FERRIC CITRATE
A NOVEL PHOSPHATE BINDER: THE TWO FACES OF JANUS

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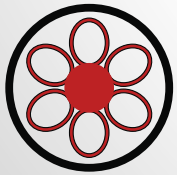
Disclosures

- Principal Investigator of Multiple Keryx Sponsored Studies of Ferric Citrate as a Phosphate Binder
- Off-label use will be discussed



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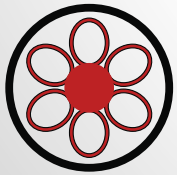
Oral Iron in Dialysis Patients

- **Dialysis patients are iron deficient.**
- Oral ferrous sulfate historically is inferior to IV iron.
- IV iron and increased iron stores reduce ESA use and increase Hgb.
- Oral iron, as ferric citrate, raises iron stores, maintains Hgb, and reduces ESA use in dialysis patients.



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Dialysis Patients are Iron Deficient

- Normal daily loss of iron is 1 mg/day through the gut.
- Dialysis patients lose 4-15 ml/day of blood and 4-6 mg/day of iron due to blood draws, blood in the dialyzer and bleeding.
- Sufficient iron stores are required for ESA responsiveness, creating a further functional iron deficiency state.

Oral Iron in Dialysis Patients

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Oral Iron does not Maintain Iron Stores

- 46 Subjects on maintenance hemodialysis randomized to oral Chromagen, Niferex, Feosol, or Tabron in ***fasting*** state
- Total elemental iron 200 mg/day over 6 months

	Chromagen	**Feosol**	**Niferex**	**Tabron**
Ferritin, Baseline (ng/mL)	140	179	137	150
Ferritin, End of Study (ng/mL)	89	113	82	143

(Wingard, 1995)

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IV Iron Raises Hgb as Compared to Oral Iron

Study Population	37 HD patients Ferritin 100-800 ng/mL Receiving EPO Hgb <8.5 g/dL
Study Intervention	Randomized to: • IV iron dextran, or • PO ferrous sulfate 200 mg TID, or • No iron
Primary Outcome	Change in Hgb

(Macdougall, 1996)

