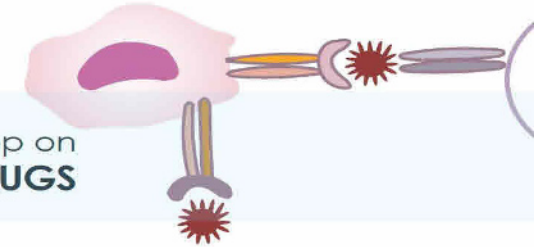
Haemoglobin evolution over the study period





Serum ferritin and TSAT parameters: comparison between P1 and September 2009

	Period 1	September 2009	p*
Number of patients	n=75	n=75	
Serum ferritin (µg/L)			
Mean (SD)	533.8 (327.5)	457.7 (290.4)	0.04
Median (min - max)	551.2 (38.3-1,051.5)	432.1 (13.7-1,541.1)	
TSAT %			
Mean (SD)	49.3 (10.9)	23.3 (10.2)	<0.0001
Median (min - max)	47.7 (32.0-80.0)	23.0 (5.0-44.0)	



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Serum ferritin and TSAT parameters

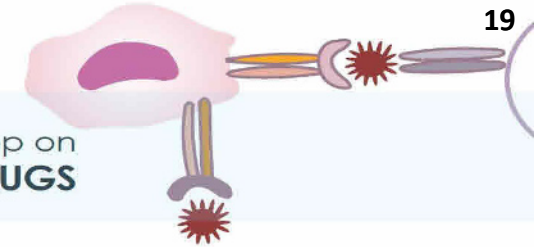
	Dec 08	Mar 09	Jun 09	Average P1	Sep 09	Dec 09	Average P2
Serum ferritin (µg/L)				p=0.25 between P1 and P2*			
No. of patients	70	73	75	75	75	69	75
Mean (SD)	613 (369)	563 (506)	458 (298)	534 (328)	458 (290)	549 (334)	495 (280)
Median (min-max)	632 (11-1727)	435 (25-3063)	447 (15-1416)	551 (38-1502)	432 (14-1541)	498 (13-1751)	475 (14-1595)
TSAT %				p<0.0001 between P1 and P2*			
No. of patients	70	73	75	75	75	69	75
Mean (SD)	49.2 (12.5)	48.1 (14.5)	50.0 (13.1)	49.3 (10.9)	23.3 (10.2)	26.4 (10.7)	24.5 (9.4)
Median (min-max)	49.0 (27-86)	44.0 (23-110)	48.0 (26-86)	47.7 (32-80)	23.0 (5-44)	24.0 (4-55)	24.0 (6-44.5)

GENERIC AND BIOSIMILARS INITIATIVE

Building trust in cost-effective treatments

* Paired Student's t-test

Pro Pharma
 Communications
 International

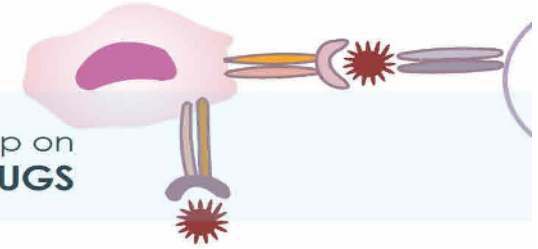


Iron consumption according to period

	Period 1 n=75	Period 2 n=75	% change	P*
Cumulative dose (mg) – all patients	92,300	124,250	+34.6%	
Mean dose per patient (SD) (mg)	1,230.7 (879)	1,656.7 (836)	+34.6%	0.001
Median (range)	1,300 (0-2,800)	1,500 (0-4,100)		
Number of vials – all patients	923.0	1,242.5	+34.6%	0.001
Number of vials / patient (SD)	12.3 (8.8)	16.6 (8.4)	+34.6%	

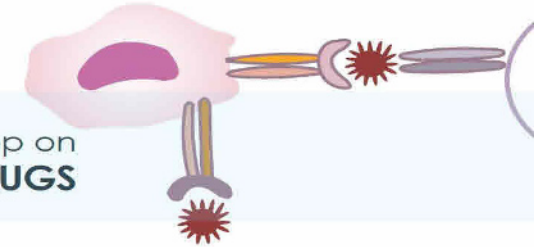
- 6 patients without iron during Period 1
- 1 patient without iron during Period 2

