Triferic™
(Ferric Pyrophosphate Citrex)

Iron Replacement Therapy for Maintenance of Hemoglobin in Dialysis Patients

Oncologic Drugs Advisory Committee

November 6, 2014

ROCKWELL MEDICAL

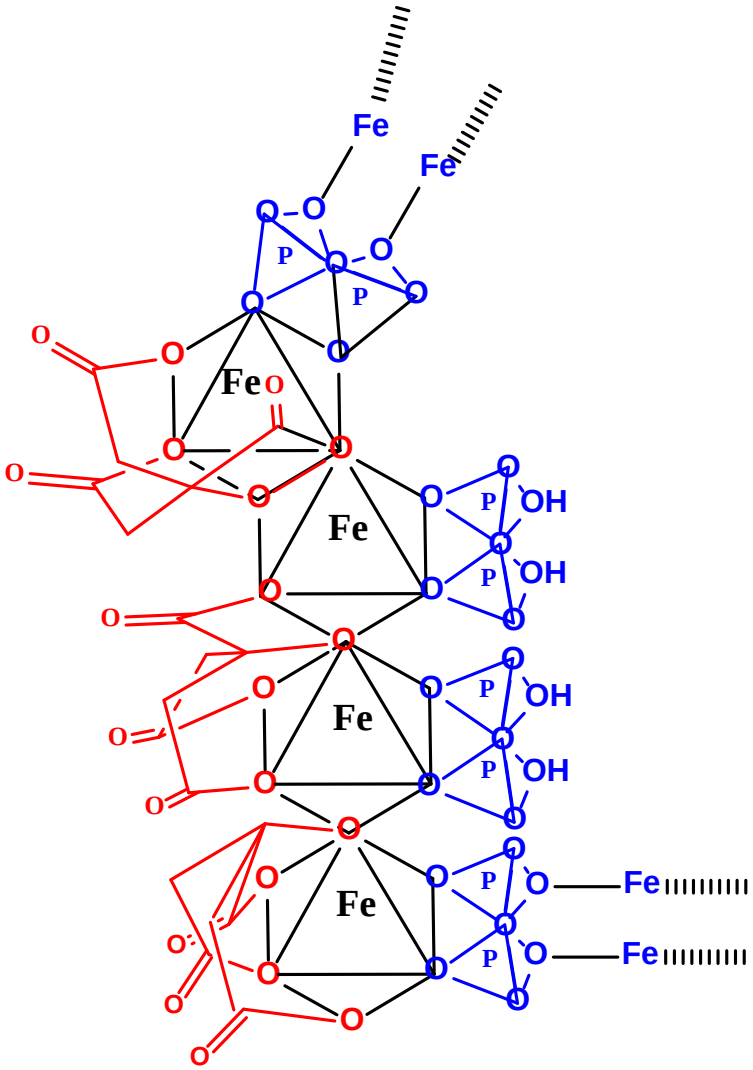
Introduction

Ajay Gupta, MBBS, MD
Chief Scientific Officer
Rockwell Medical, Inc.

About Rockwell Medical

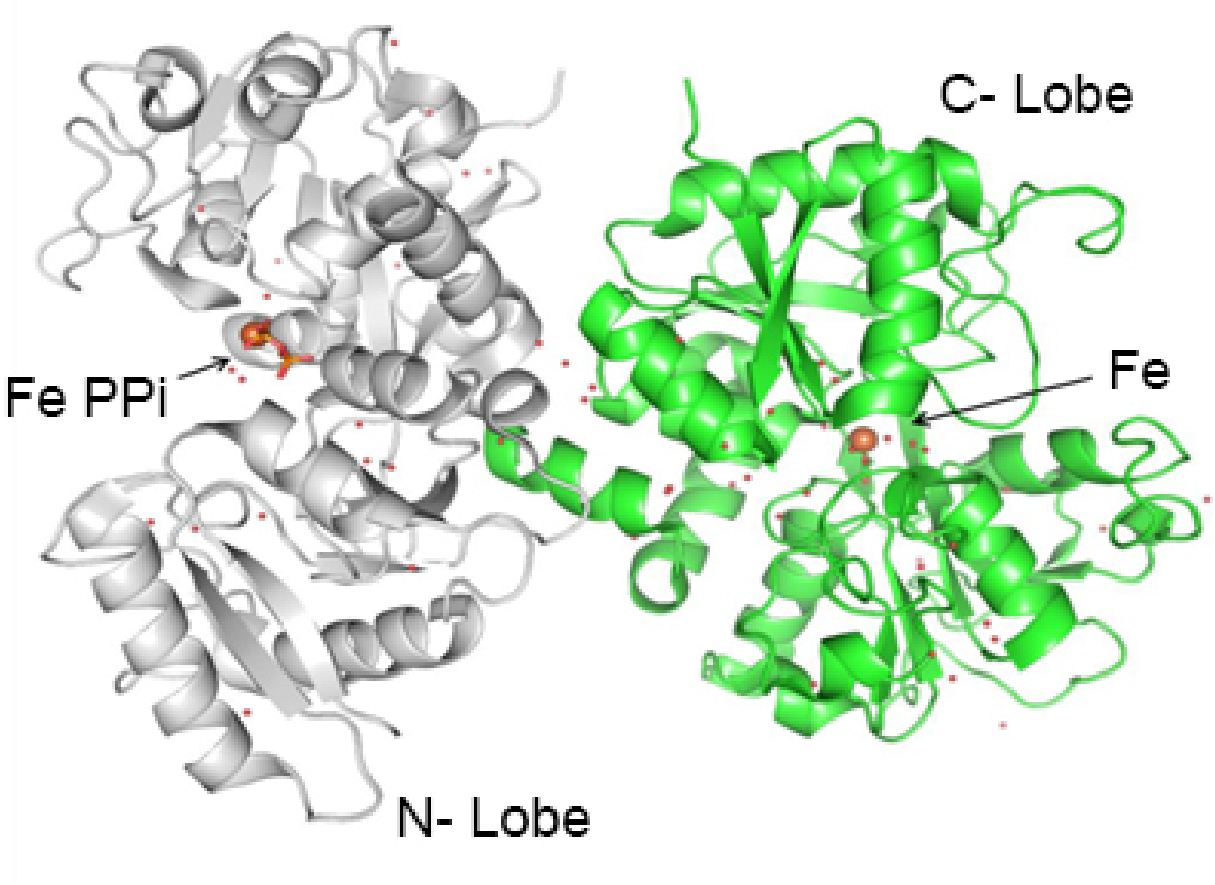
- **Leader in manufacturing and delivering high-quality hemodialysis products**
- **Servicing hemodialysis patients for 20 years providing standard of care therapies**
- **Developing innovative products that address unmet needs**

Triferic—Novel Structure

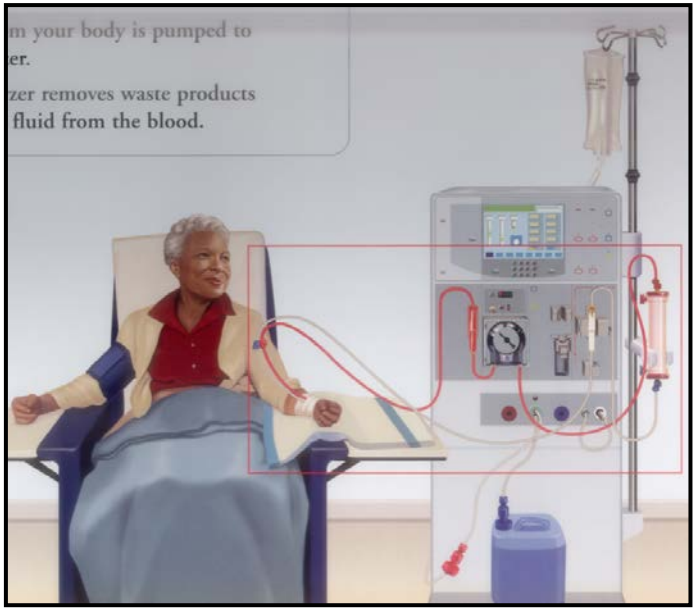


- **First and only parenteral iron compound**
  - Salt
  - Delivered via hemodialysate (water soluble)
- **No carbohydrate moiety**
- **Iron (III) tightly bound to pyrophosphate and citrate by coordinate covalent bonds**

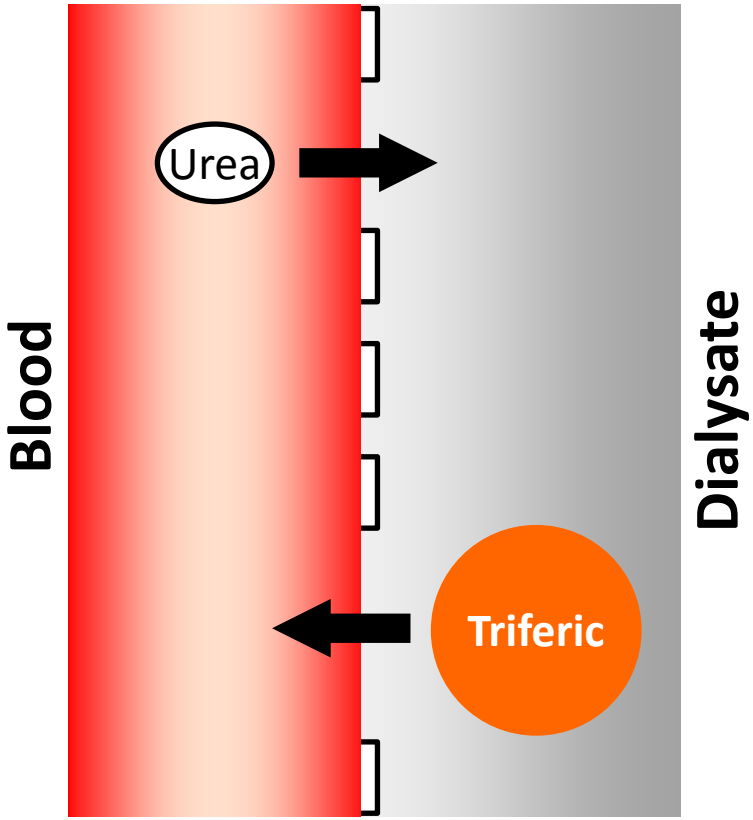
Triferic—Direct Iron Delivery to Transferrin Via Dialysate



Triferic Replaces Iron Loss Via Dialysis Solution



- Dialysis removes waste and excess fluids during the 3-4 hour treatment 3-4 times weekly
- Iron loss equivalent to an average of 5-7 mg per session occurs



- Triferic crosses the dialyzer membrane and replaces ~5-7 mg of iron during every dialysis treatment

Triferic—Maintenance Iron Therapy

- **Replaces iron losses while bypassing iron sequestration in the macrophages**
  - Maintains iron and hemoglobin levels
  - Does not increase in iron stores
  - Reduces need for erythropoiesis stimulating agents
- **Negligible non-transferrin bound iron**
  - No evidence of oxidative stress or inflammation
- **No complex carbohydrate shell**
  - No cases of anaphylaxis observed

Triferic—Clinical Overview

- **Successfully met primary endpoint in two adequate, identical, placebo-controlled Phase 3 trials**
  - Maintained hemoglobin, reticulocyte hemoglobin and serum ferritin
- **Successfully reduced ESA dosing in placebo-controlled Phase 2 study**
  - Significant 35% ESA reduction
- **Overall, adverse event profile similar to placebo**
  - 780 patient-years of exposure

Triferic—Proposed Indication

- **Iron replacement therapy indicated for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD-5HD) and to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain hemoglobin levels**

Presentation Agenda

Triferic Introduction	**Ajay Gupta, MBBS, MD** Rockwell Medical
Clinical Landscape	**Steven Fishbane, MD** North Shore LIJ Health System
Triferic Mechanism of Action	**Gary M. Brittenham, MD** Columbia University
Efficacy	**Raymond D. Pratt, MD, FACP** Rockwell Medical
Safety	**Vivian Lin, MD** Rockwell Medical
Clinical Perspective	**Steven Fishbane, MD** North Shore LIJ Health System

Additional Experts

John Dillberger, DVM, PhD
Toxicology Consultant
J. Dillberger, LLC

Linda LaMoreaux, MPH
Statistical Consultant
MMS Holdings, Inc.

Disease Background

Steven Fishbane, MD
Chief, Division of Kidney Diseases and Hypertension
North Shore University Hospital and Long Island Jewish Medical Center
Professor of Medicine, Hofstra North Shore-LIJ School of Medicine

Anemia in Hemodialysis Patients

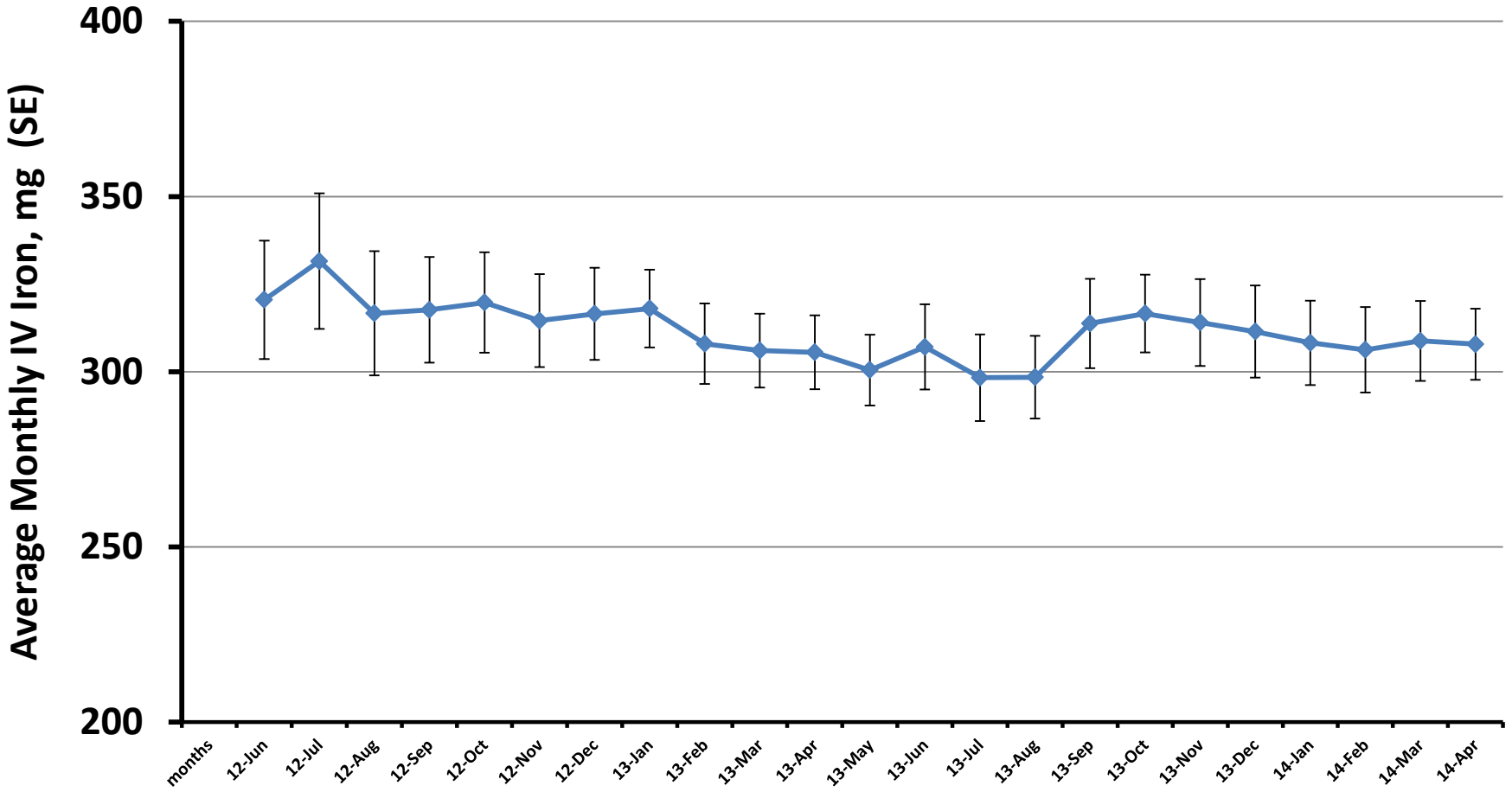
- **>20 million US adults have chronic kidney disease (CKD)[1]**
- **>400,000 hemodialysis-dependent CKD patients in US**
- **Majority of HD patients are anemic**
  - Impaired erythropoietin production
  - Chronic inflammation
  - Iron loss (~ 5-7 mg per session; ~ 1000 mg per year)
    - Retention in filter and tubing
    - Bleeding from vascular access
    - Routine blood draws
    - GI bleeding

1. Centers for Disease Control and Prevention (CDC). National Chronic Kidney Disease Fact Sheet: General Information and National Estimates on Chronic Kidney Disease in the United States, 2014. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2014;

What is Current Iron Management Practice in Hemodialysis Patients Today?