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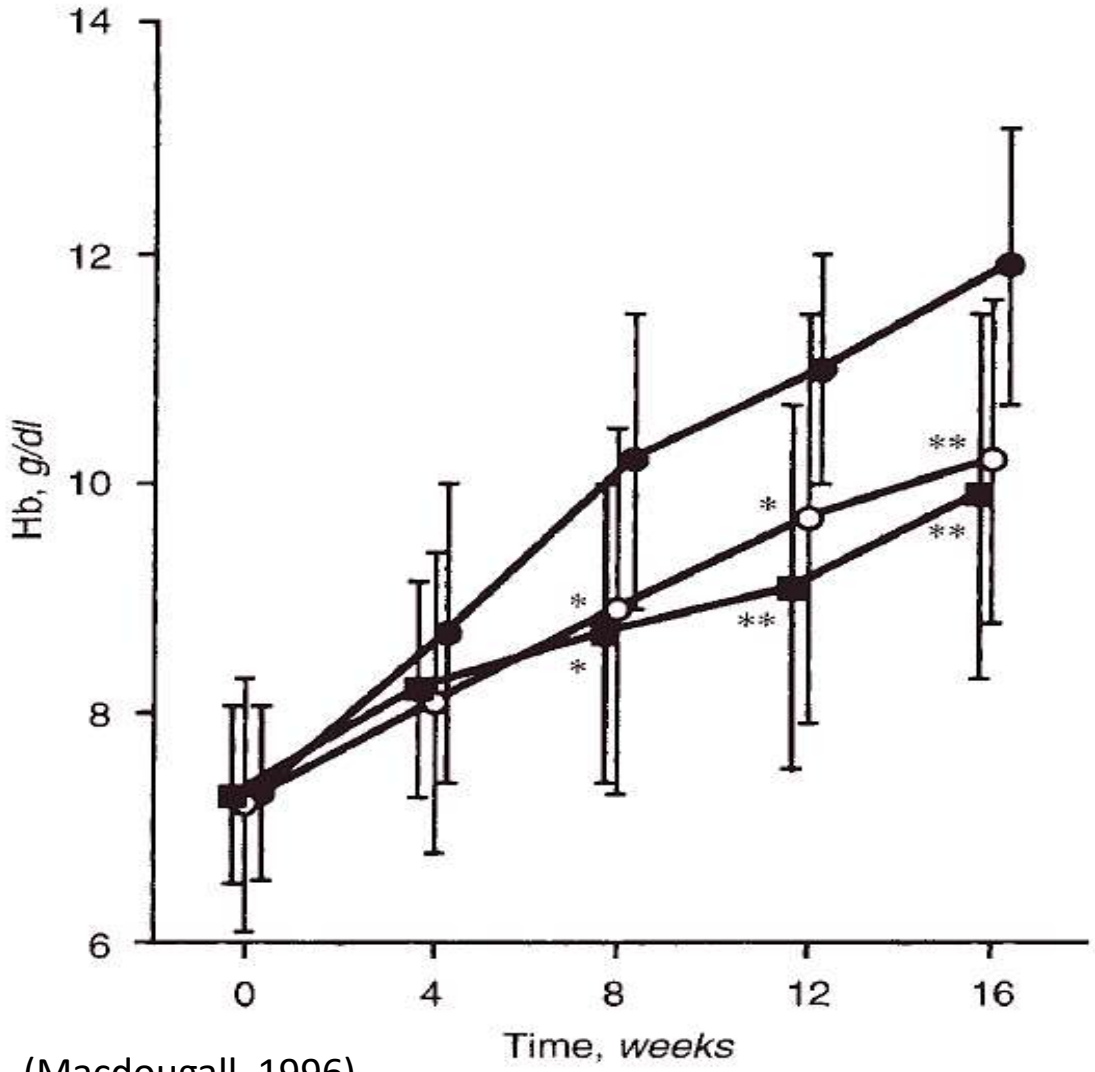
IV, But Not Oral Iron Raises Hgb



- ● IV Iron
- ○ Oral Iron
- ■ No Iron

* P < 0.05
** P < 0.005

(Macdougall, 1996)