* Paired Student's t-test

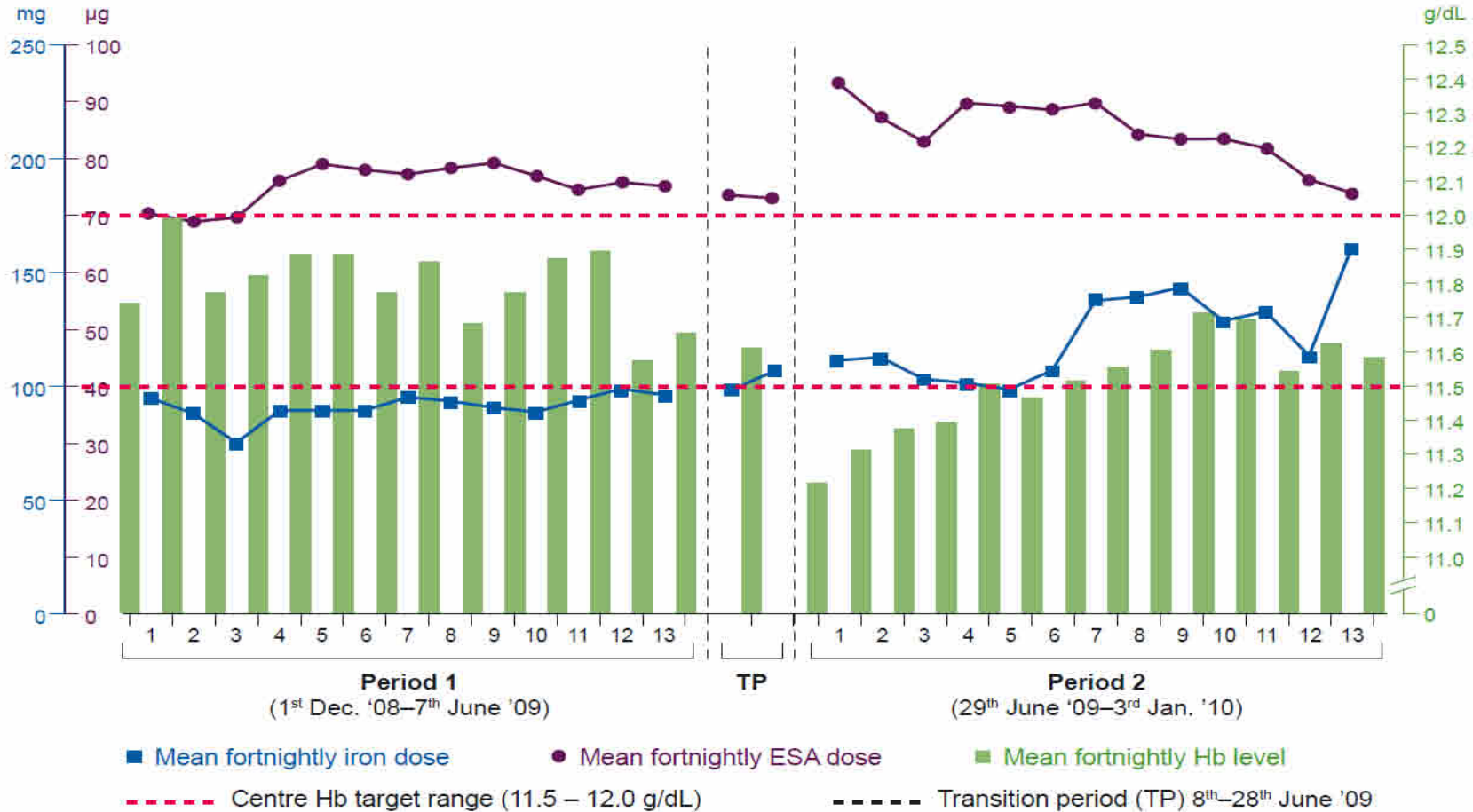


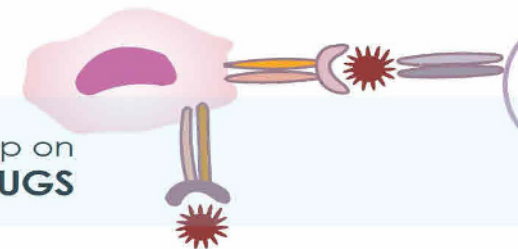
ESA consumption according to period

	Period 1 n=75	Period 2 n=75	% change	P*
Cumulative dose (µg) – all patients	73,510	82,750	+12.6%	
DA µg/kg/week dose per patient (SD)	0.58 (0.52)	0.66 (0.64)	+13.8%	0.13
Mean dose per patient (SD) (µg)	980.1 (756)	1,103.3 (908)	+12.6%	0.12
Median (min – max)	780 (0-4,200)	780 (0-4,000)	–	



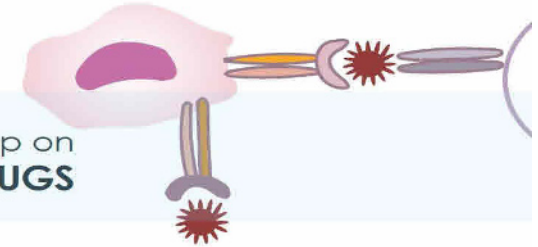
Hb evolution in relation to iron and ESA usage in P1 and P2





Biological Parameters

	Period 1	Period 2	p*
Number of patients	n=75	n=75	
Calcium (mmol/L) Mean (SD) / median (min-max)	2.24 (0.16) / 2.22 (1.78-2.62)	2.23 (0.14) / 2.20 (1.88-2.56)	0.35
Phosphorus (mmol/L) Mean (SD) / median (min-max)	1.76 (0.48) / 1.69 (0.61-3.10)	1.63 (0.35) / 1.64 (0.81-2.33)	0.0002
Ca x P Mean (SD) / median (min-max)	3.96 (1.12) / 4.00 (1.35-6.42)	3.65 (0.83) / 3.71 (1.75-5.09)	<0.0001
Alkaline phosphatase (IU/L) Mean (SD) / median (min-max)	109.7 (96.2) / 91.5 (46.5-869)	110.6 (83.4) / 94.5 (46-726.5)	0.83
PTH ng/L Mean (SD) / median (min-max)	359.2 (294.6) / 249 (36-1456.5)	340.5 (262.9) / 273 (31.1290)	0.47



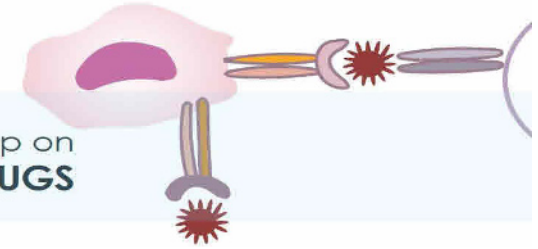
Biological Parameters

	Period 1	Period 2	p*
Number of patients	n=75	n=75	
CRP mg/L Mean (SD) / median (min-max)	6.45 (6.85) / 3.00 (3.00-42.00)	8.43 (10.46) / 4.00 (3.00-57.5)	0.15
Total Bilirubin (mg/L) Mean (SD) / median (min-max)	7.71 (1.76) / 7.67 (4.33-13.33)	8.77 (2.27) / 8.50 (5.00-18.00)	0.001
Fibrinogen (g/L) Mean (SD) / median (min-max)	4.35 (1.21) / 4.00(2.60-9.53)	4.37 (1.43) / 4.10 (2.00-10.60)	0.8210
γ-GT (U/L) Mean (SD) / median (min-max)	47.76 (54.00) / 28.00 (9.33-295.00)	46.95 (49.01) / 27.00 (10.00-276.00)	0.8268
Aspartate aminotransferase (AST) (UI/L) Mean (SD) / median (min-max)	22.28 (10.87) / 19.33 (11.33-89.33)	22.36 (8.41) / 19.50 (10.50-56.50)	0.9190