- **Repletion therapy in iron deficient patients:**
  - ~500-1000 mg over 5-10 dialysis treatments
  - IV iron approved
- **Maintenance therapy in iron replete patients:**
  - ~50-100 mg IV iron 1-4 times per month
  - IV iron not approved for this purpose in adults

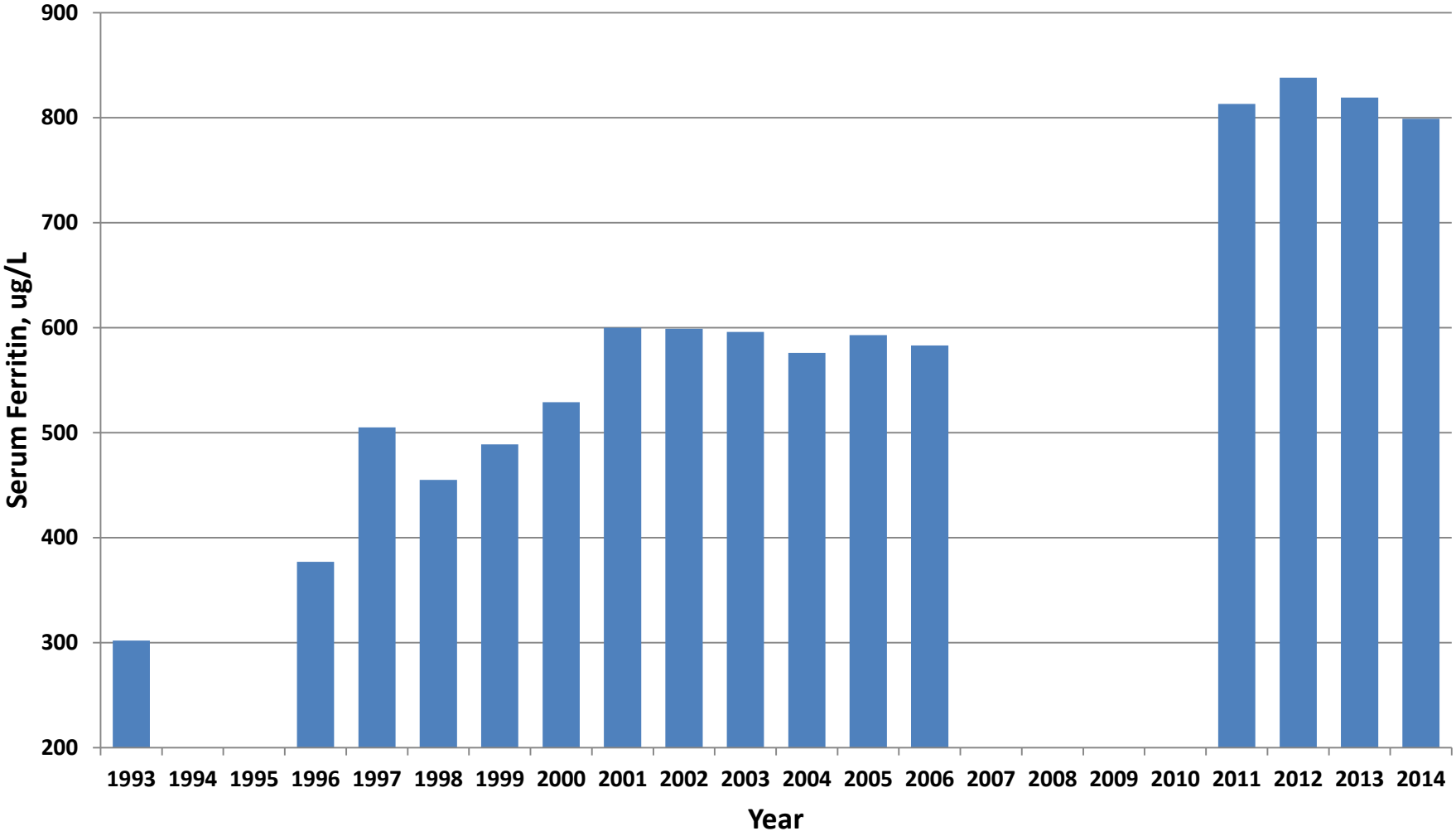
High Amounts of Monthly IV Iron Administered in US



MISMATCH: Iron lost (1 gram/year) and IV iron administered (3.6 grams/year)

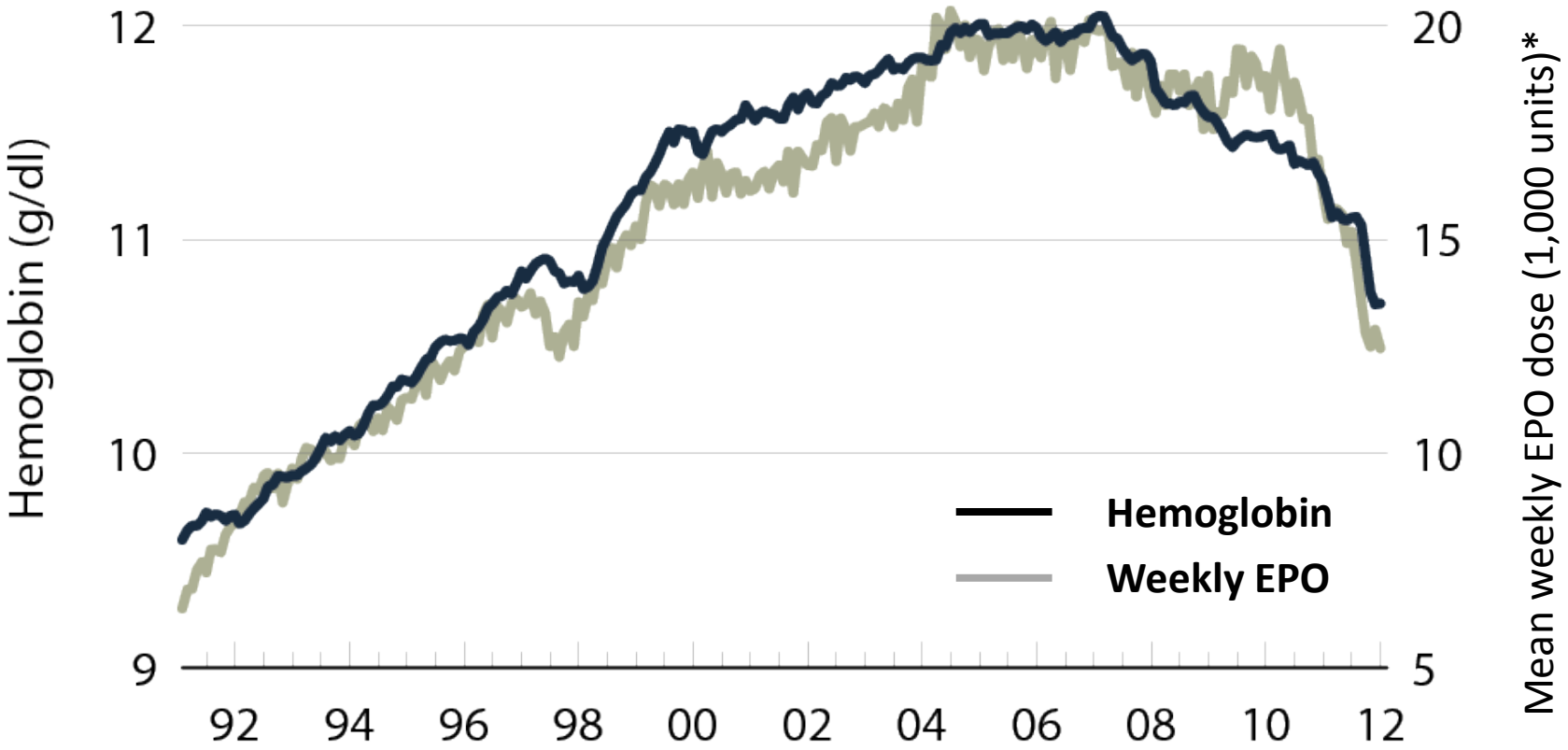
Data from US-DOPPS Practice Monitor, August 2014; http://www.dopps.org/DPM

Rise in Serum Ferritin Levels With IV Iron Use



Adapted from Fishbane et al Clin J Am Soc Nephrol 2014.

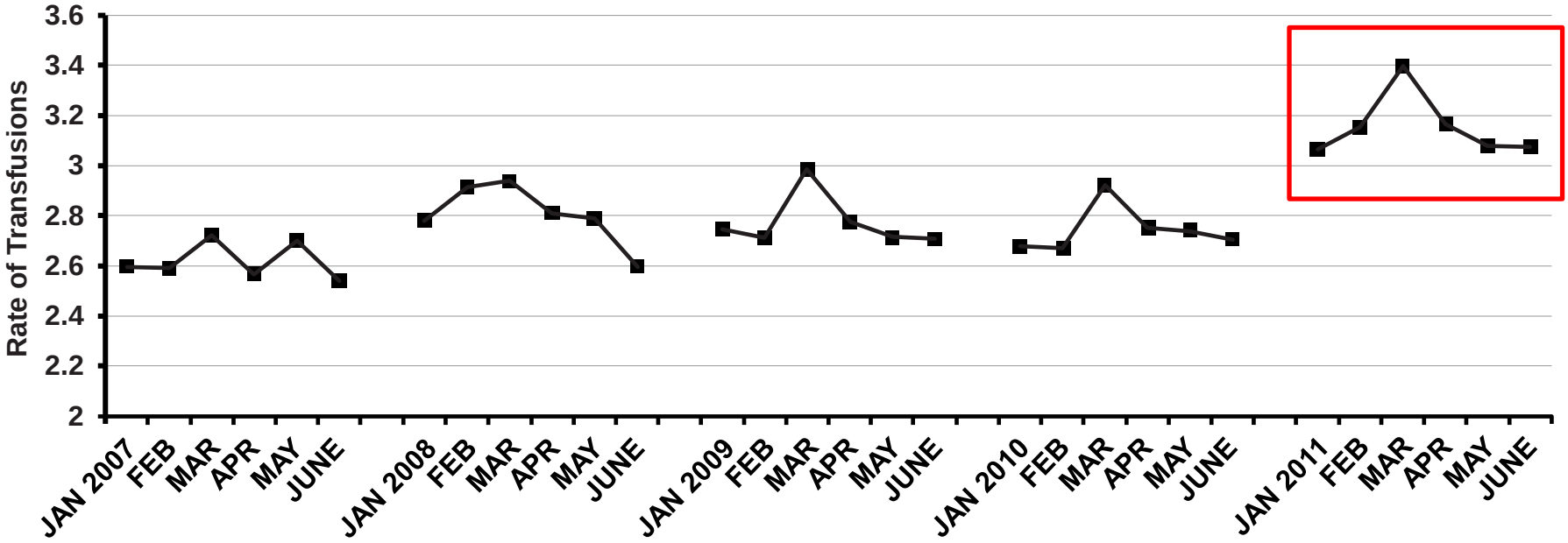
Weekly Mean Hemoglobin and EPO Dose in Hemodialysis Patients



*Averaged on a monthly basis.

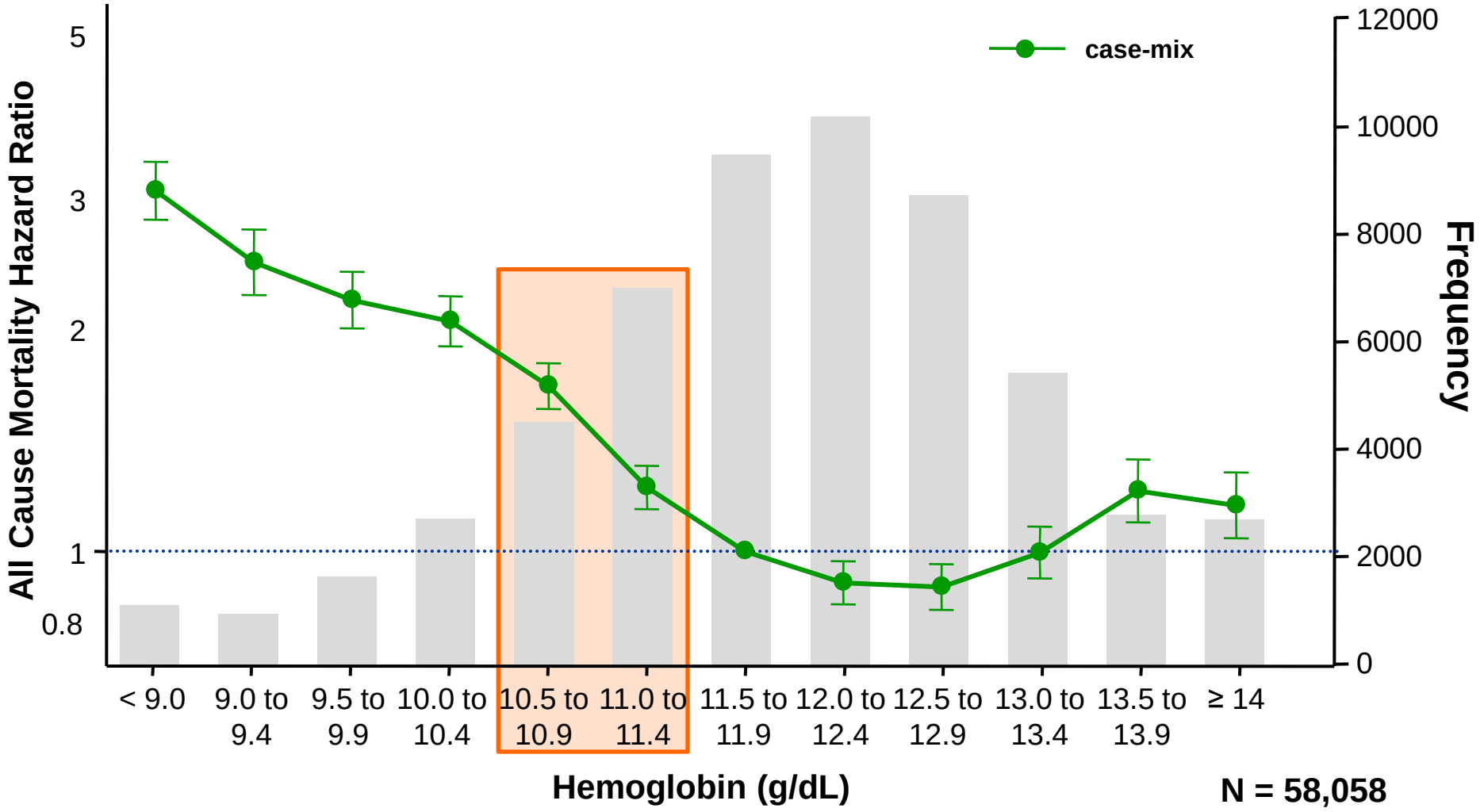
US Renal Data System, USRDS 2014 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2014.

Increase in Transfusions in Dialysis Patients With Hgb <10 g/dL



Reprinted from Collins et al. *Am J Kidney Dis*. 63(6):997-1006

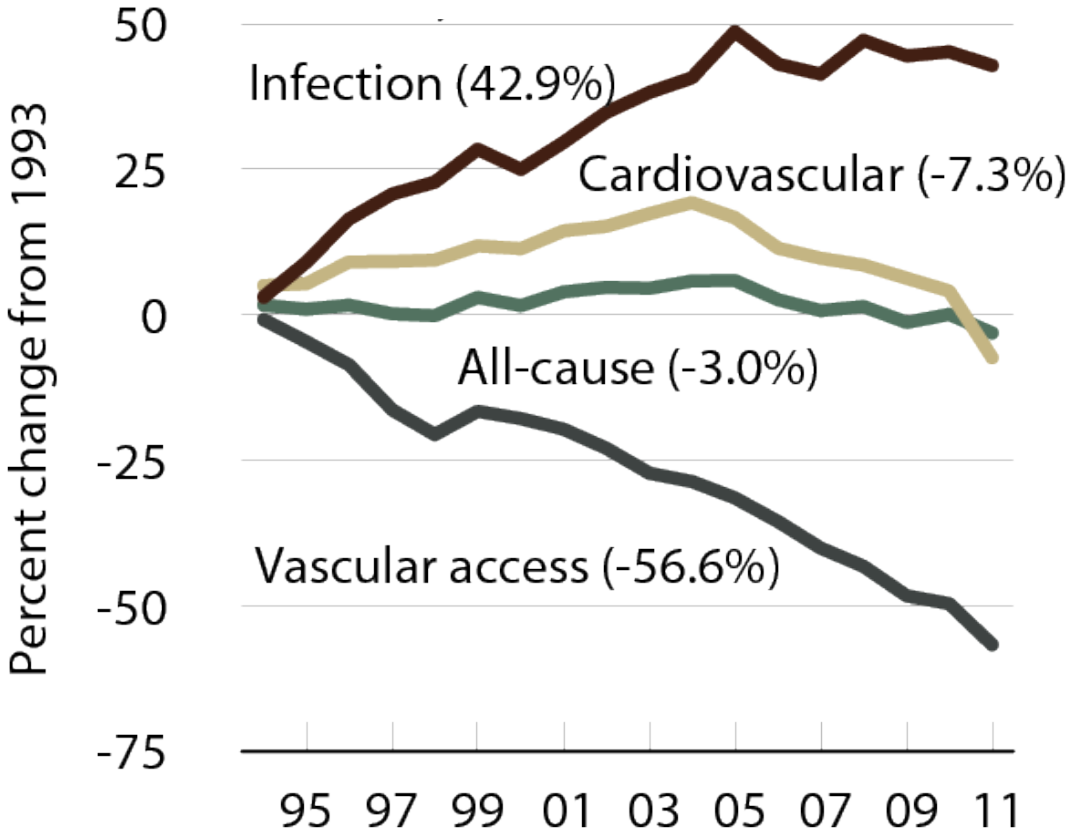
Hemoglobin Levels and All-Cause Death in Hemodialysis Patients