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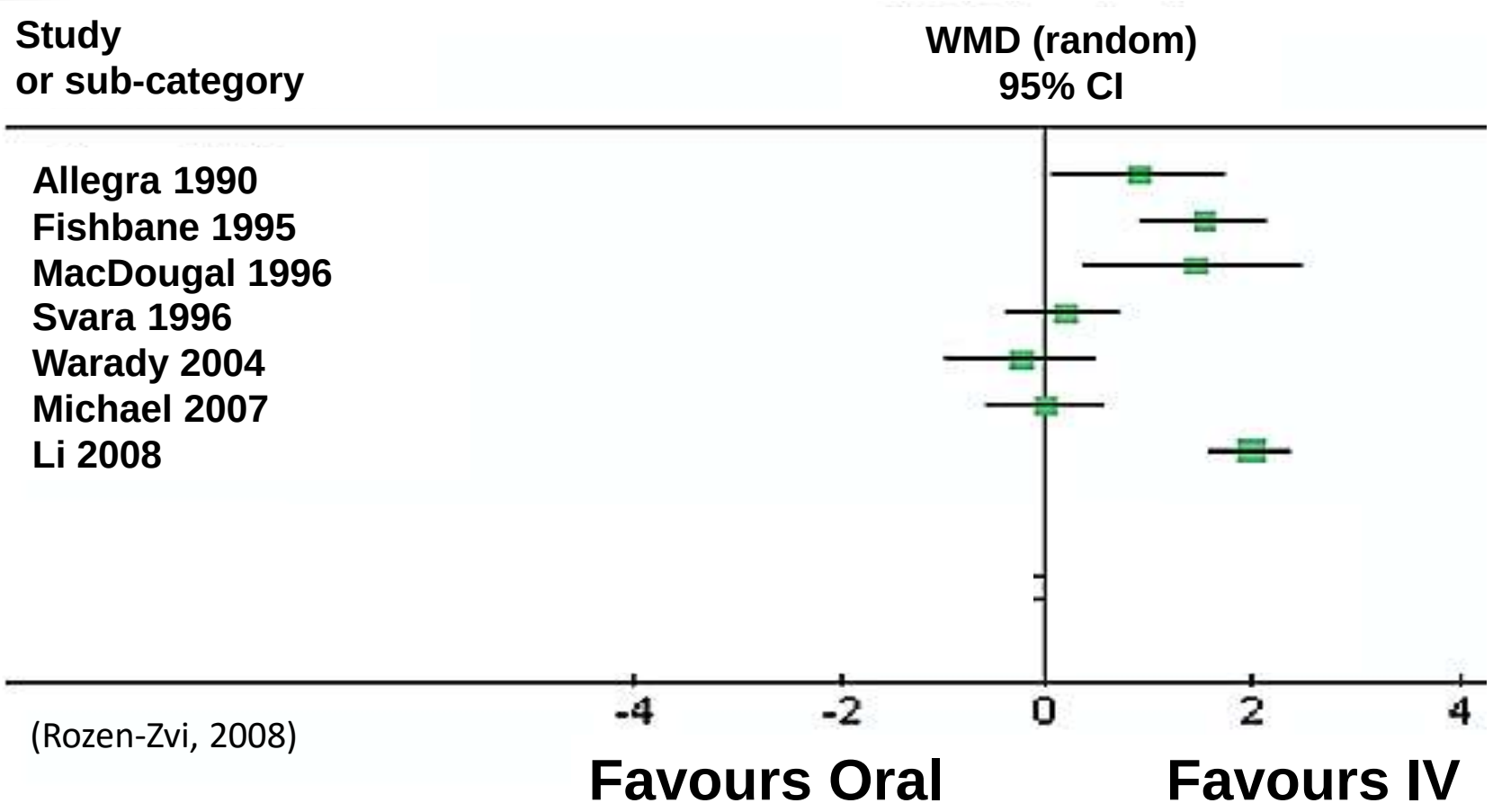
Meta-Analysis: IV Iron Raises Hgb Compared to Oral Iron



(Rozen-Zvi, 2008)