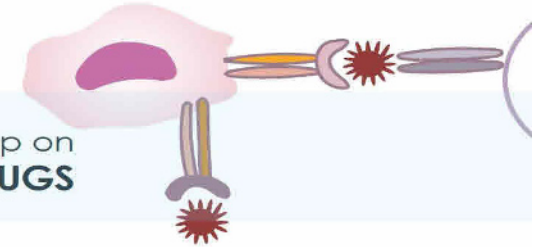
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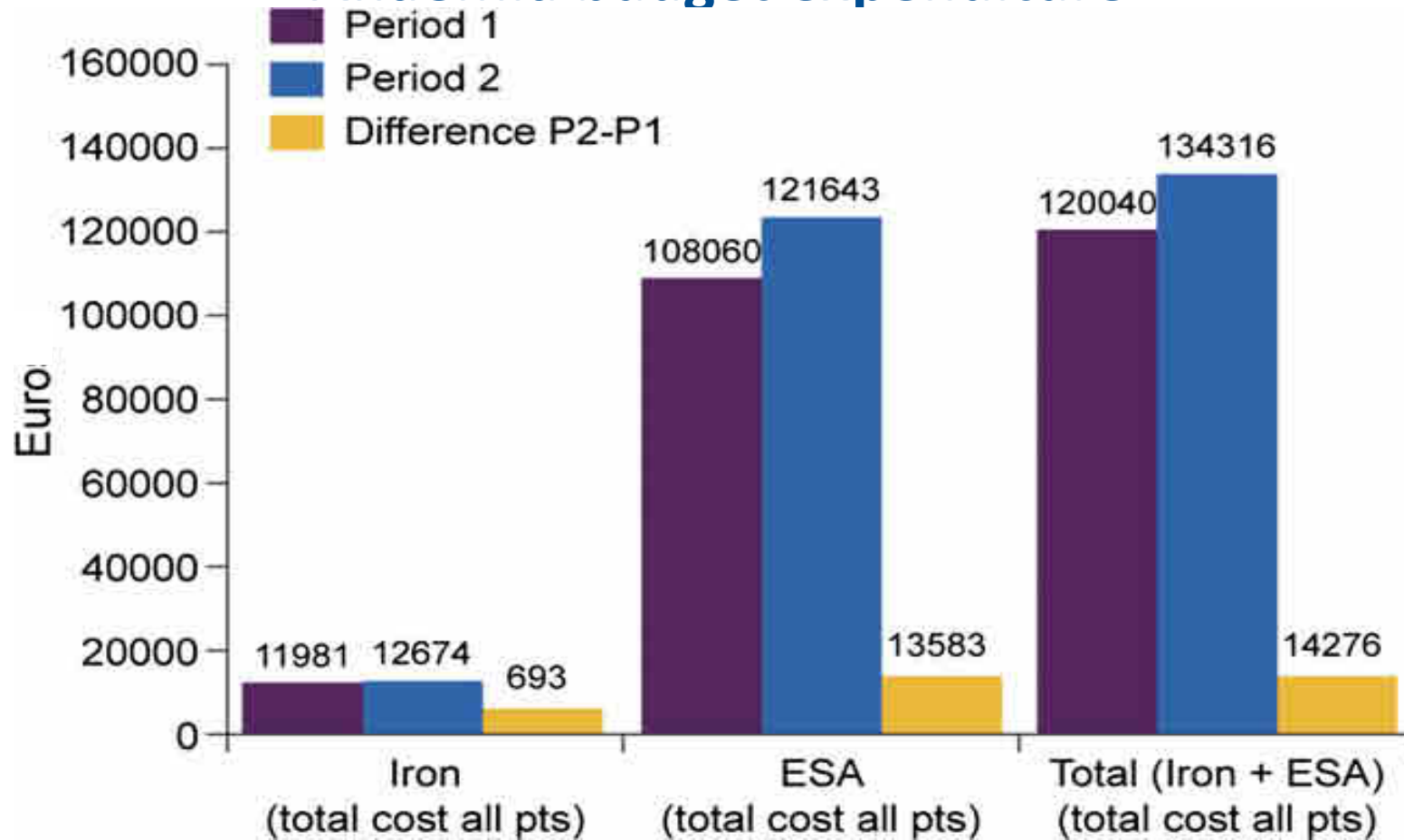
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Economic aspects of the study



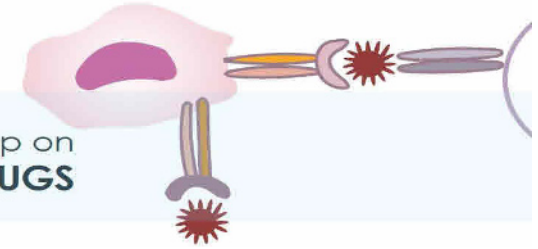
Anaemia budget expenditure



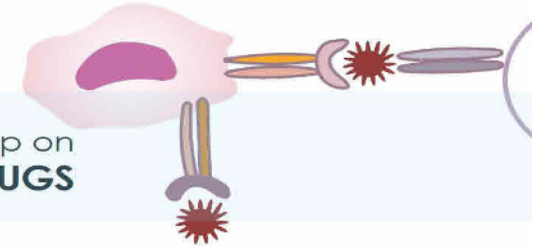
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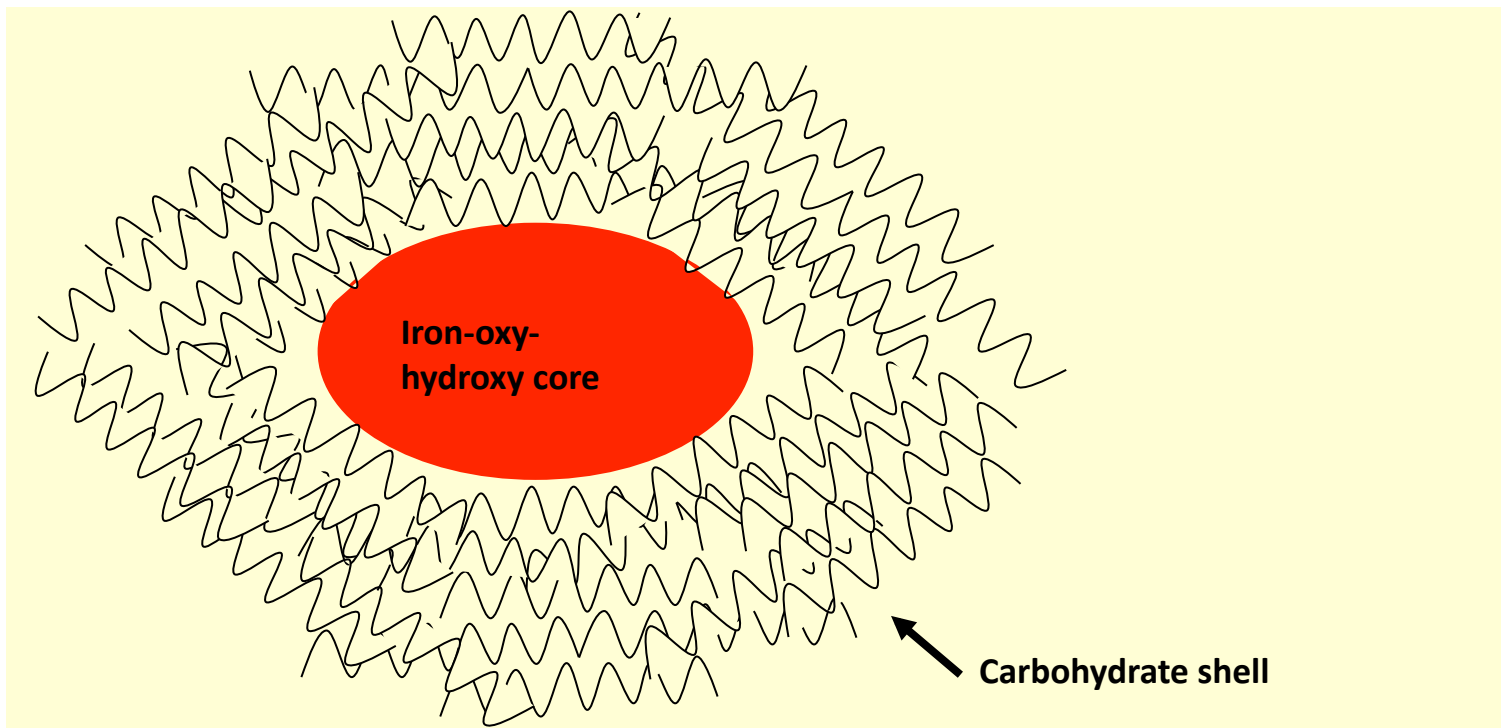
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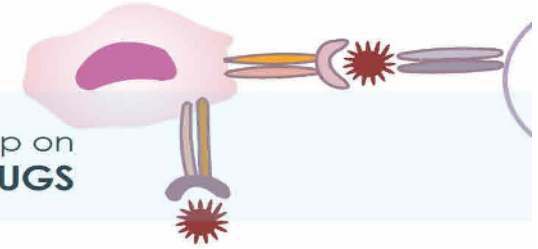