Adapted from Regidor et al. *J Am Soc Nephrol*. 17:1181-91; 2006

High Morbidity Burden in HD Patients

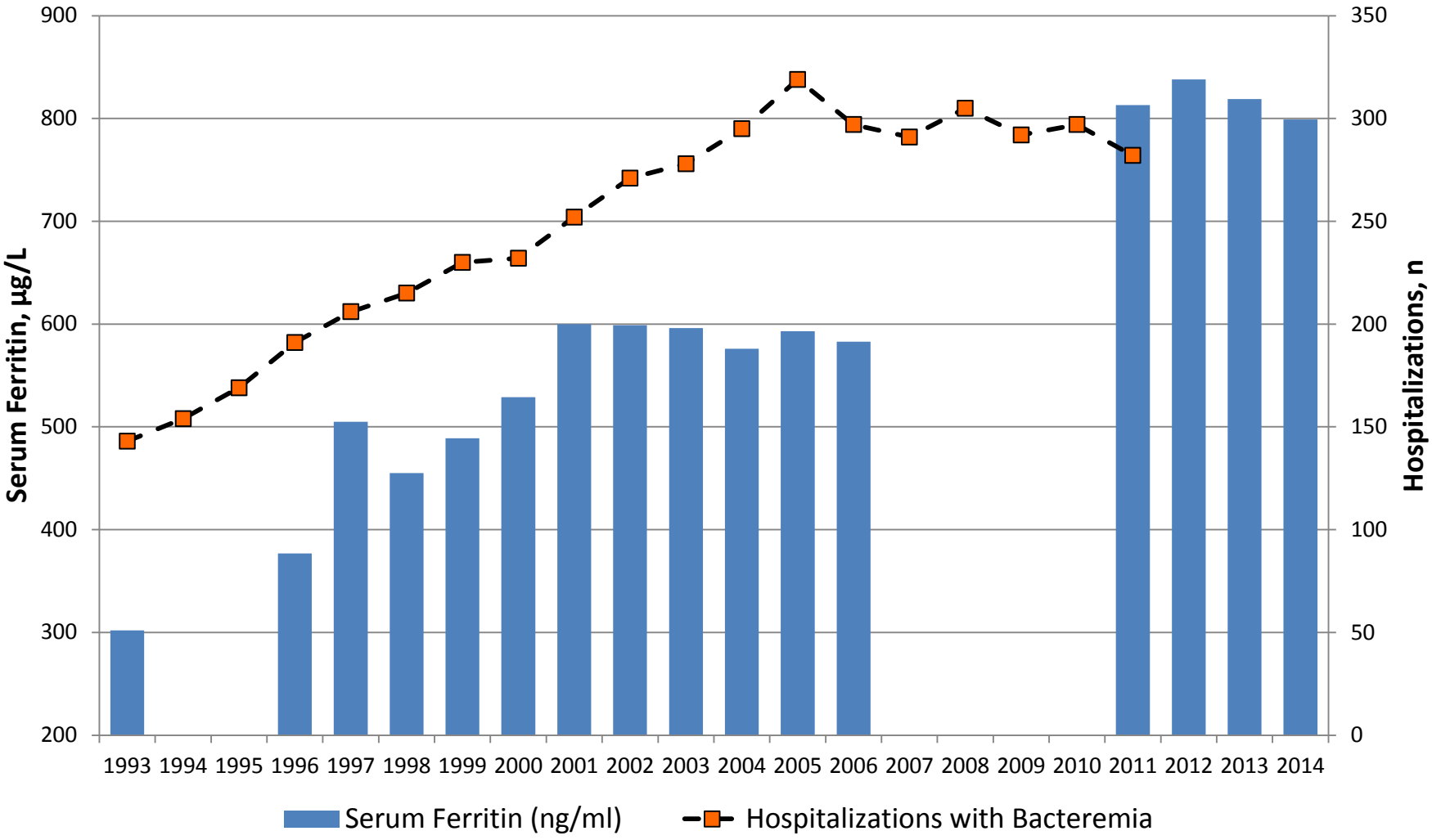
Hospitalization Rates: 1995 to 2011



Period prevalent ESRD patients. Adj: age/gender/race/primary diagnosis; ref: ESRD patients, 2010.

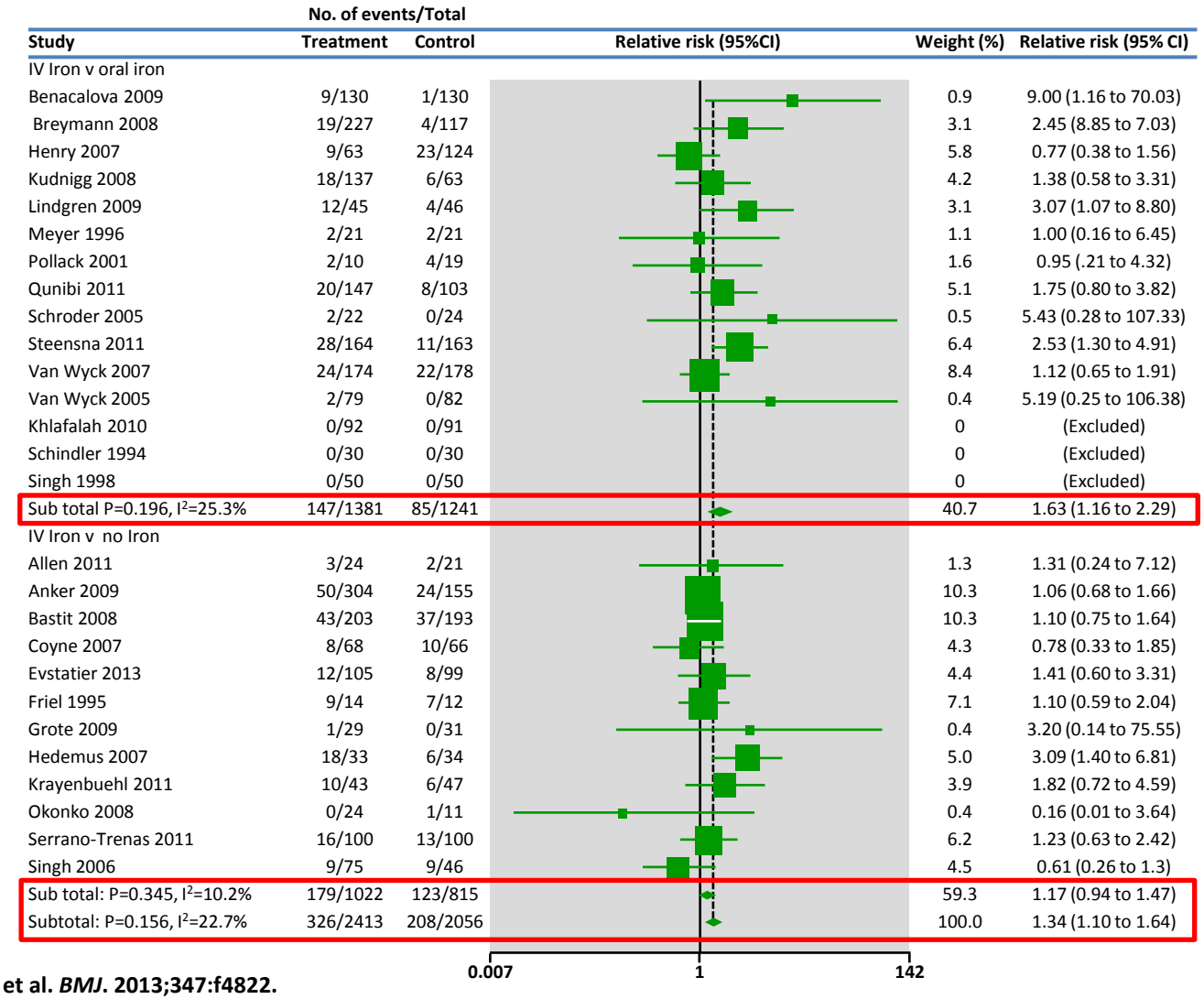
US Renal Data System, USRDS 2014 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2014.

Rise in Serum Ferritin Levels and Bacteremia



Reprinted from Fishbane et al Clin J Am Soc Nephrol 2014

IV Iron Associated With Increased Risk for Infections



Study	No. of events/Total: Treatment	Control	Weight (%)	Relative risk (95% CI)
IV Iron v oral iron				
Benacalova 2009	9/130	1/130	0.9	9.00 (1.16 to 70.03)
Breymann 2008	19/227	4/117	3.1	2.45 (8.85 to 7.03)
Henry 2007	9/63	23/124	5.8	0.77 (0.38 to 1.56)
Kudnigg 2008	18/137	6/63	4.2	1.38 (0.58 to 3.31)
Lindgren 2009	12/45	4/46	3.1	3.07 (1.07 to 8.80)
Meyer 1996	2/21	2/21	1.1	1.00 (0.16 to 6.45)
Pollack 2001	2/10	4/19	1.6	0.95 (.21 to 4.32)
Qunibi 2011	20/147	8/103	5.1	1.75 (0.80 to 3.82)
Schroder 2005	2/22	0/24	0.5	5.43 (0.28 to 107.33)
Steensna 2011	28/164	11/163	6.4	2.53 (1.30 to 4.91)
Van Wyck 2007	24/174	22/178	8.4	1.12 (0.65 to 1.91)
Van Wyck 2005	2/79	0/82	0.4	5.19 (0.25 to 106.38)
Khlafalah 2010	0/92	0/91	0	(Excluded)
Schindler 1994	0/30	0/30	0	(Excluded)
Singh 1998	0/50	0/50	0	(Excluded)
Sub total P=0.196, I^2=25.3%	147/1381	85/1241	40.7	1.63 (1.16 to 2.29)
IV Iron v no Iron				
Allen 2011	3/24	2/21	1.3	1.31 (0.24 to 7.12)
Anker 2009	50/304	24/155	10.3	1.06 (0.68 to 1.66)
Bastit 2008	43/203	37/193	10.3	1.10 (0.75 to 1.64)
Coyne 2007	8/68	10/66	4.3	0.78 (0.33 to 1.85)
Evstatier 2013	12/105	8/99	4.4	1.41 (0.60 to 3.31)
Friel 1995	9/14	7/12	7.1	1.10 (0.59 to 2.04)
Grote 2009	1/29	0/31	0.4	3.20 (0.14 to 75.55)
Hedemus 2007	18/33	6/34	5.0	3.09 (1.40 to 6.81)
Krayenbuehl 2011	10/43	6/47	3.9	1.82 (0.72 to 4.59)
Okonko 2008	0/24	1/11	0.4	0.16 (0.01 to 3.64)
Serrano-Trenas 2011	16/100	13/100	6.2	1.23 (0.63 to 2.42)
Singh 2006	9/75	9/46	4.5	0.61 (0.26 to 1.3)
Sub total: P=0.345, I^2=10.2%	179/1022	123/815	59.3	1.17 (0.94 to 1.47)
Subtotal: P=0.156, I^2=22.7%	326/2413	208/2056	100.0	1.34 (1.10 to 1.64)

RR= 1.63

RR= 1.17

RR= 1.34

Reprinted from Litton E, et al. *BMJ*. 2013;347:f4822.

Unmet Needs in Iron Management for Hemodialysis Patients

- **Without iron replacement, hemoglobin levels decline**
  - Associated risk of mortality and transfusions
  - Higher ESA doses
- **Current IV iron administration may not be an ideal maintenance therapy**
  - High ferritin levels
  - Increased risk for infections
- **Iron remains a basic health need for dialysis patients**

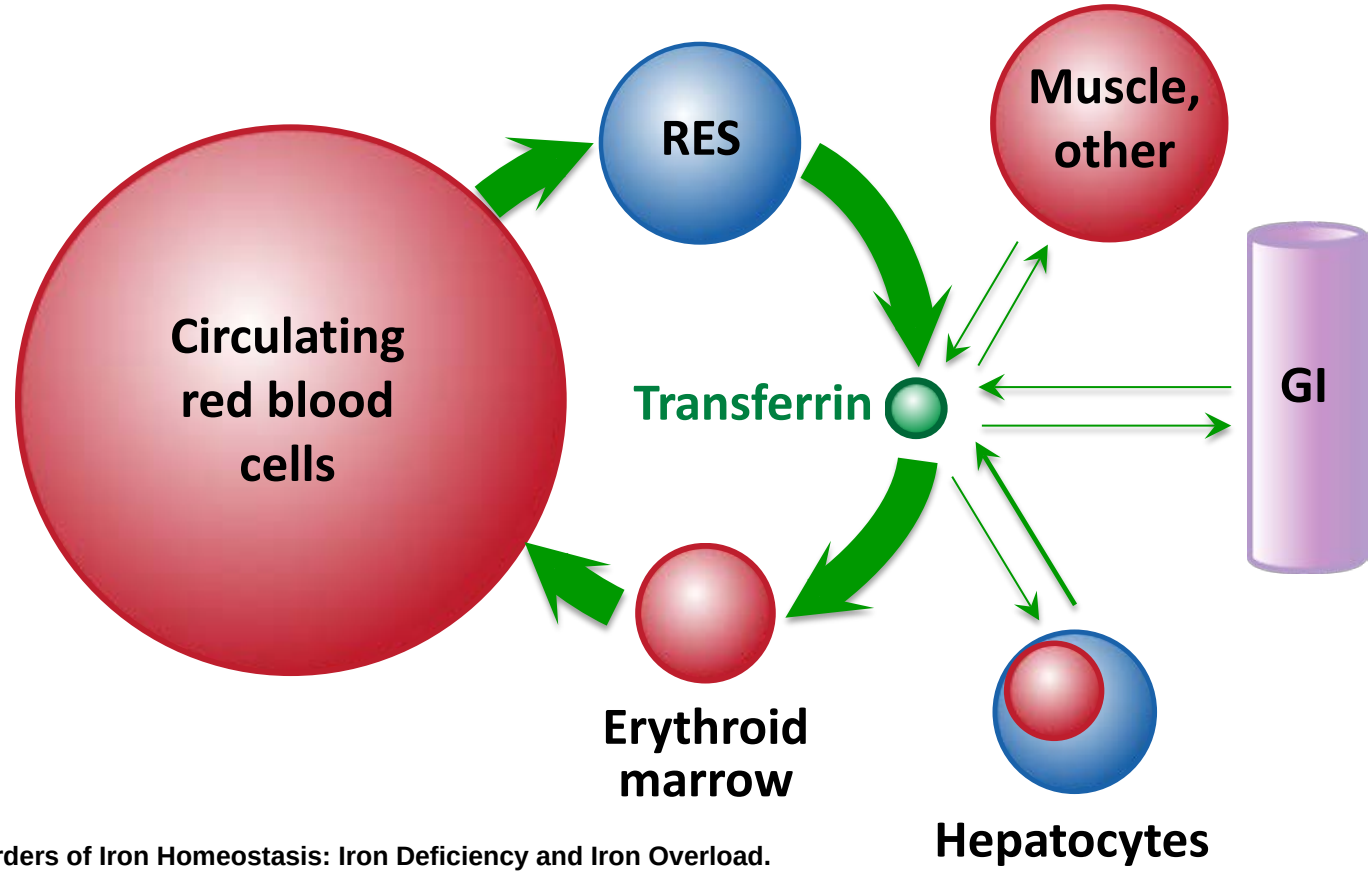
Triferic:
Mechanism of Replacement of Iron Losses in Patients Receiving Chronic Hemodialysis