Discussion



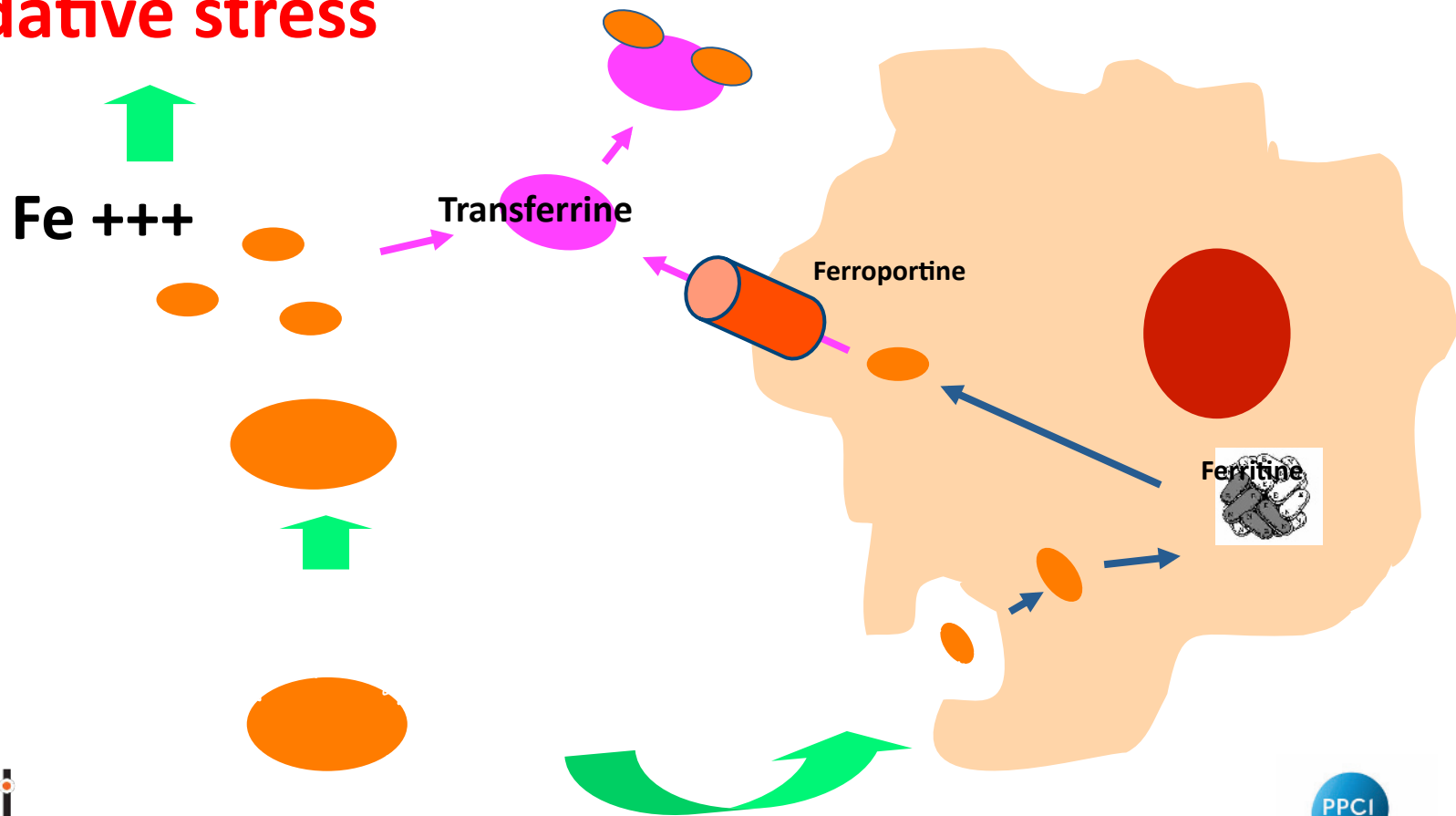
The structure of I.V. iron is delicate

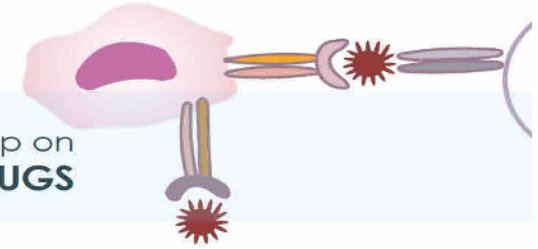




Physiopathology

Oxydative stress





There is now **FOUR** evidence-papers showing that **ISS** and **Venofer[®]** are not therapeutically equivalent

Do two intravenous iron sucrose preparations have the same efficacy.

J Rottembourg et al Nephrol Dial Transplant 2011;26:3262-3267.

Clinical case reports raise doubts about the therapeutic equivalence of an iron sucrose similar preparation compared with iron sucrose originator.

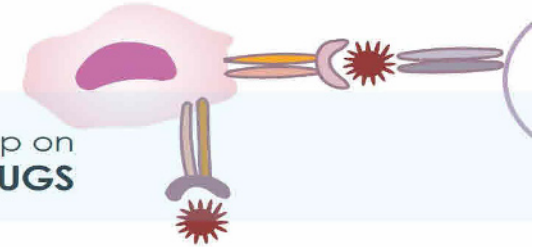
J Stein et al Curr Med Res Opin 2012;28:241-243.

Effects of intravenous iron on mononuclear cells during the haemodialysis session.

A Martin-Malo et al . Nephrol Dial Transpl 2012;27:2465-71.

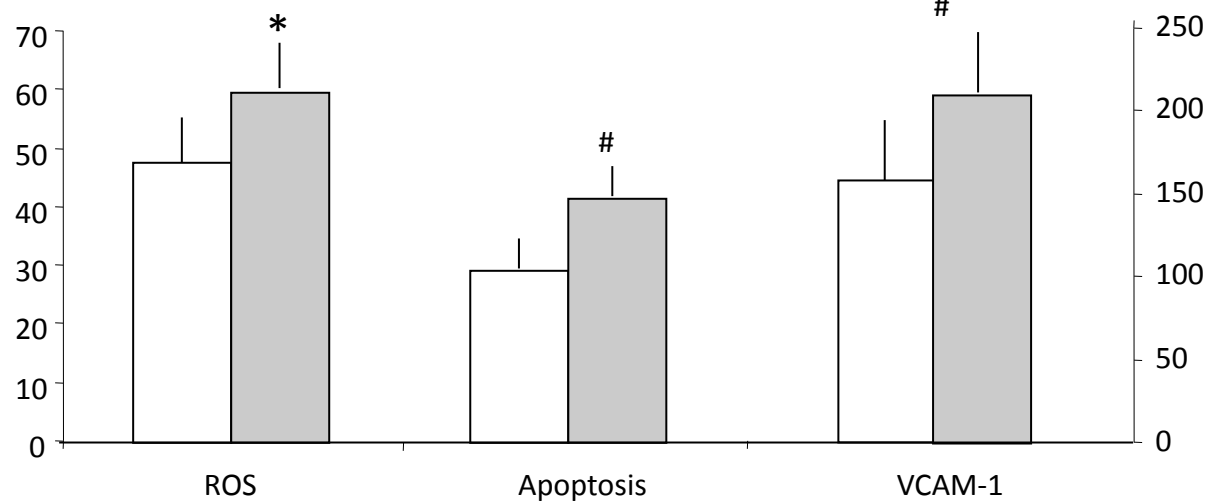
Comparison of adverse events profile of Intravenous iron sucrose and Iron sucrose similar in post-partum and Gynecologic operative patients.