Gary M. Brittenham, MD

James A. Wolff Professor of Pediatrics and Professor of Medicine

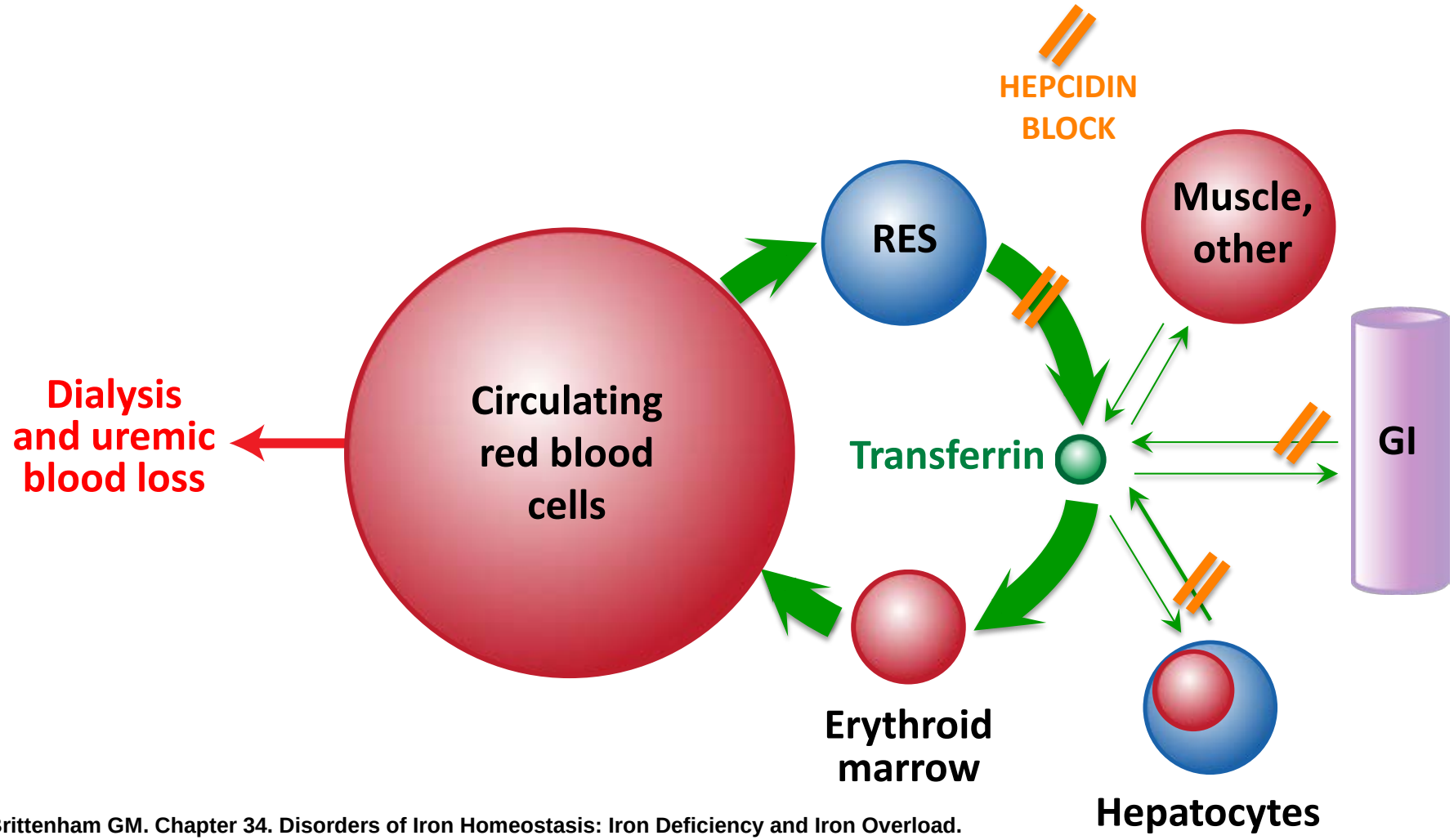
Columbia University

Recycling of Iron for Red Blood Cell Production in Healthy Individuals



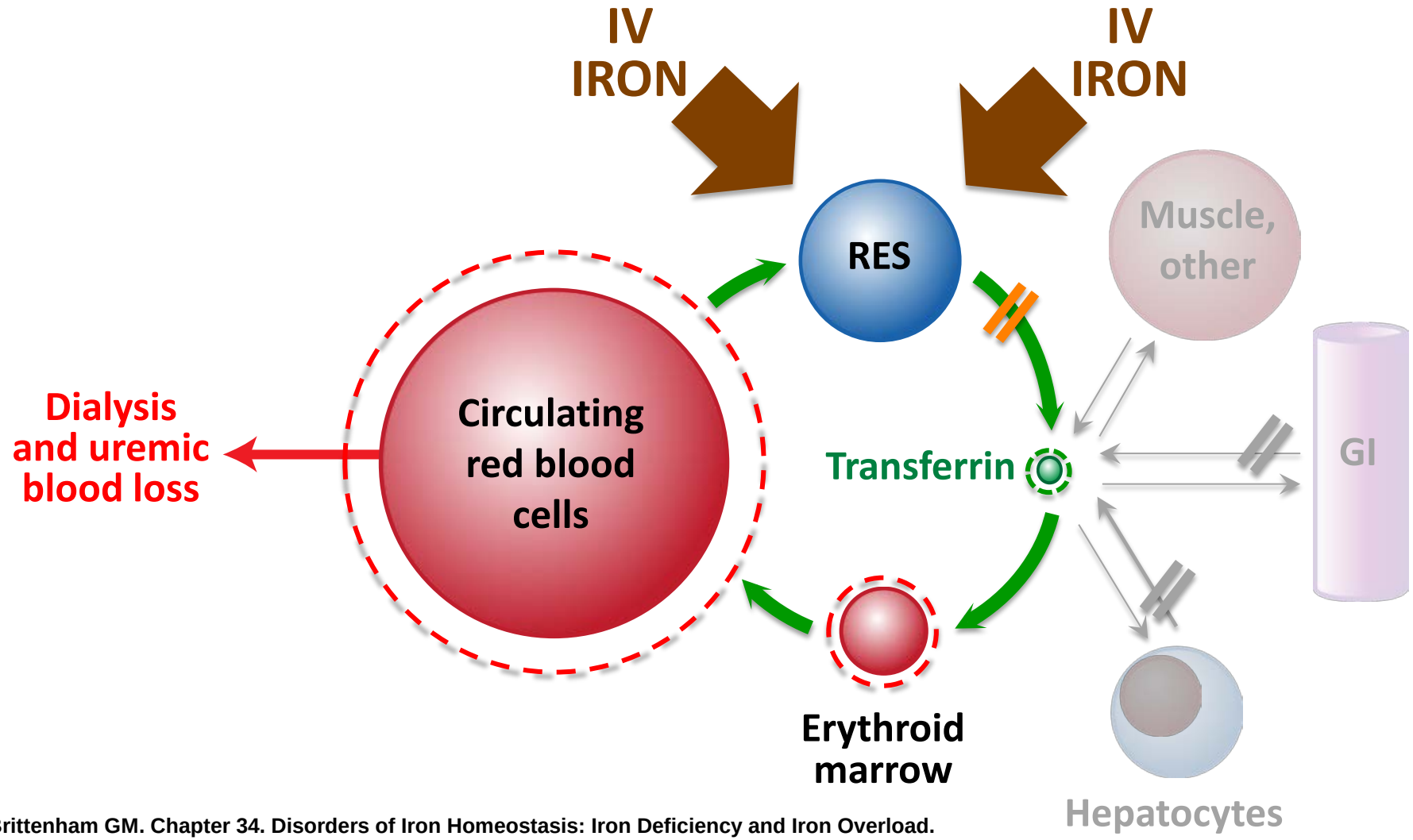
Brittenham GM. Chapter 34. Disorders of Iron Homeostasis: Iron Deficiency and Iron Overload. In Hoffman R. and Furie B. eds. Hematology: Basic Principles and Practice. Saunders, 6th ed., 2013.

With Inflammation in Hemodialysis, Increased Hepcidin Blocks Recycling of IV Iron



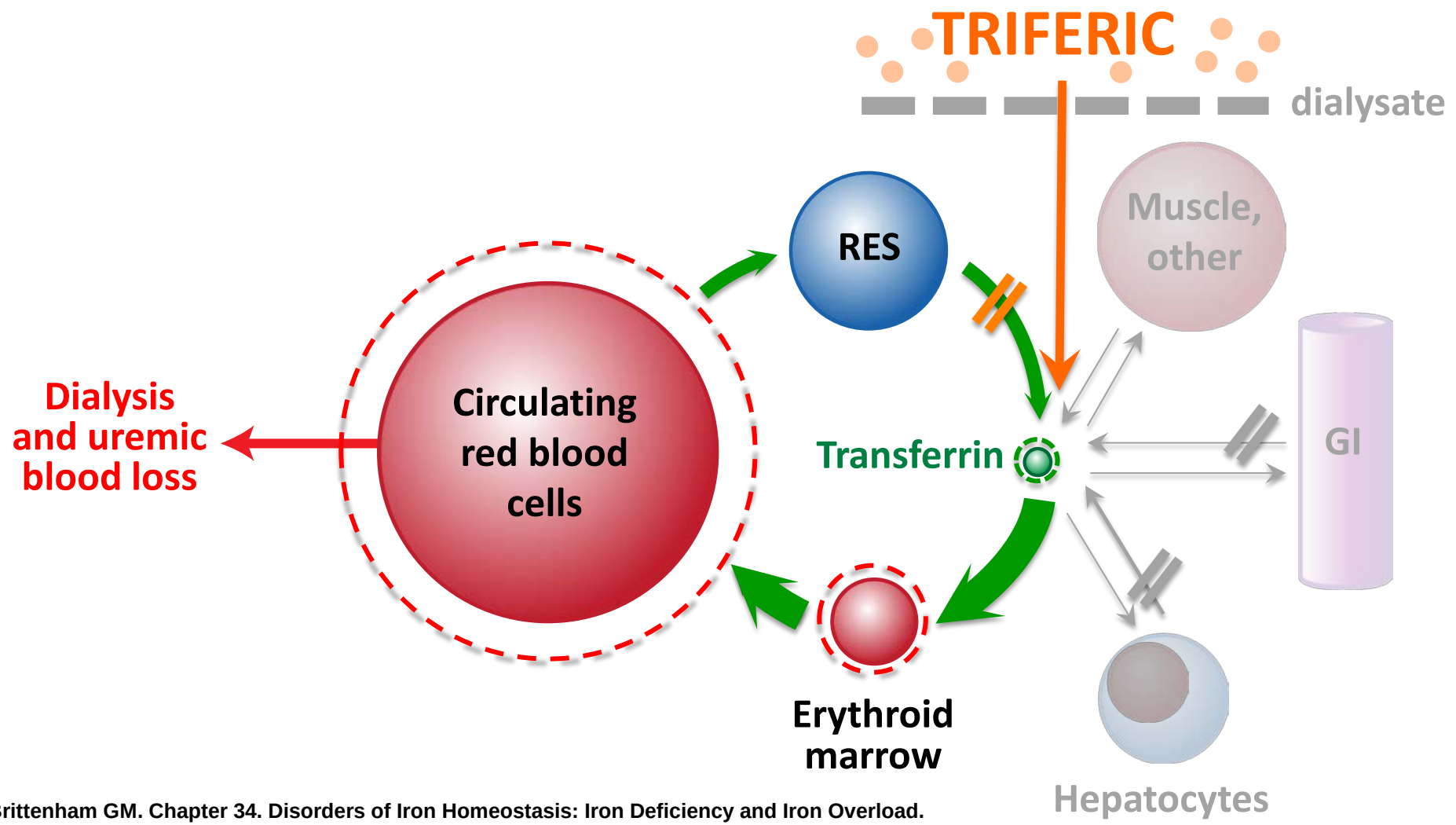
Brittenham GM. Chapter 34. Disorders of Iron Homeostasis: Iron Deficiency and Iron Overload. In Hoffman R. and Furie B. eds. Hematology: Basic Principles and Practice. Saunders, 6th ed., 2013.

In Hemodialysis, Increased Hepcidin Blocks Utilization of IV Iron



Brittenham GM. Chapter 34. Disorders of Iron Homeostasis: Iron Deficiency and Iron Overload. In Hoffman R. and Furie B. eds. Hematology: Basic Principles and Practice. Saunders, 6th ed., 2013.

Triferic Replaces Iron Losses by Directly Donating Iron to Transferrin, Bypassing the Hepcidin Block



Brittenham GM. Chapter 34. Disorders of Iron Homeostasis: Iron Deficiency and Iron Overload. In Hoffman R. and Furie B. eds. Hematology: Basic Principles and Practice. Saunders, 6th ed., 2013.

Triferic Clinical Development Program and Efficacy Results

Raymond D. Pratt, MD, FACP

Chief Medical Officer
Rockwell Medical, Inc.

Triferic Phase 2/3 Studies in CKD-HD

Phase 2/3 Blinded, Controlled Studies	Triferic	Placebo
NIH-1 (after 02 DEC 2010 protocol)	54	49
SFP-4-RC	149	151
SFP-5-RC	143	145
Total	346	345

Other Controlled Studies	Triferic	Placebo
SFP-1, SFP-2, SFP-3, NIH-1*	152	43
SFP-6-RC (safety study)	693	686
Total	845	729

Uncontrolled OL Extension Studies	Re-exposure to Triferic	New exposure to Triferic
SFP-4-OL	98	107
SFP-5-OL	101	113
SFP-6-OL	309	0
Total	508	220

Total Triferic patients N = 1411

***Before 02 DEC 2010 protocol**

Patient Population

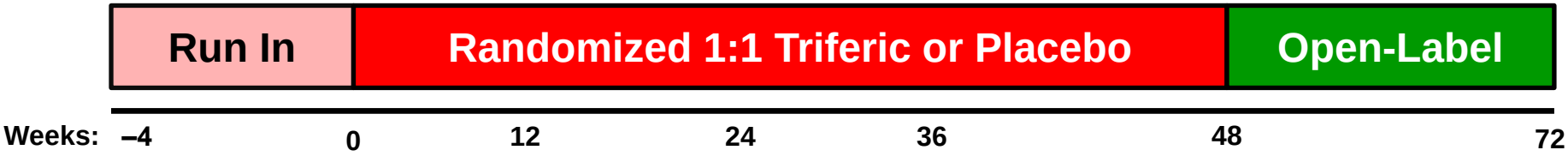
- **Adult patients undergoing chronic HD**
- **Mean Hgb of ≥9.5 to ≤11.5 g/dL**
- **TSAT of ≥15% to ≤40%**
- **Mean serum ferritin of ≥200 to ≤800 µg/L**
- **Stable prescribed ESA doses during the 4 weeks prior to randomization**
  - Epoetin ≤45,000 U/week
  - Darbepoetin ≤200 µg/week

Study Design

- **Maintenance design**
  - Start with iron replete patients
  - Placebo controlled study with ESA held constant
  - No supplemental iron
  - Maintain Hgb at baseline levels while placebo declines due to iron restricted erythropoiesis
  - Effect will be constrained by the limits on Hgb which require a change in anemia management
- **Hgb concentration maintained between 9-12 g/dL**
  - ESA warnings to use lowest dose to avoid transfusion

Study Design-2

SFP-4 and SFP-5



Randomized Stage:

- No change in ESA dose allowed
- No oral or IV iron supplementation

Triferic 2 µM (110 µg/L) Iron

Patients completed randomized treatment if:

- Hgb <9 or >12 g/dL for 2 weeks
- Serum ferritin <100 µg/L for 2 weeks
- Hgb >11.5 g/dL AND Hgb increases by ≥1.0 g/dL
- 48 weeks total randomized treatment

Placebo

Patients who complete Randomized Stage

- Allowed to continue in OL stage for up to 18 months treatment

Study Endpoints

SFP-4 and SFP-5

Primary Endpoint:

- **Mean change from baseline in Hgb during the last one-sixth (1/6) of the randomized treatment period**

Select Secondary Endpoints:

- **Mean change in reticulocyte hemoglobin from baseline every 4 weeks**
- **Mean change in Hgb from baseline every 4 weeks**
- **Mean percentage change in ferritin from baseline every 4 weeks**
- **Mean change from pre-dialysis to post-dialysis in serum iron, UIBC and TSAT over the course of the randomized treatment period**