ES Lee, BR Park. Curr Med Res Opin 2013 29:147-151.



Markers of the Oxydative Stress

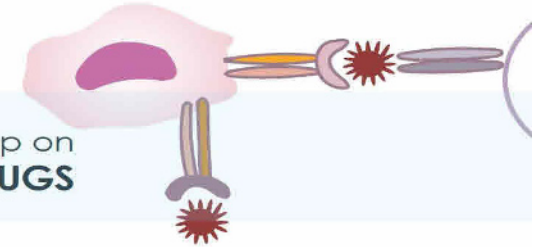
% CELLS



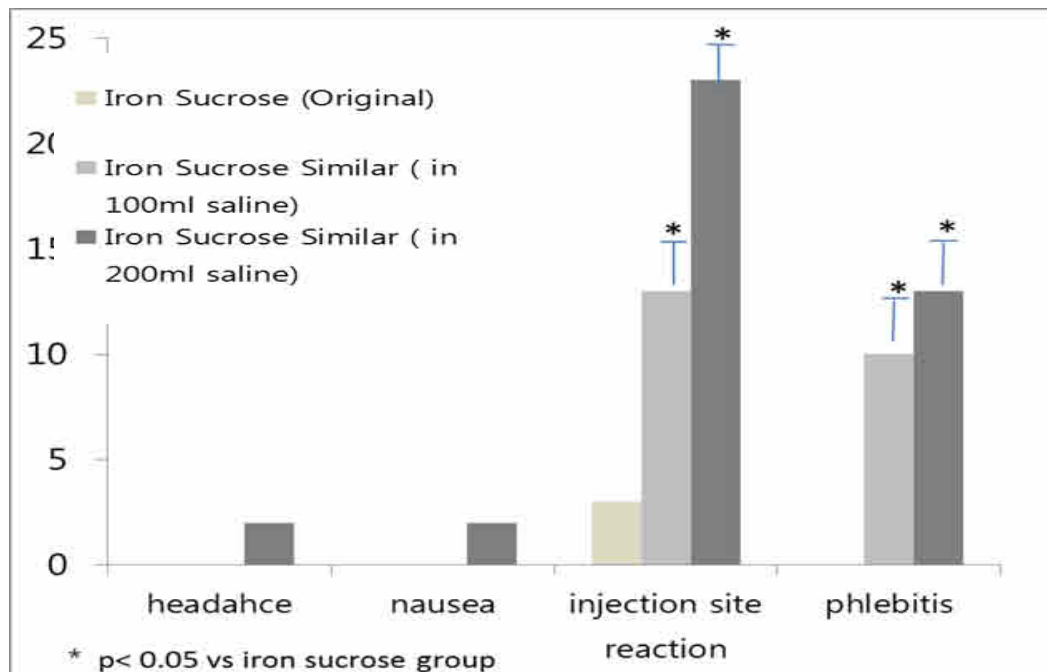
□ Iron sucrose
■ Iron sucrose generic

ROS: Reactive Oxygen Species. VCAM-1 Vascular cell adhesion molecule 1

Effects of intravenous iron on mononuclear cells during the haemodialysis session. A Martin-Malo et al . Nephrol Dial Transpl.2012;27:2465.

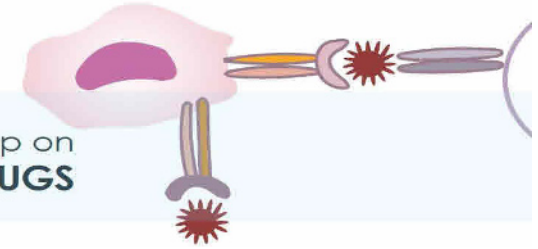


Comparison of adverse event profile of Intravenous Iron Sucrose and Iron Sucrose Similar in Post partum and Gynecologic operative patients



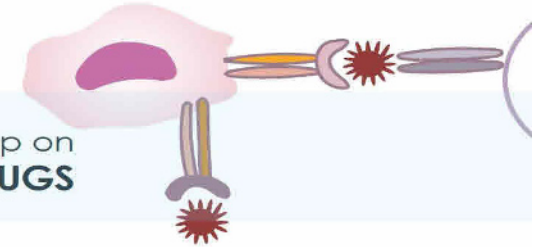
Retrospective analysis of patients treated in a single site over a period of 4 years with the originator Venofer® or ISS

Data collected for all treated patients in an anonymous manner with data points focusing on tolerability (adverse events during and after injection of IV iron)

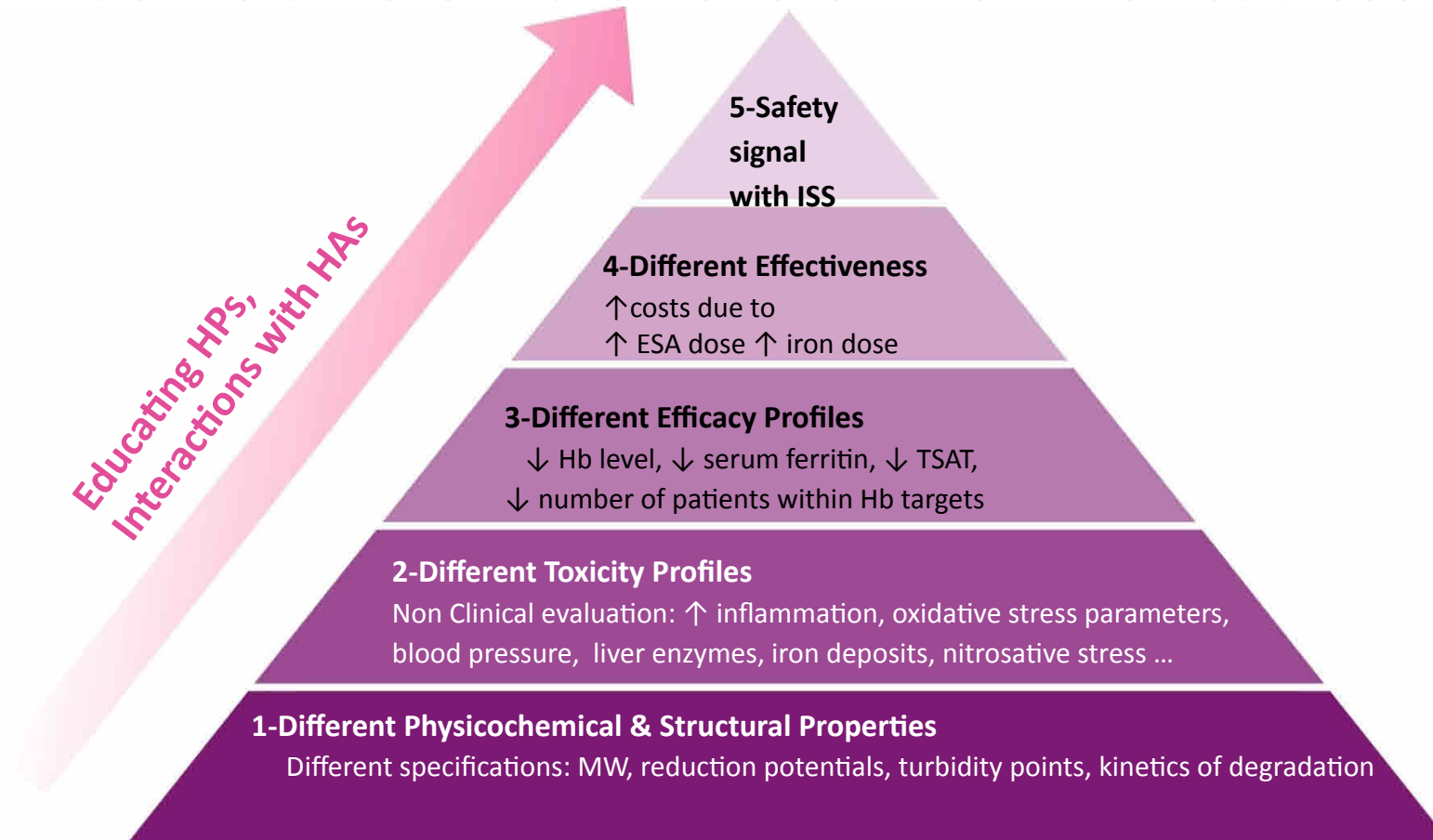


Conclusions of the observational study

- **Venofer[®] and Fer Mylan[®] may not be therapeutically equivalent.**
- **Switching to Fer Mylan[®] led to a destabilization of patients causing a significant decrease in Hb levels and iron indices.**
- **The change in iron indices raises questions on the stability of the Fer Mylan[®] complex and its impact on iron distribution (potentially deposited in the wrong compartment) and oxidative stress.**
- **Drug consumption to reach and maintain target Hb levels increased, resulting in patients being exposed to higher doses of DA and I.V. iron, which is a concern in a vulnerable population such as HD patients.**
- **The increase in total drug costs negated the economic rationale of the switch.**
- **These findings can have important consequences for the treatment of anaemia in HD patients**



How do we differentiate Venofer® from iron sucrose similars?

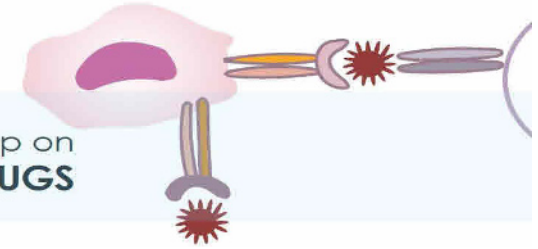


HPs = Healthcare Professionals, HAs = Healthcare Authorities

**GaBi
Educational
Workshops**

8 October 2013, Hilton Kuala Lumpur, Kuala Lumpur, Malaysia

First Asia Pacific Educational Workshop on
NON-BIOLOGICAL COMPLEX DRUGS



How the evidence on ISSs may change stakeholders' perspective



Healthcare Authorities Hospital Pharmacists



Are there enough data to evaluate ISSs?

Do ISSs really help save money?

Physicians



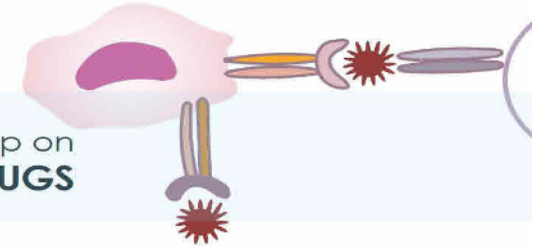
Are ISSs as effective as Venofer® ?



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Back Up Slides

Avis relatif à l'octroi d'autorisation de mise sur le marché de spécialités pharmaceutiques

Spécialité dénommée **ENALAVIS 20 mg/12,5 mg**, comprimé sécable, code identifiant de spécialité : 6 694 984 8 :

MEDIS EHF.

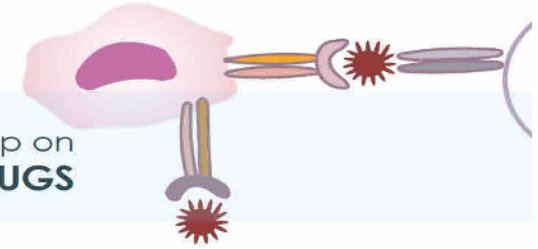
Composition : maléate d'énalapril 20 mg, hydrochlorothiazide 12,5 mg, pour un comprimé. – Codes identifiants de présentation : 388 396-8 ou 34009 388 396 8 5 (28 comprimés sous plaquettes thermoformées [aluminium/PVC]) ; 388 397-4 ou 34009 388 397 4 6 (28 comprimés en flacon [polypropylène] avec fermeture de sécurité enfant) ; **cette spécialité est un générique de CO RENITEC**, comprimé sécable (décision du 16 octobre 2008).

Spécialité dénommée **FER MYLAN 100 mg/5 ml**, solution à diluer pour perfusion, code identifiant de spécialité : 6 388 943 1 :