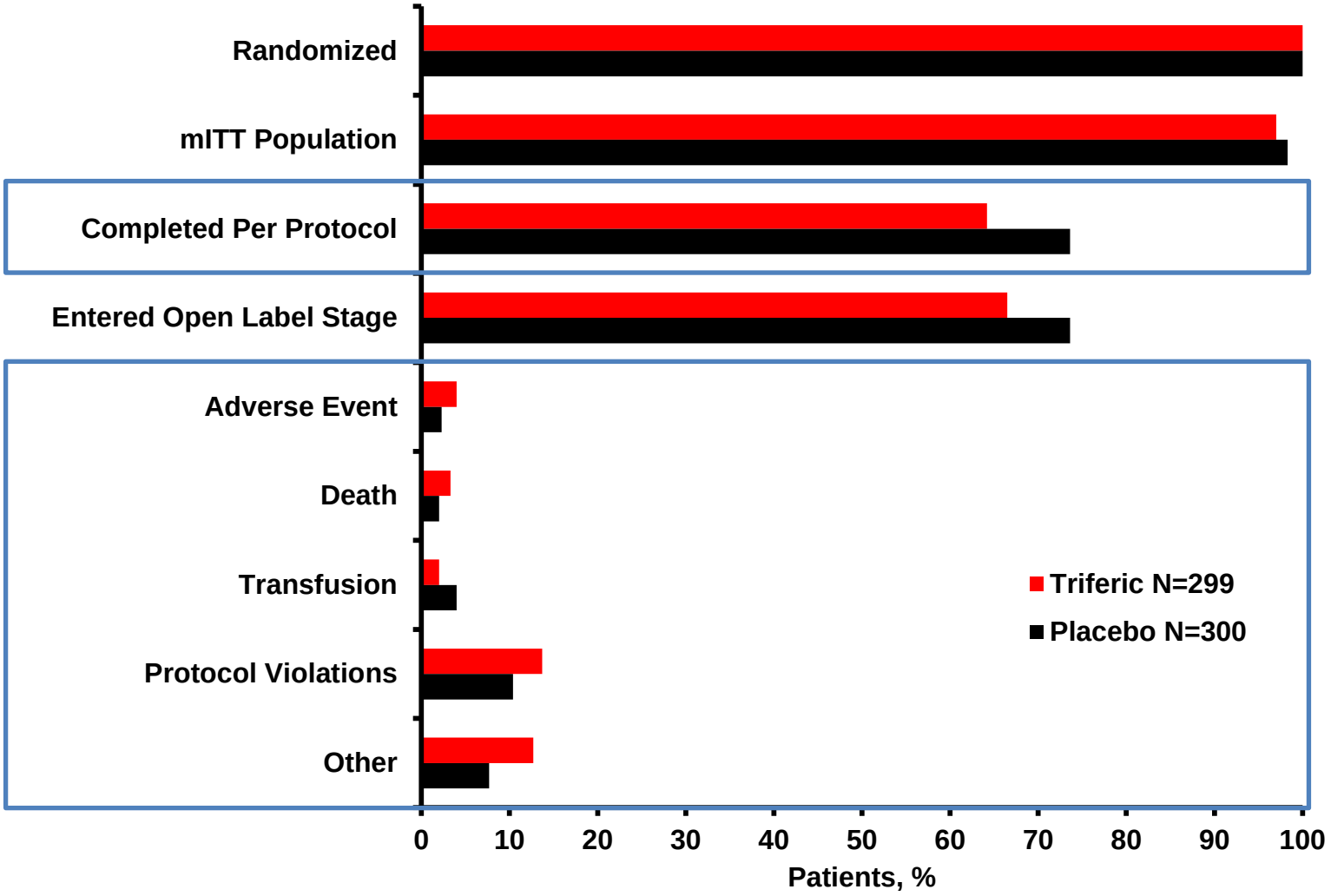
Statistical Considerations

SFP-4 and SFP-5

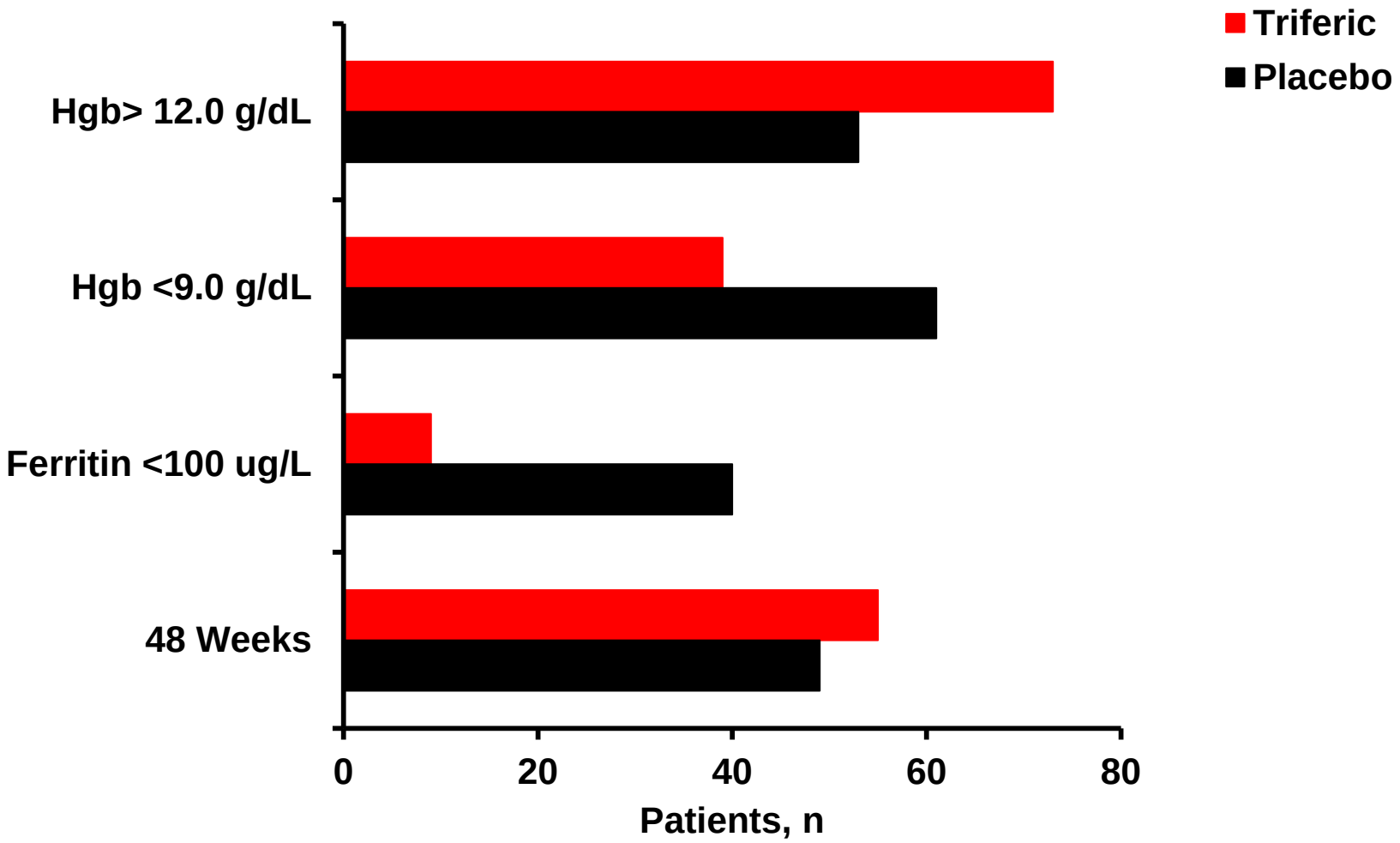
- **Primary endpoint**
  - Last 1/6th of the treatment period
  - ANCOVA model
  - Modified-ITT population
- **Prespecified sensitivity analysis**
  - ITT population
  - Efficacy evaluable population
  - MMRM
- **Post-hoc analysis**
  - Multiple imputation

Patient Disposition

SFP-4 and SFP-5 Pooled



Completers According to Prespecified Protocol



Patient Demographics

SFP-4 and SFP-5 Pooled

	Triferic N = 290	Placebo N = 295
Age (years)		
Median	59.0	60.0
Gender, n (%)		
Male	177 (61.0)	195 (66.1)
Race, n (%)		
Black or African American	111 (38.3)	99 (33.6)
White	153 (52.8)	165 (55.9)
Undergoing hemodialysis >1 year, n (%)	253 (87.2)	259 (87.7)
Heart failure	77 (26.6)	63 (21.4)
Diabetes	174 (60.0)	171 (58.0)
Whole blood hemoglobin, g/dL (SD)	10.96 (0.60)	10.92 (0.63)
Ferritin, µg/L (SD)	511.5 (197.39)	495.9 (206.0)

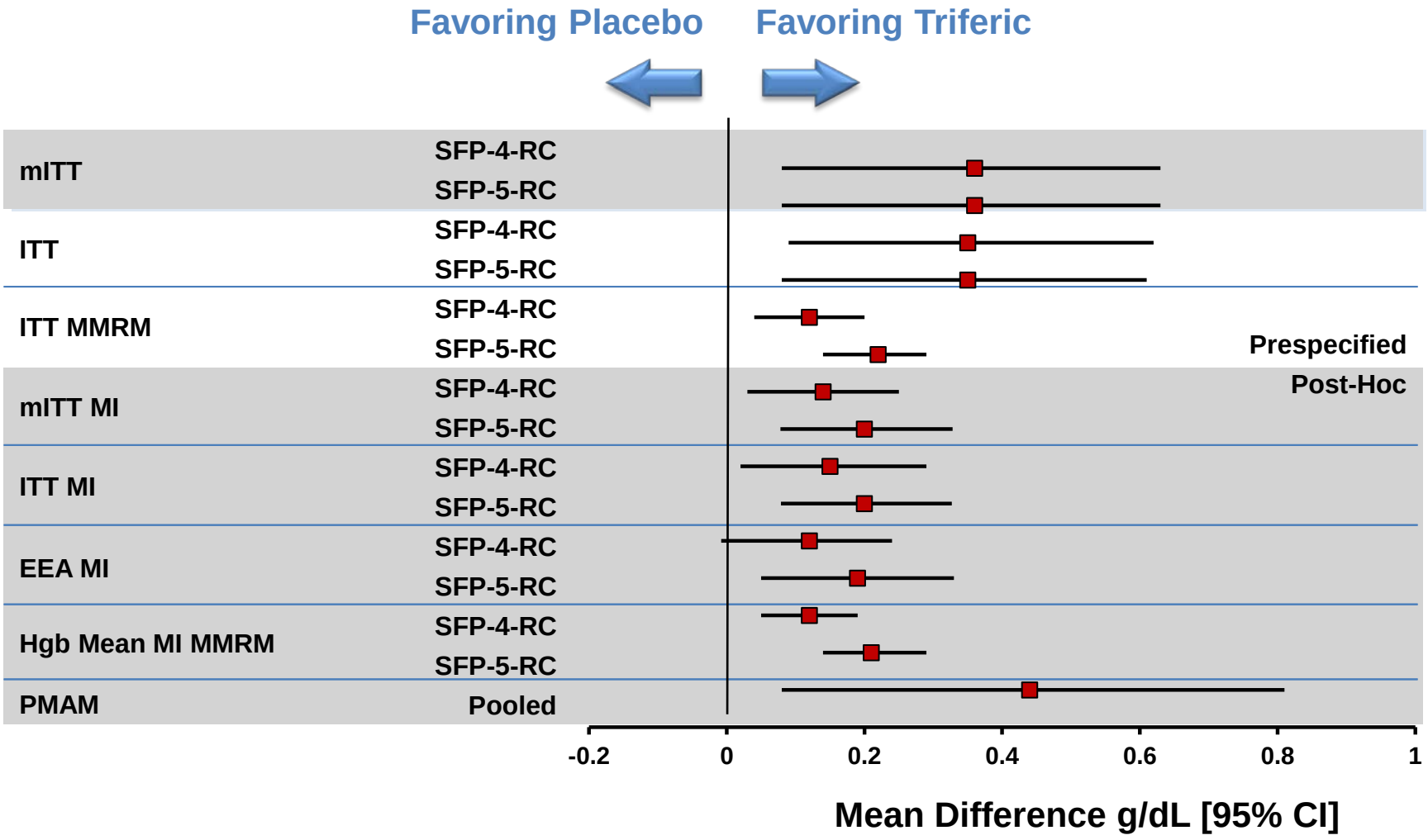
Triferic Maintains Hemoglobin Concentration

SFP-4 and SFP-5 (Primary Endpoint)

	SFP-4-RC		SFP-5-RC	
	Triferic N = 148	Placebo N = 151	Triferic N = 142	Placebo N = 144
Baseline Hgb, mean g/dL (SD)	10.96 (0.591)	10.90 (0.636)	10.96 (0.609)	10.93 (0.625)
EoT Hgb mean g/dL	10.9 (1.25)	10.5 (1.35)	10.9 (1.38)	10.5 (1.33)
Mean change from baseline g/dL (SE)	0.06 (0.115)	-0.30 (0.114)	-0.05 (0.108)	-0.40 (0.109)
Mean difference g/dL (SE)	**0.36** (0.140)		**0.36** (0.139)	
P-value	**0.011**		**0.011**	
(95% CI)	(0.08, 0.63)		(0.08, 0.63)	

Sensitivity Analysis

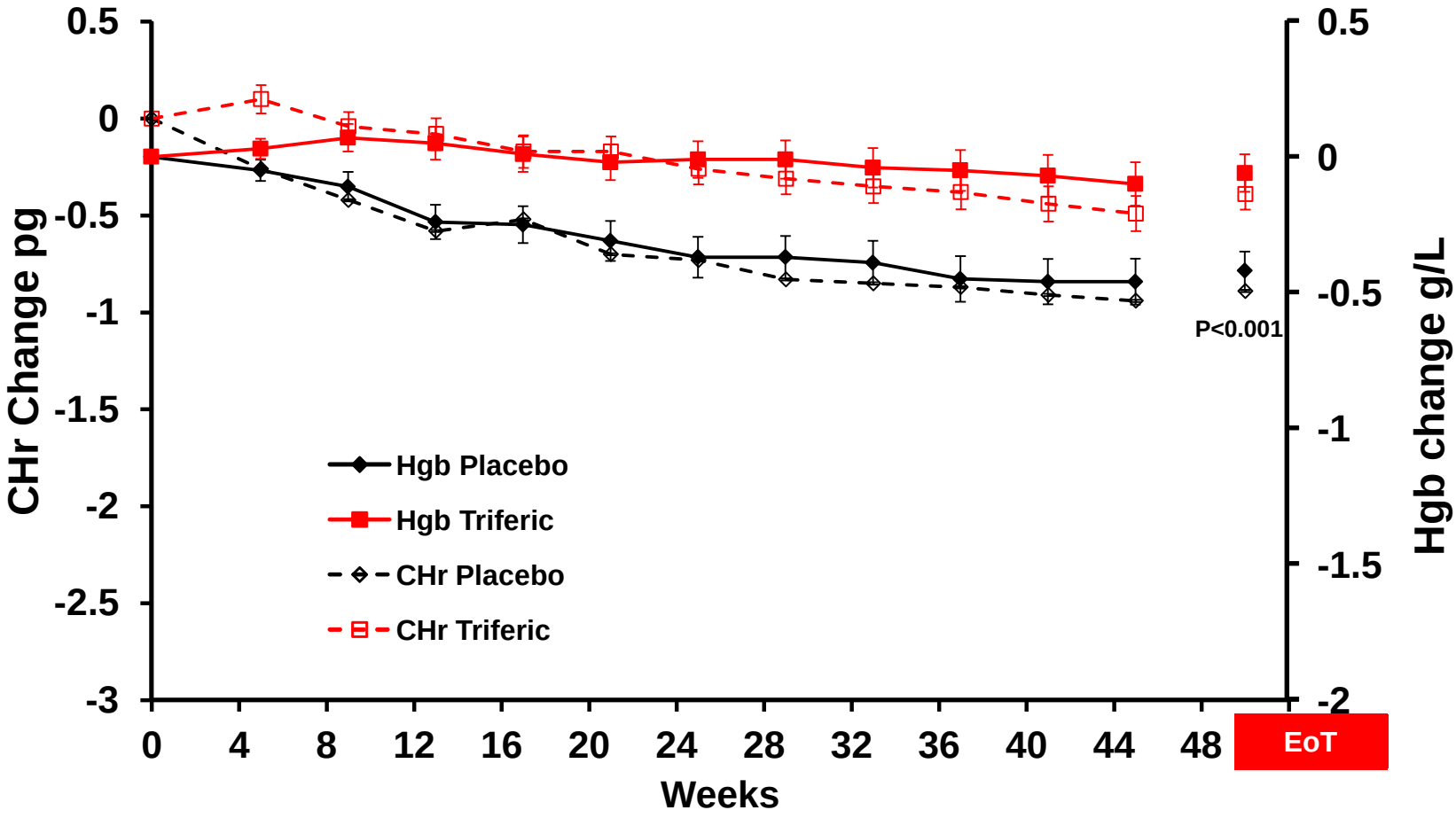
SFP-4 and SFP-5



MMRM, mixed model repeat measures; MI, multiple imputations; EEA, efficacy evaluable; PMAM, protocol-mandated change in anemia management.

Triferic Maintains Hemoglobin and Reticulocyte Hemoglobin

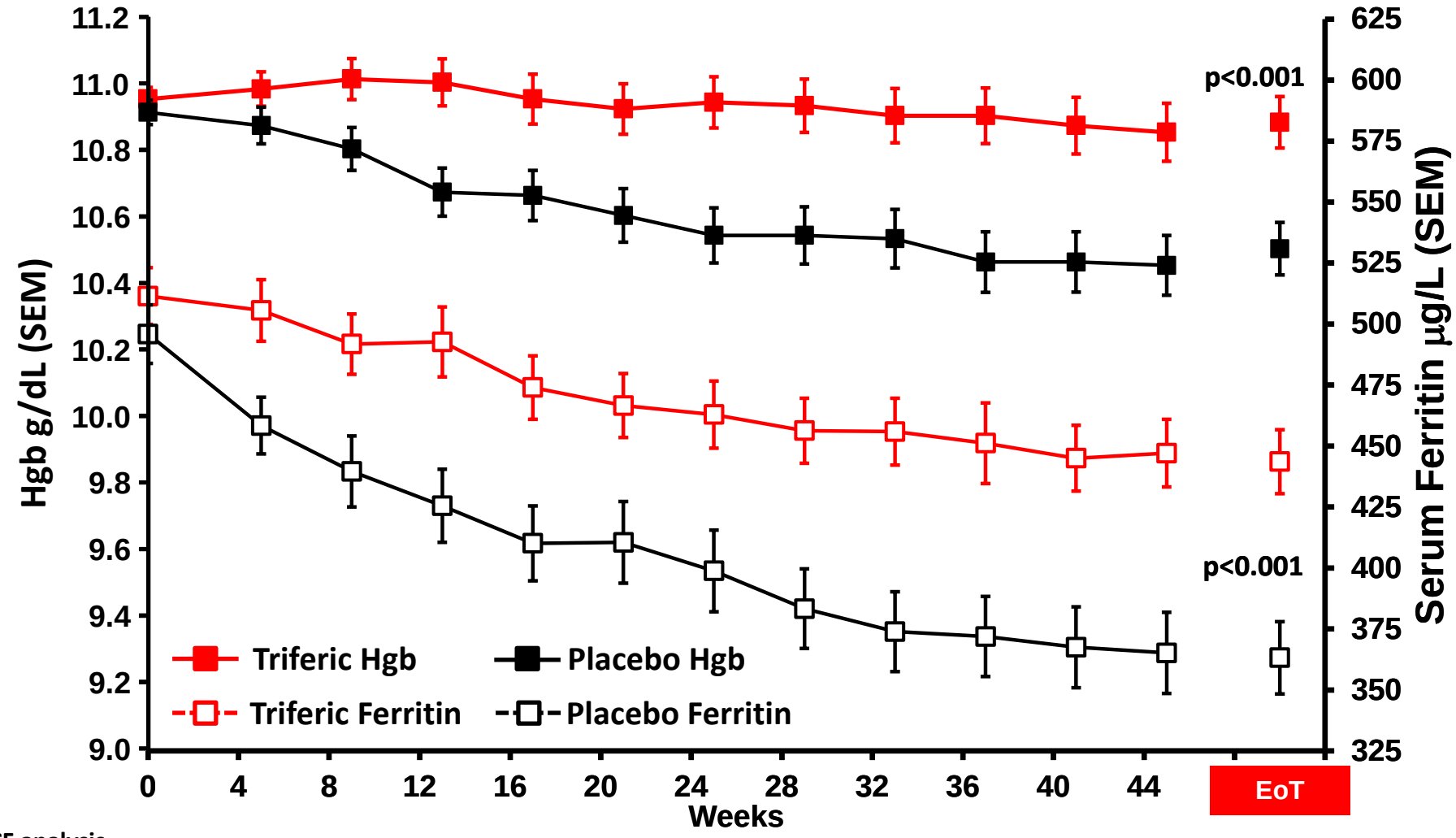
SFP-4 and SFP-5 Pooled



LOCF analysis

Triferic Maintains Hemoglobin Without increasing Iron Stores

SFP-4 and SFP-5 Pooled



LOCF analysis

NIH-1 Study

Supportive Study

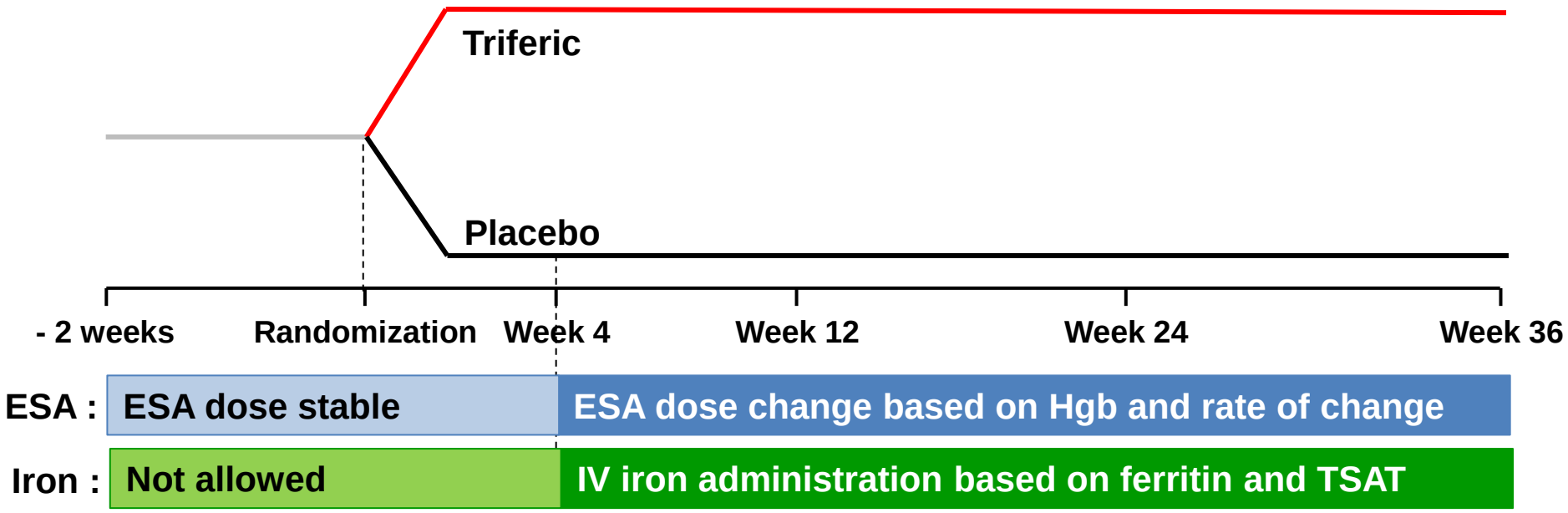
Primary Study Objectives

NIH-1

- **Efficacy of Triferic**
  - Determine if Triferic spares the need for ESAs while maintaining iron balance
    - Including hyporesponders
      - Defined as ESA dose >13,000 epoetin U/wk