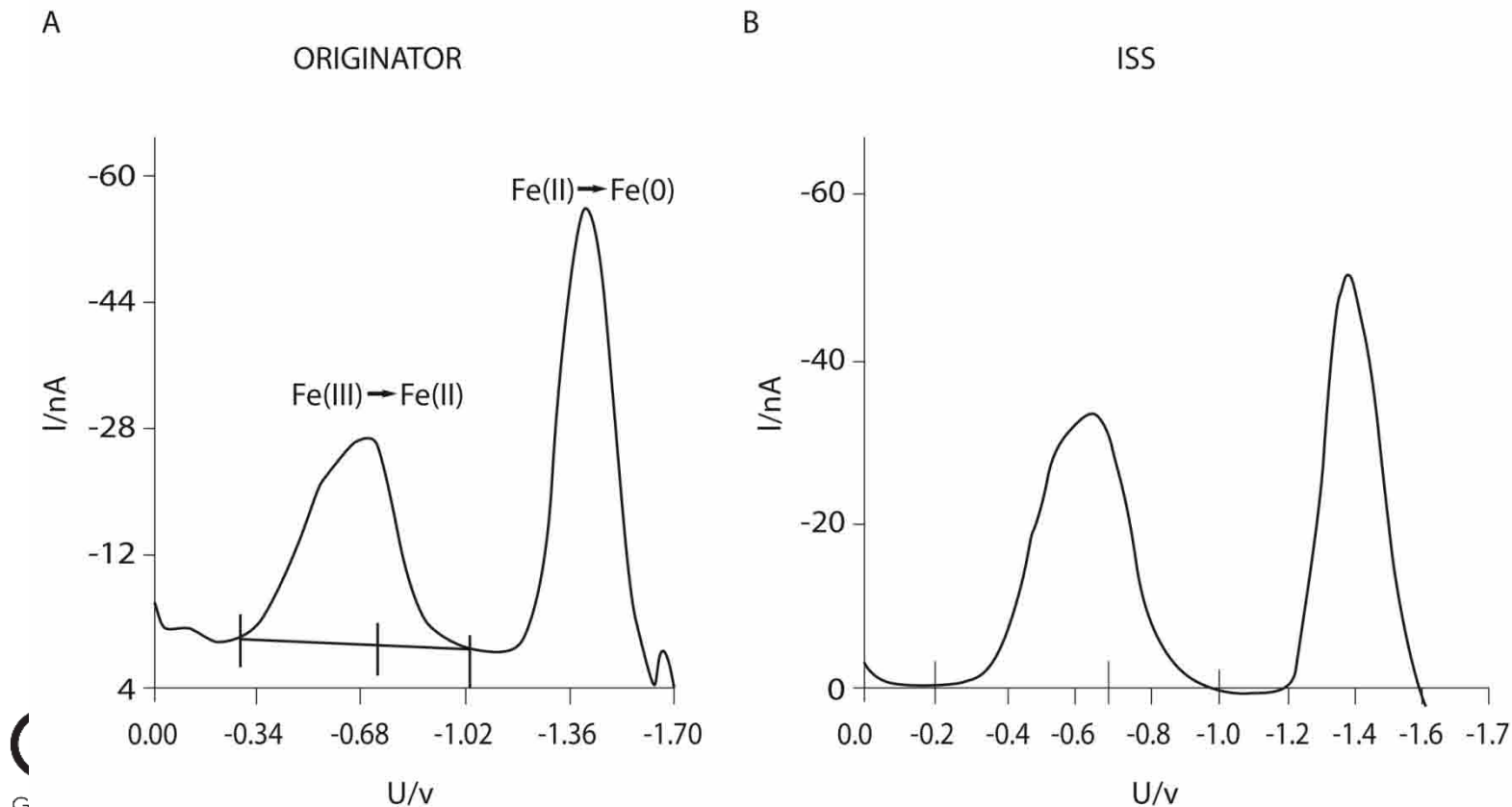
MYLAN SAS.

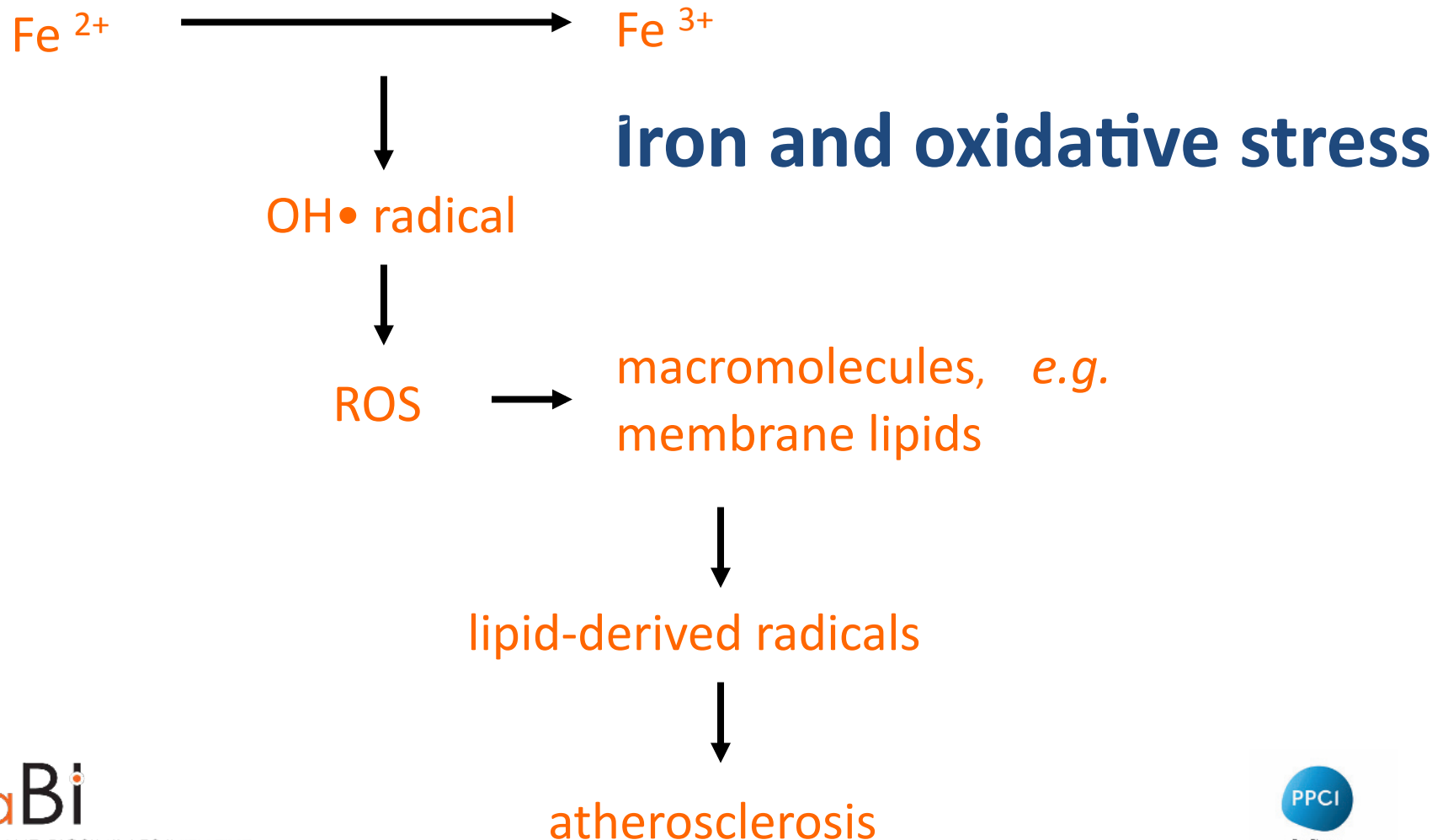
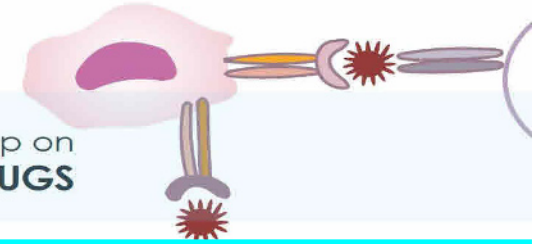
Composition : fer 100 mg (sous forme de complexe d'hydroxyde ferrique, saccharose 2 700 mg), pour 5 ml de solution injectable. – Codes identifiants de présentation : 574 036-8 ou 34009 574 036 8 3 (5 ml en ampoule [en verre/brun] ; boîte de 1) ; 574 037-4 ou 34009 574 037 4 4 (5 ml en ampoule [en verre/brun] ; boîte de 5) ; 574 038-0 ou 34009 574 038 0 5 (5 ml en ampoule [en verre/brun] ; boîte de 10) ; 574 039-7 ou 34009 574 039 7 3 (5 ml en ampoule [en verre/brun] ; boîte de 20) (décision du 27 octobre 2008).

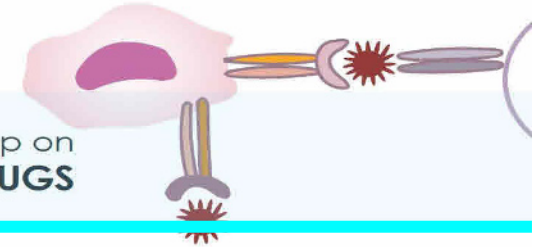




The polarographic representation of Venofer[®] and an ISS are not the same

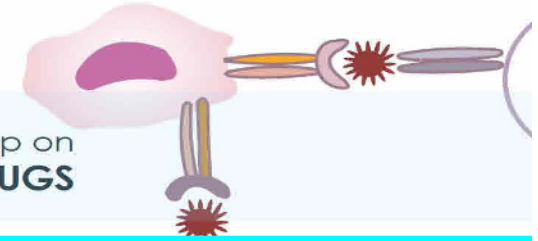




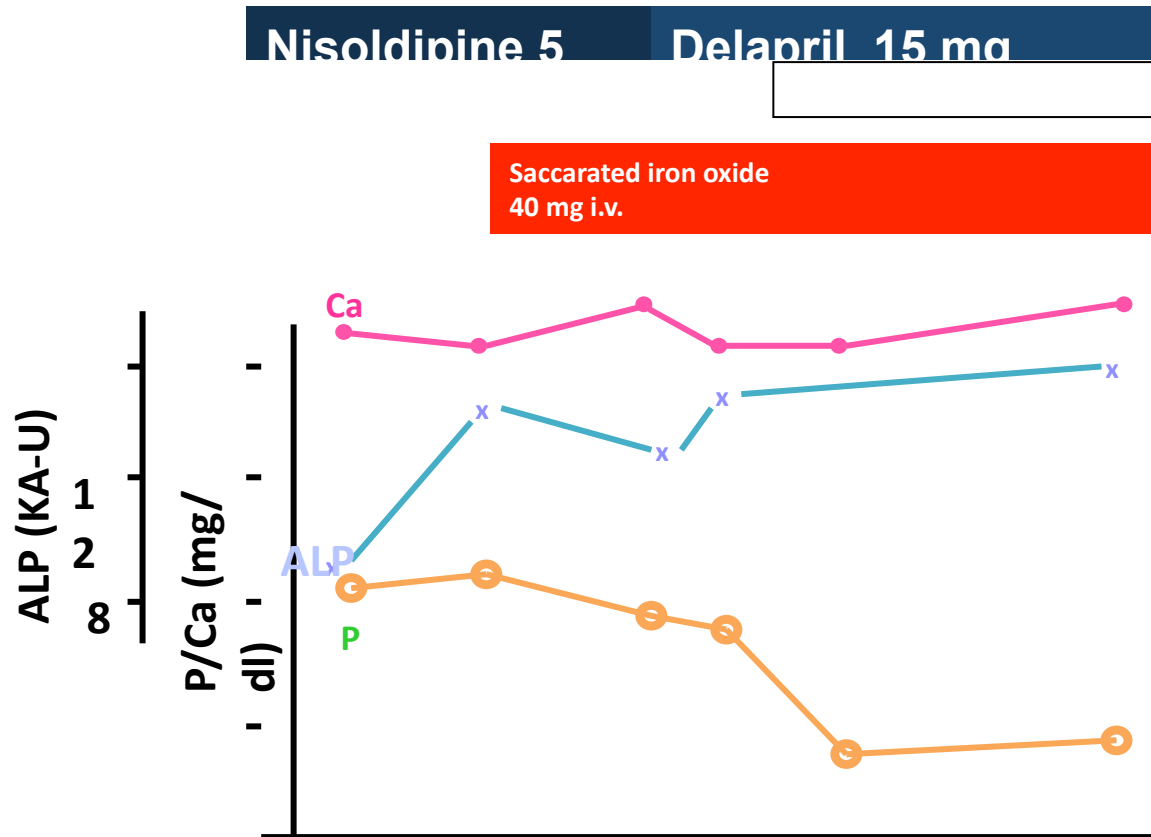


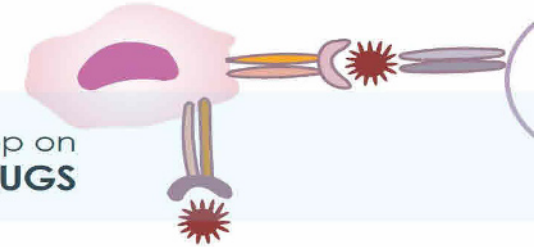
Increased oxidative stress

- Because of its ability to generate radical formation *in vitro*, iron has been implicated as a cause of oxidative stress
- Association between iron and oxidative stress in *in vitro* studies^{1,2}
- All i.v. iron preparations show potential to increase oxidative stress, but evidence is transient and lacking in clinical situations³



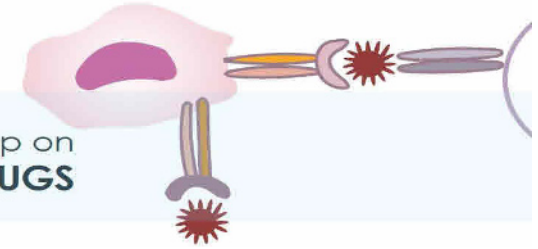
Hypophosphataemia following i.v. iron





Anaemia drug expenditure

	Period 1 n=75	Period 2 n=75	Difference P2-P1	% change
Iron – total cost – all patients	11,981 €	12,674 €	693 €	+6%
Mean iron cost/patient	160 €	169 €	9 €	+6%
DA total cost – all patients	108,060 €	121,643 €	13,583 €	+13%
Mean DA cost/patient	1,441 €	1,622 €	181 €	+13%
Anaemia drug total costs	120,040 €	134,316 €	14,276 €	+12%
Mean cost/patient	1,601 €	1,791 €	190 €	+12%



Consumo de erythropoyetina en relacion con el tipo de hierro sacarosa administrado

J. Carreras Bassa, R. Gallo, T. Olaya, G Villalobos, A. Foraster

- **Patients received Venofer® in 2009 and Feriv® in 2010.**
- **The mean Hemoglobin level was 11.52±0.1 g/dl in 2009 and 11.37±0.2 g/dl in 2010.**
- **There was an increase of about 12% in the use of different ESA.**
- **Ferritin levels was quite maintained.**

- **But nothing about the consumption of Iron.**
- **And the patients are not the same.**