Study Design

NIH-1



- Randomization stratified by ESA dose (≤13K U/wk and >13K U/wk)
- Independent, blinded Central Anemia Management Group for ESA prescription

Triferic Reduced ESA Use

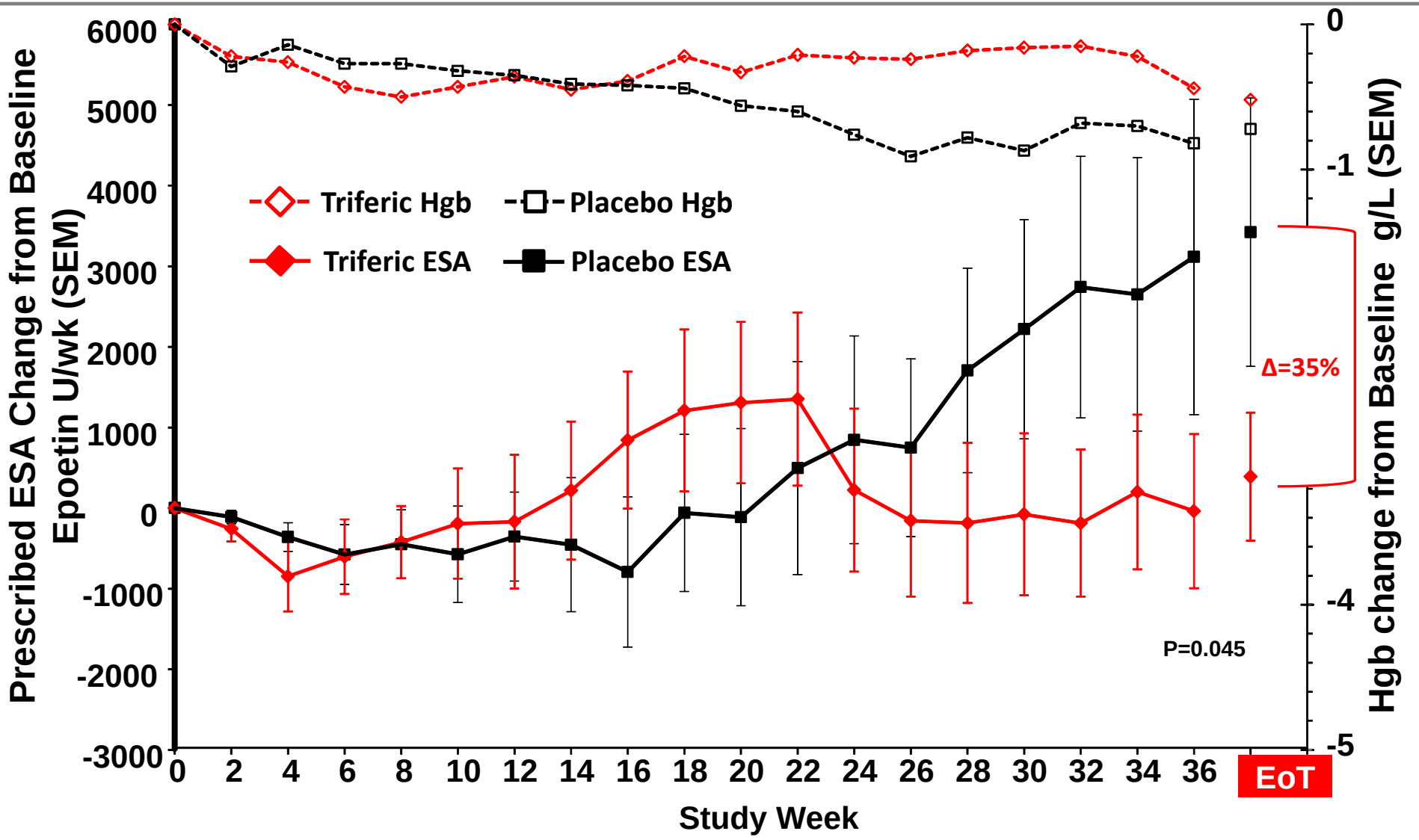
NIH-1 (Primary Endpoint)

Prescribed ESA dose*, U/wk	Triferic N = 52	Placebo N = 51
Baseline dose (SD)	9483 (5414)	9206 (5500)
Mean change from baseline, % (SE)	4.9 (12.07)	39.8 (12.18)
Mean difference between arms, % (SE)	**-35.0** (17.20)	
P-value	**0.045**	
(95% CI)	(-69.1, -0.8)	

*All ESA doses for the last 2 weeks on treatment were included.

Hemoglobin and ESA Change From Baseline

NIH-1



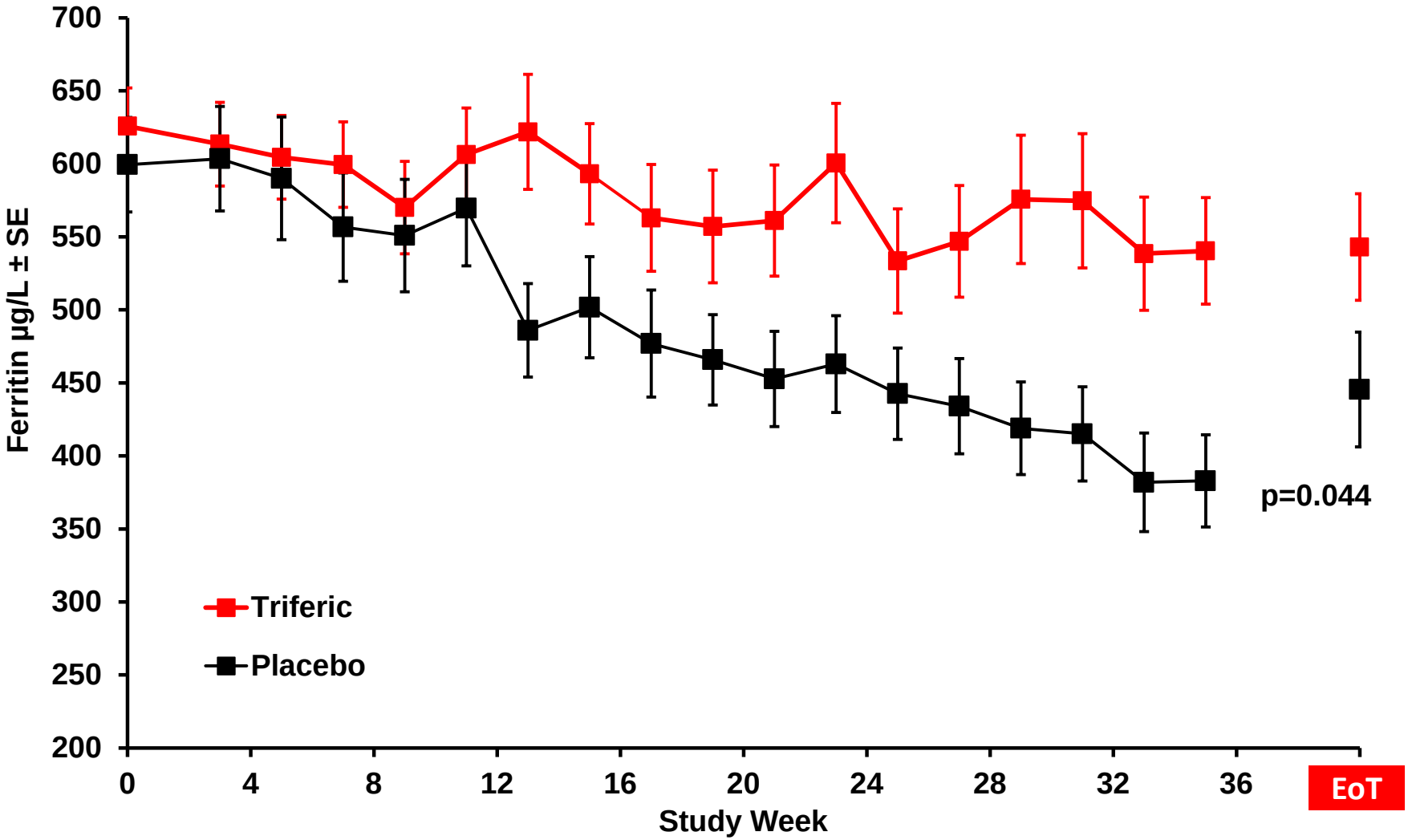
Efficacy in ESA Hyporesponders

NIH-1

	ESA ≤13K U/wk N = 80		ESA >13K U/wk N = 23	
	Triferic N = 40	Placebo N = 40	Triferic N = 12	Placebo N = 11
Hgb (g/dL) baseline	10.9	11.1	11.1	11.0
Hgb (g/dL) EoT	10.4	10.4	10.9	10.5
ESA (U/wk) baseline	7083	7300	17,483	16,136
ESA (U/wk) EoT	7917	9252	16,386	24,909
LS Mean % Change Mean (SE)	7.6 (12.1)	34.0 (12.1)	-8.5 (33.4)	65.9 (34.8)
LS Mean Difference Mean (SE) (95% CI)	**-26.4 (17.2) (-60.6, 7.8)**		**-74.4 (48.2) (-175, 26.2)**	
	p=0.128		p=0.138	

No Increase in Ferritin Levels

NIH-1



Summary of Overall Efficacy Results

- **Consistently met primary endpoint in 3 adequate and well-controlled clinical trials**
  - Consistent efficacy demonstrated across studies, subgroups, and sensitivity analyses
- **Matches iron needs with replacement**
- **Maintained hemoglobin**
- **No increase in iron stores (ferritin)**
- **Reduced prescribed ESA**

Triferic Safety Results

Vivian Lin, MD

Senior Director, Clinical

Rockwell Medical

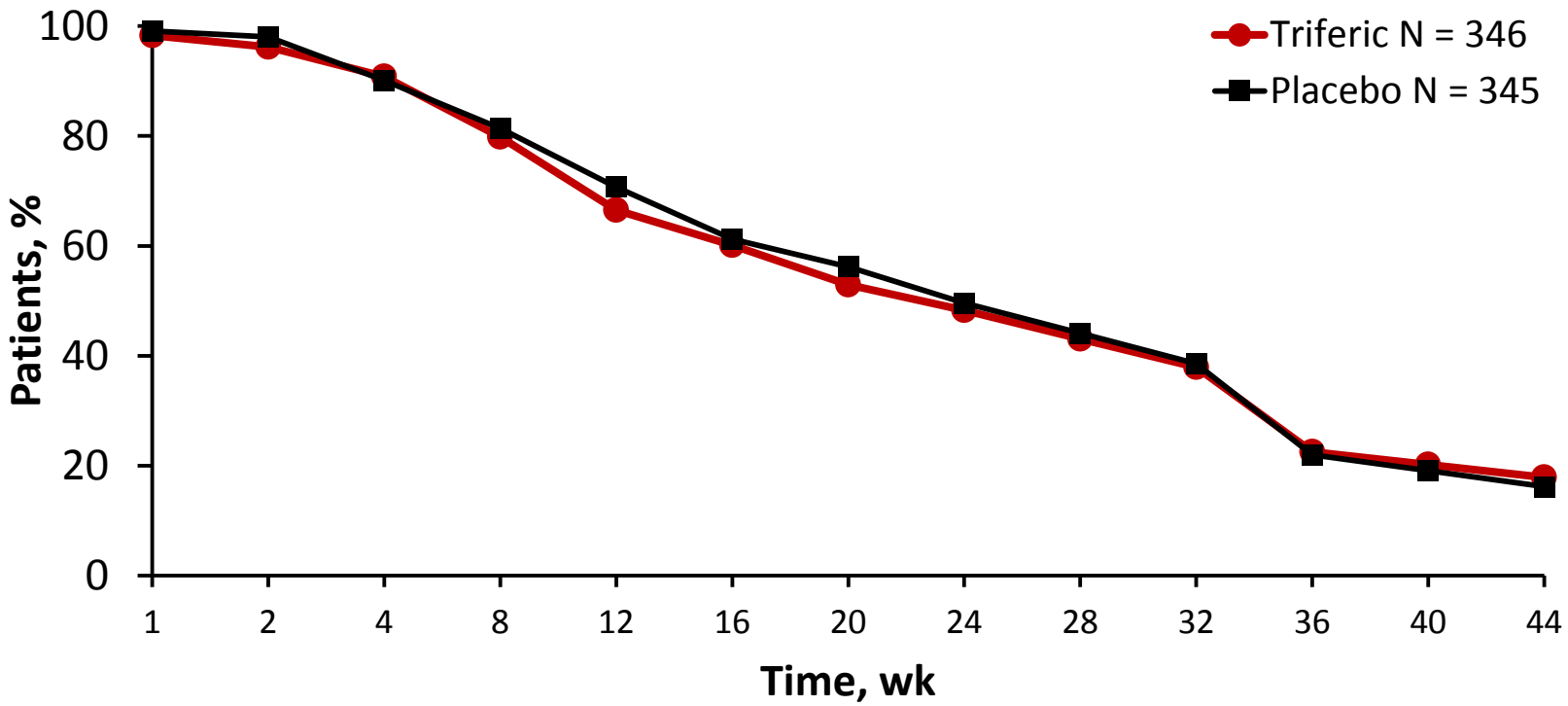
Overview of Safety Populations

- **Controlled Phase 2/3**
  - 3 blinded, Phase 2/3, randomized, placebo-controlled studies (NIH-1, SFP-4-RC, and SFP-5-RC)
- **All Phase 2/3**
  - All patients who received at least 1 dose of Triferic (all formulations, all doses) in one of the 7 Phase 2 or Phase 3 studies: SFP-1, SFP-2, SFP-3, NIH-1, SFP-4, SFP-5, and SFP-6
  - All Triferic

Triferic Safety Based on a Large Database

Controlled and All Studies

	Controlled		All
	Triferic N = 346	Placebo N = 345	All Triferic N = 1411
Duration of exposure, mean days (SD)	167.7 (109.57)	170.5 (107.03)	201.9 (175.85)
Total exposure, patient-years	158.9	161.1	780.0



Triferic Overall AEs Similar to Placebo

Controlled Studies

	Patients, n (%)	
	Triferic N = 346	Placebo N = 345
≥1 Adverse events	278 (80.3)	268 (77.7)
Adverse events, by maximum severity		
Mild	104 (30.1)	96 (27.8)
Moderate	126 (36.4)	113 (32.8)
Severe	48 (13.9)	59 (17.1)
Related adverse events	26 (7.5)	15 (4.3)
Adverse events leading to study discontinuation	17 (4.9)	8 (2.3)
Deaths	14 (4.0)	10 (2.9)
Serious adverse events	98 (28.3)	101 (29.3)

In the placebo group, one patient died prior to being dosed.

Common AEs (≥ 5%)

Controlled Studies

Preferred Term	Patients, n (%) Triferic N = 346	Placebo N = 345
Procedural hypotension	81 (23.4)	77 (22.3)
Arteriovenous fistula site complication	36 (10.4)	45 (13.0)
Diarrhea	34 (9.8)	37 (10.7)
Headache	34 (9.8)	24 (7.0)
Cough	33 (9.5)	27 (7.8)
Nausea	30 (8.7)	36 (10.4)
Hemodialysis-induced symptom	29 (8.4)	20 (5.8)
Dizziness	26 (7.5)	27 (7.8)
Dyspnea	25 (7.2)	18 (5.2)
Pain in extremity	24 (6.9)	25 (7.2)
Edema peripheral	23 (6.6)	10 (2.9)
Vomiting	22 (6.4)	32 (9.3)
Fluid overload	22 (6.4)	27 (7.8)
Muscle spasms	18 (5.2)	21 (6.1)
Upper respiratory tract infection	18 (5.2)	19 (5.5)
Asthenia	18 (5.2)	12 (3.5)

Common SAEs (≥ 2%)

Controlled Studies

	Patients, n (%)	
	Triferic N = 346	Placebo N = 345
Cardiac disorders	24 (6.9)	30 (8.7)
Congestive heart failure	8 (2.3)	9 (2.6)
Infections and infestations	28 (8.1)	31 (9.0)
Pneumonia	8 (2.3)	10 (2.9)
Metabolism and nutrition disorders	14 (4.0)	23 (6.7)
Fluid overload	9 (2.6)	16 (4.6)

AEs of Special Interest

Controlled and All Studies

	Patients, n (%)		
	Controlled		All
	Triferic N = 346	Placebo N = 345	All Triferic N = 1411
Intradialytic hypotension	80 (23.1)	77 (22.3)	262 (18.6)
Suspected hypersensitivity reactions	2 (0.6)	1 (0.3)	6 (0.4)
Related	1 (0.3)	0	2 (0.1)
Anaphylaxis	0	0	0
HD vascular access thrombotic events	21 (6.1)	15 (4.3)	121 (8.6)
Other thrombotic events	0	4 (1.2)	13 (0.9)
Systemic/serious infections	28 (8.1)	32 (9.3)	143 (10.1)
Composite cardiovascular events	30 (8.7)	35 (10.1)	139 (9.9)

Triferic Mortality Rate Similar to Placebo

All Controlled Studies of Triferic 2 µM and All Phase 2/3 Studies

Study	Patients, n		
	Triferic N = 1039	Placebo N = 1031	All Triferic N = 1411
NIH-1	2	4	
SFP-4-RC	5	3	
SFP-5-RC	7	3	
SFP-6-RC crossover	0	3	
Total	14	13	51
Exposure, patient-years	177.3	179.5	780.0
Events/100 PYE	7.9	7.2	6.5

PYE, patient-years of exposure.
In the SFP-5-RC study, one of the placebo patients died before being dosed.

No deaths occurred during administration of Triferic, and none were considered by the investigator to be related to Triferic.

Causes of Death

All Controlled Studies of Triferic 2 µM

	Patients, n	
	Triferic N = 1039	Placebo N = 1031
Any event with outcome of death, n	14	13
Potential cardiac events, n	12	8
Cardiac/cardio-respiratory/respiratory arrest	7	4
Sudden death/sudden cardiac death	2	2
Death	2	0
Acute myocardial infarction	1	2
Cardiac failure congestive	0	1
Other (non-cardiac) events, n	2	5

One of the placebo patients with a non-cardiac event died before receiving study drug.

Fatal and Non-fatal Cardiac Arrest, Sudden Death, and Death

All Controlled Studies of Triferic 2 µM

	Patients, n	
	Triferic N = 1039	Placebo N = 1031
Exposure, patient-years	**177.3**	**179.5**
Any event of cardiac arrest, sudden death, death	11	8
Cardiac/cardio-respiratory/respiratory arrest	7	6
Sudden death/sudden cardiac death	2	2
Death	2	0
Events/100 PYE	6.2	4.5

For cardiac arrest, in the placebo group there were 2 cases that were witnessed and successfully resuscitated. For one of the two, life support was withdrawn 6 days later.

Triferic Mortality Case Review Similar to Placebo

All Controlled Studies of Triferic 2 µM

Triferic- and placebo-treated patients with fatal events:

- Independent DSMB review
- Similar ages (mean Triferic 66 yrs (46-94); placebo 62 yrs (39-80))
- Similar timing (mean Triferic 125 days (8-328); placebo 106 days (15-248))

Triferic patients with fatal events:

- CV risk factors: All had ESRD, DM, HTN, and either hyperlipidemia or known heart disease
- Labs (controlled studies)—overall similar to the rest of the population; higher glucose at baseline and EoT

Overall no differences between Triferic and placebo:

- Serious arrhythmias
- Serious cardiovascular ischemic events
- Composite cardiovascular events or other special safety events

Labs and Vitals

Controlled and All Studies

- **No changes in liver function tests**
  - Most patients had normal values at baseline and throughout study
  - No Hy's law cases
- **No changes in calcium or phosphorus**
- **No increases in ferritin indicative of iron overload**
- **No increases in markers of inflammation (CRP) or oxidative stress (PGF-2α, isofurans, MDA)**
- **No changes in predialysis or postdialysis blood pressure or other vital signs**

Red Blood Cell and Whole Blood Transfusions

SFP-4-RC and SFP-5-RC

	Triferic N = 299	Placebo N = 300
SFP-4-RC		
Patients who received transfusion, n	3	11
Total number of units received	5	19
SFP-5-RC		
Patients who received transfusion, n	6	12
Total number of units received	15	29
Total		
Patients who received transfusion, n (%)	9 (3.0)	23 (7.7)
Total number of units received	20	48
Mean number of units received, per patient	2.22	2.18

Transfusions received during Stage 2 (randomized treatment period) and in the interval between Stage 2 and Stage 3 (open-label extension period) were counted.
For one placebo patient, the total number of units received was unknown; thus, the denominator for the placebo group was 22 patients.

Safety Conclusions

- **Large safety database with 780 patient-years of exposure**
- **Overall adverse event profile similar to placebo**
- **Adverse events of special interest similar to placebo**
  - Intradialytic hypotension
  - Suspected hypersensitivity reactions
  - Thrombotic events
  - Infections
  - Composite cardiac events
- **No anaphylaxis in >100,000 doses administered**
- **No iron toxicity or overload**
- **No evidence of increased inflammation or oxidative stress**

Triferic demonstrated a consistent and well-defined safety profile suitable for use as a long-term maintenance therapy.

Clinical Perspective

Steven Fishbane, MD

Chief, Division of Kidney Diseases and Hypertension

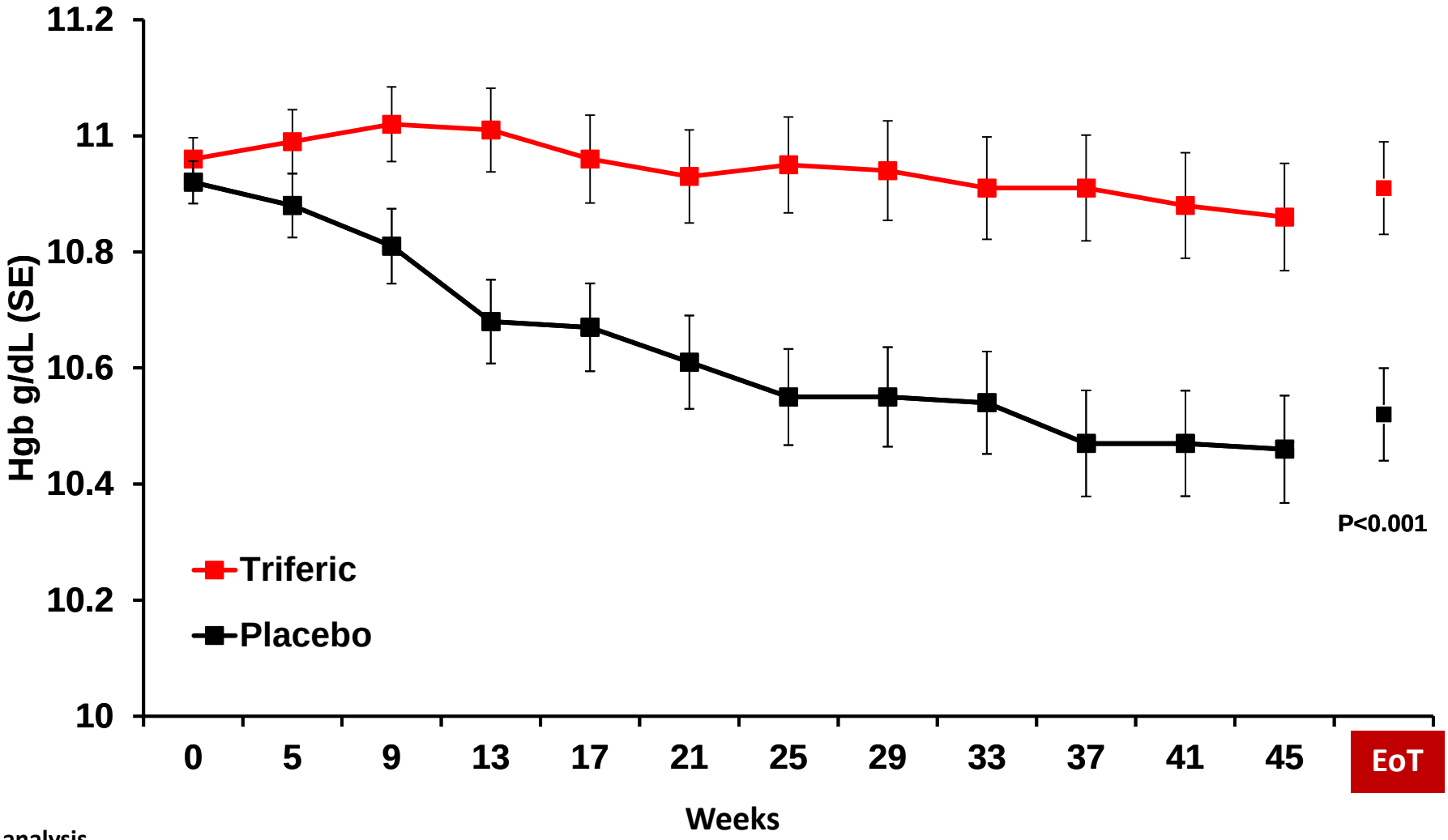
North Shore University Hospital and Long Island Jewish Medical Center

Professor of Medicine, Hofstra North Shore-LIJ School of Medicine

Triferic Effectively Maintains Iron Balance

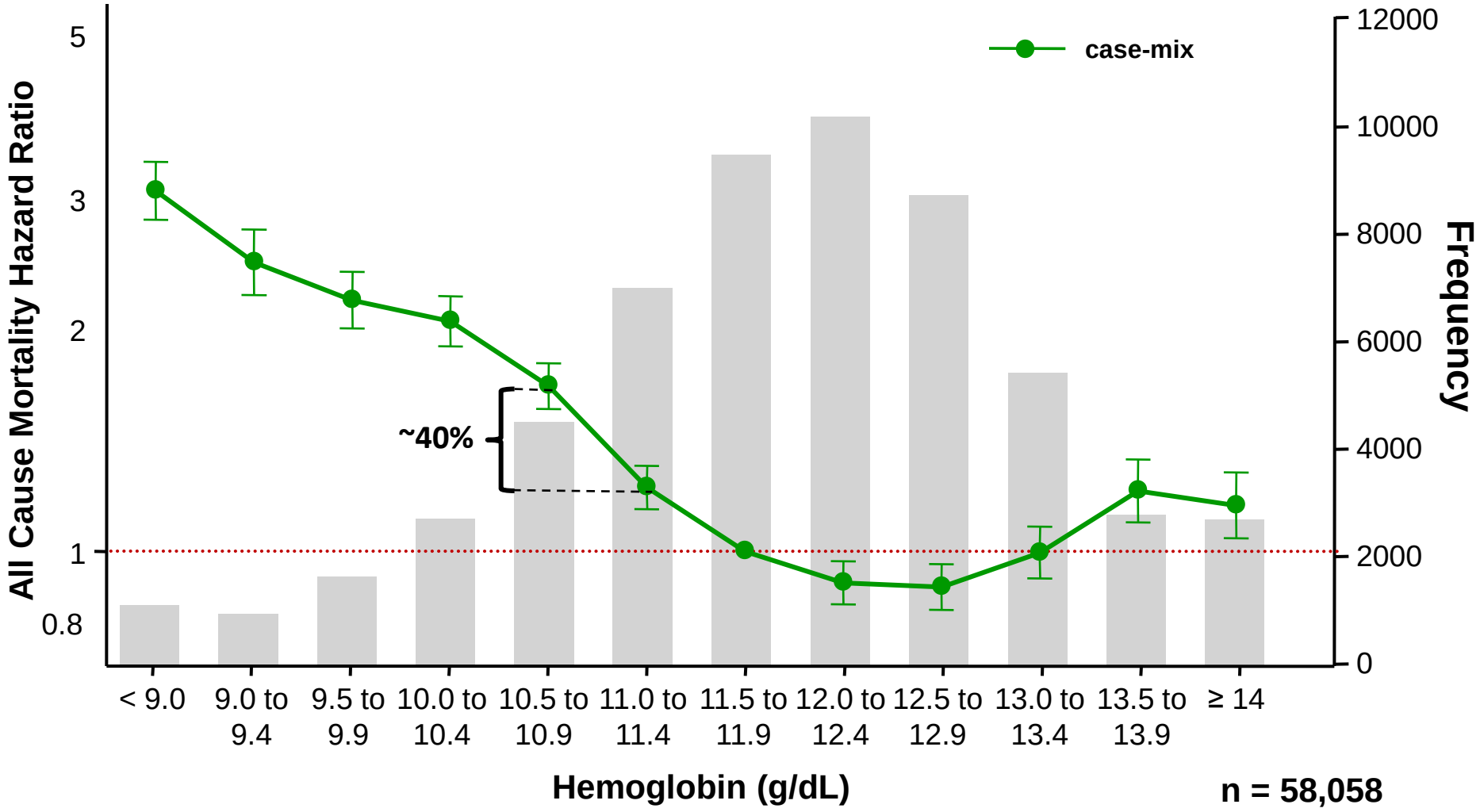
- Novel mode of delivery
- Met primary endpoint in 2 Phase 3 clinical trials
- Maintains hemoglobin levels
- Reduces ESA dose requirements
- Does not increase iron stores (ferritin)
- Matches iron needs with replacement
- Decreases transfusions

Triferic Maintains Hemoglobin Levels



LOCF analysis

Lower Hemoglobin Level Associated With Mortality After Adjusting for Case Mix



Adapted from Regidor et al. *J Am Soc Nephrol*. 17:1181-91; 2006

Triferic Reduces Need for Transfusions in Phase 3 Clinical Trials

	Triferic N = 299	Placebo N = 300
Patients who received transfusion, n (%)	9 (3.0)	23 (7.7)
Total units received, n	20	48

Triferic Reduces ESA Dose Requirements

Prescribed ESA dose, U/wk	Triferic N = 52	Placebo N = 51
Baseline dose (SD)	9483 (5414)	9206 (5500)
Mean change from baseline, % (SE)	4.9 (12.07)	39.8 (12.18)
Mean difference between arms, % (SE)	**-35.0** (17.20)	
P-value	**0.045**	
(95% CI)	(-69.1, -0.8)	

Triferic Alternative for IV Iron

	Triferic	IV Iron
Indication	Maintenance (proposed)	Repletion only
Iron mg Needs	Matched	Mismatched
Rate of Infusion	Slow	Fast
Iron Sequestration	No	Yes
Infections	Similar to Placebo	Increased Risk
Anaphylaxis	Not Observed	Occasional

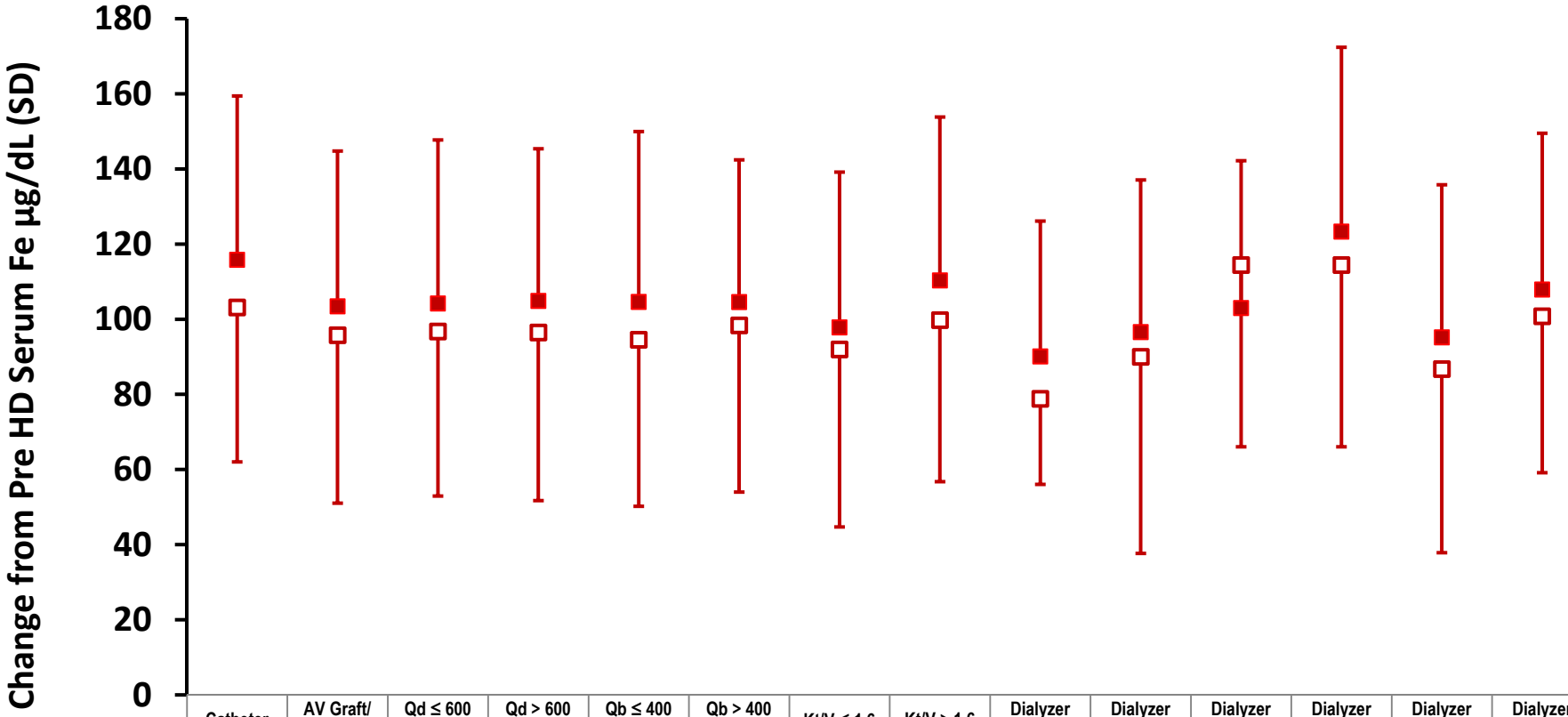
Triferic Favorable Benefit : Risk Profile

- **Benefit: Directionally consistent for all variables**
  - Maintains hemoglobin levels
  - Reduces ESA dose requirements
  - Reduces need for IV iron
  - Decreases transfusions
- **Safety:**
  - Low risk
  - Does not increase iron stores (ferritin)
  - No anaphylaxis during >100,000 doses
  - Similar rates of infection as placebo
- **Overall favorable benefit : risk profile**

SFP-4-OL and SFP-5-OL Summary

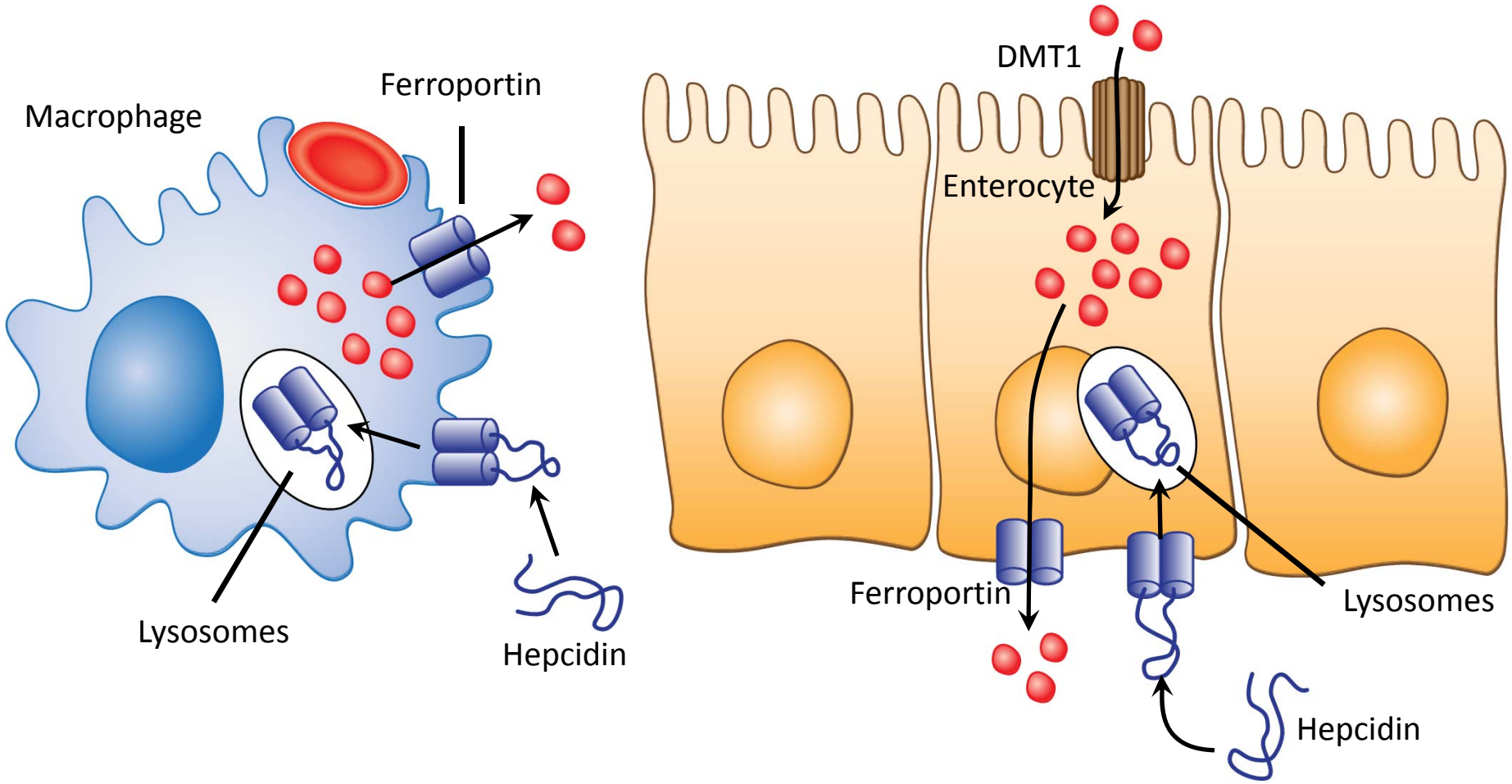
Pre-HD Values mean (SD)		SFP-4-OL N=205 Value	SFP-4-OL N=205 Change	SFP-5-OL 215 Value	SFP-5-OL 215 Change
Hgb g/dL	Baseline	10.9 (1.5)		10.7 (1.5)	
	EoT	10.6 (1.0)	-0.24 (1.1)	10.7 (1.0)	-0.03 (1.7)
CHr pg	Baseline	31.7 (1.9)		31.4 (2.2)	
	EoT	31.4 (2.0)	-0.31 (1.6)	31.2 (2.1)	-0.25 (1.8)
Ferritin μg/L	Baseline	366.2 (216.6)		350.1 (256.0)	
	EoT	302.5 (199.1)	-62.9 (195.4)	304.2 (214.5)	-76.5 (235.2

Triferic Consistently Delivers Iron



	Catheter	AV Graft/ Fistula	Qd ≤ 600 mL/min	Qd > 600 mL/min	Qb ≤ 400 mL/min	Qb > 400 mL/min	Kt/V ≤ 1.6	Kt/V > 1.6	Dialyzer Cellulose	Dialyzer Polyamide	Dialyzer Polysulfone	Dialyzer PAES	Dialyzer Reuse	Dialyzer New
SFP Controlled	115.85	103.46	104.20	104.89	104.63	104.60	97.84	110.35	90.10	96.58	102.98	123.32	95.21	107.93
SFP OL	103.14	95.78	96.75	96.49	94.54	98.37	91.98	99.77	78.82	89.98	114.42	114.42	86.73	100.79

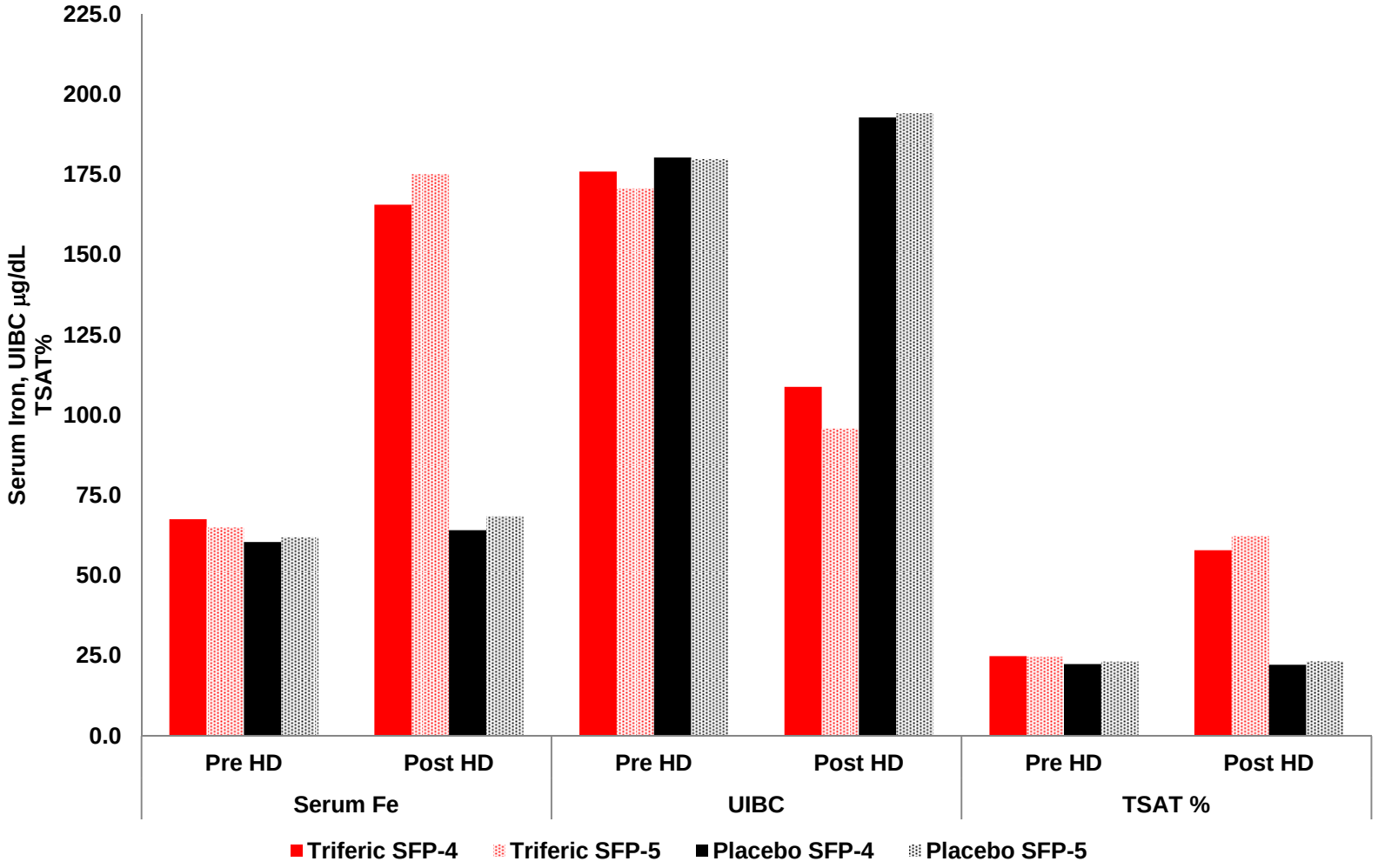
Hepcidin-ferroportin Interaction Controls Iron Entry Into Plasma



Brittenham GM. Hematology: Basic Principles and Practice. Saunders, 6th ed., 2013

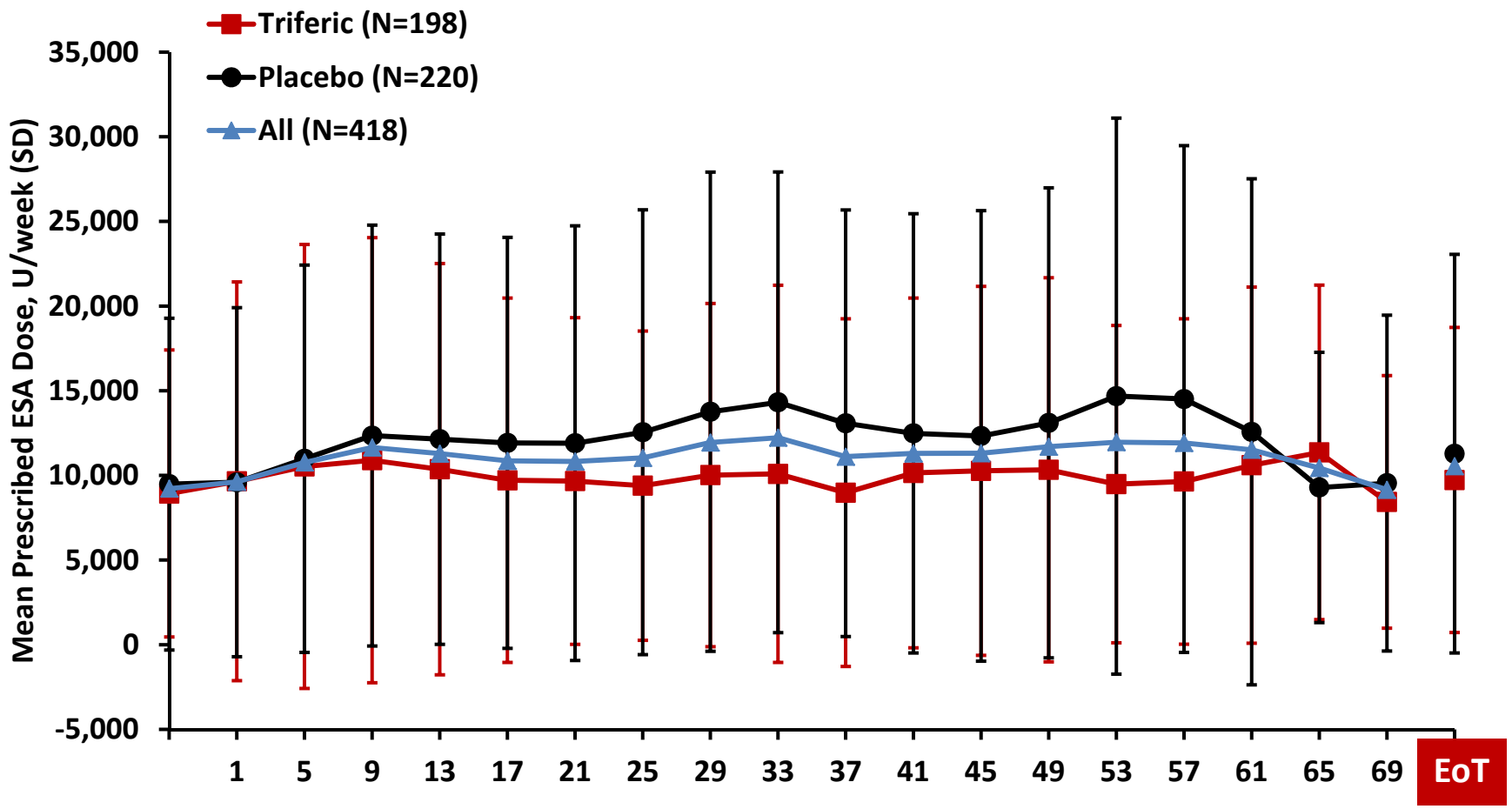
Serum Iron, Unsaturated Iron-binding Capacity[O-56] and TSAT: Pre- and Post-dialysis

SFP-4 and SFP-5



Prescribed ESA Dose by Time Point

SFP-4-OL and SFP-5-OL



Abbreviations: ESA, erythropoiesis-stimulating agent; SD, standard deviation.

Treatment Duration in Randomized Phase

SPF-4 and SFP-5

Treatment Duration	Triferic N=148	Placebo N=151	Triferic N=142	Placebo N=144
Mean days (SD)	157.7 (115.42)	154.6 (111.80)	161.2 (111.10)	157.9 (109.76)
Median days (Min, Max)	125 (1, 332)	143 (1, 333)	132 (1, 333)	135 (3, 332)
Duration of exposure				
≥1 day	148 (100)	151 (100)	142 (100)	144 (100)
≥1 week	147 (99.3)	149 (98.7)	141 (99.3)	143 (99.3)
≥2 weeks	140 (94.6)	147 (97.4)	140 (98.6)	140 (97.2)
≥4 weeks	130 (87.8)	137 (90.7)	133 (93.7)	126 (87.5)
≥8 weeks	109 (73.6)	118 (78.1)	117 (82.4)	114 (79.2)
≥12 weeks	90 (60.8)	103 (68.2)	89 (62.7)	96 (66.7)
≥16 weeks	84 (56.8)	87 (57.6)	77 (54.2)	78 (54.2)
≥20 weeks	68 (45.9)	78 (51.7)	67 (47.2)	71 (49.3)
≥24 weeks	62 (41.9)	65 (43.0)	60 (42.3)	63 (43.8)
≥28 weeks	55 (37.2)	57 (37.7)	51 (35.9)	50 (34.7)
≥32 weeks	46 (31.1)	48 (31.8)	42 (29.6)	44 (30.6)
≥36 weeks	41 (27.7)	40 (26.5)	37 (26.1)	36 (25.0)
≥40 weeks	36 (24.3)	35 (23.2)	34 (23.9)	31 (21.5)
44-47 weeks	30 (20.3)	32 (21.2)	32 (22.5)	24 (16.7)

Triferic Patients With Fatal TEAEs—Labs (5)

Controlled Studies

	Mean Values at EoT		
	Triferic 14	Triferic n=333	Placebo n=338
WBC, K/µL	6.6	6.4	6.2
Hgb, g/dL*	10.5	10.8	10.5
Platelets, K/µL	191	210	213
CRP, nmol/L	483**	121	149
Ferritin, µg/L	449	457	369

*For Hgb, the ns are 340 and 342 for Triferic and placebo, respectively.
**Increase driven by 2 outliers; without these the result is 159.

Triferic Patients With Fatal TEAEs—Labs (6)

Controlled Studies

	Mean Values at EoT		
	Triferic 14	Triferic n=333	Placebo n=338
Serum iron, µmol/L	9.1*	11.6	10.6
UIBC, µmol/L	29.2	31.1	32.7
Transferrin, g/L	1.80	1.92	1.96
TIBC, µmol/L	38.3	42.7	43.4
TSAT, %	24	27	25

*Decrease driven by 2 outliers; without these the result is 10.3.