WMD = Weighted Mean Difference

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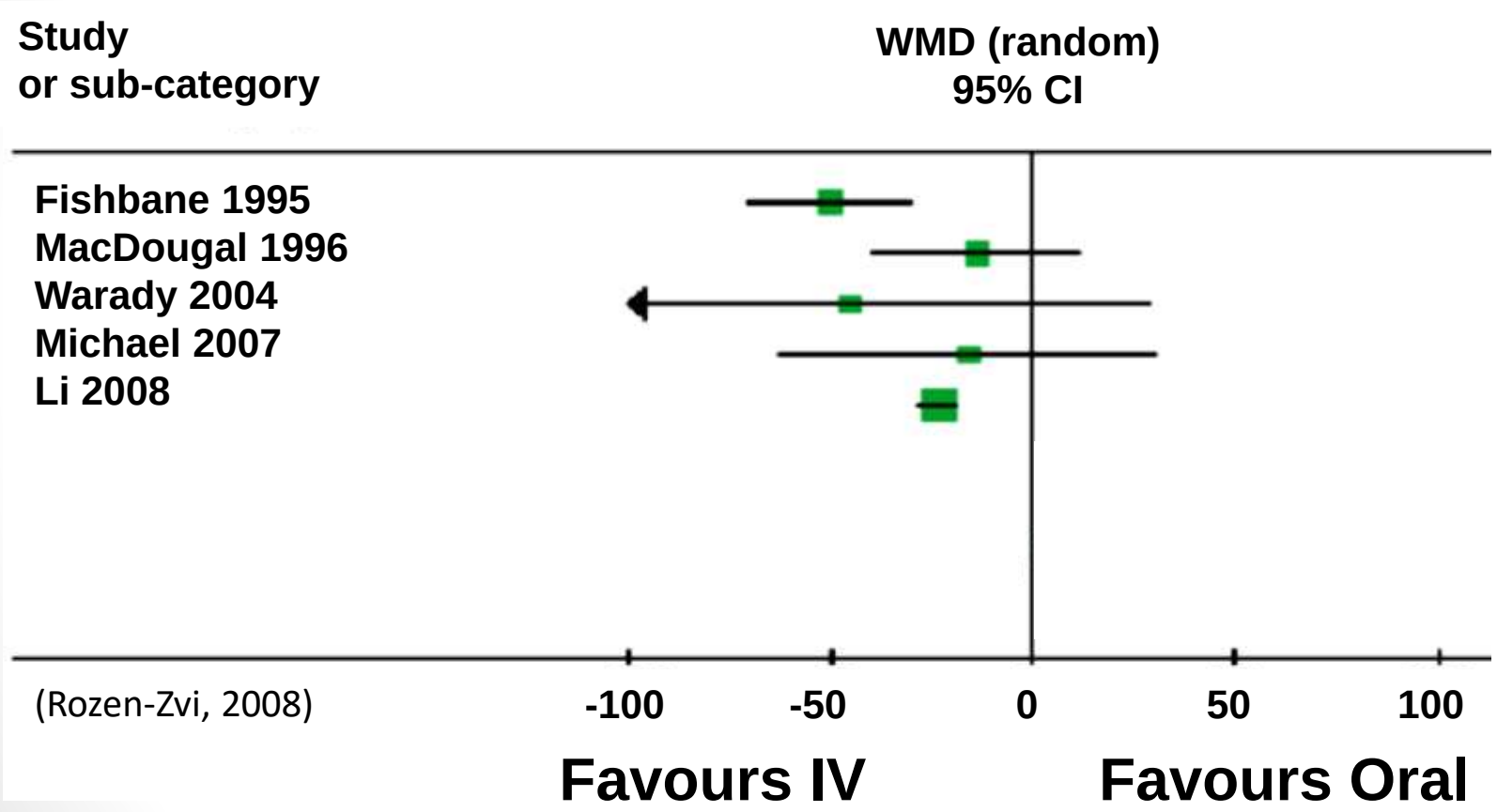
Meta-Analysis: IV Iron Reduces ESA use vs Oral Iron



(Rozen-Zvi, 2008)

WMD = Weighted Mean Difference

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Oral Iron vs IV Iron **HISTORICALLY**

	ADVANTAGES	DISADVANTAGES
PO Iron	• Simple, cheap • Avoids complications of IV use • Avoids allergic reactions seen with IV use • Tight GI regulation of iron absorption avoids "iron overload."	• GI side effects when given in the fasting state • Dose limited to 250-1000 mg ferrous sulfate or 200 mg elemental iron per day • Poor compliance • Low efficacy
IV Iron	• Efficacious • Dose unlimited • Compliance good • Reduces ESA use • Increases Hgb	• Expensive • IV use risks introducing infection • Allergic reactions • Bypassing GI regulations of iron absorptions introduces risk of "iron overload."

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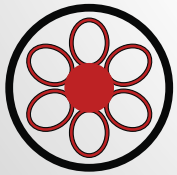

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DRIVE Study: IV Iron Efficacious in HD Patients with HIGH Ferritin

Study Population	• 134 HD patients • Hgb ≤ 11 g/dL • Ferritin 500-1200 ng/mL • ESA ≥22,500 IU/wk (>100 U/HD treatment)
Study Design	Randomized to: • No iron, or • Ferric gluconate 125 mg for 8 HD sessions
Primary Outcome	Change in Hgb

(Coyne, 2007)

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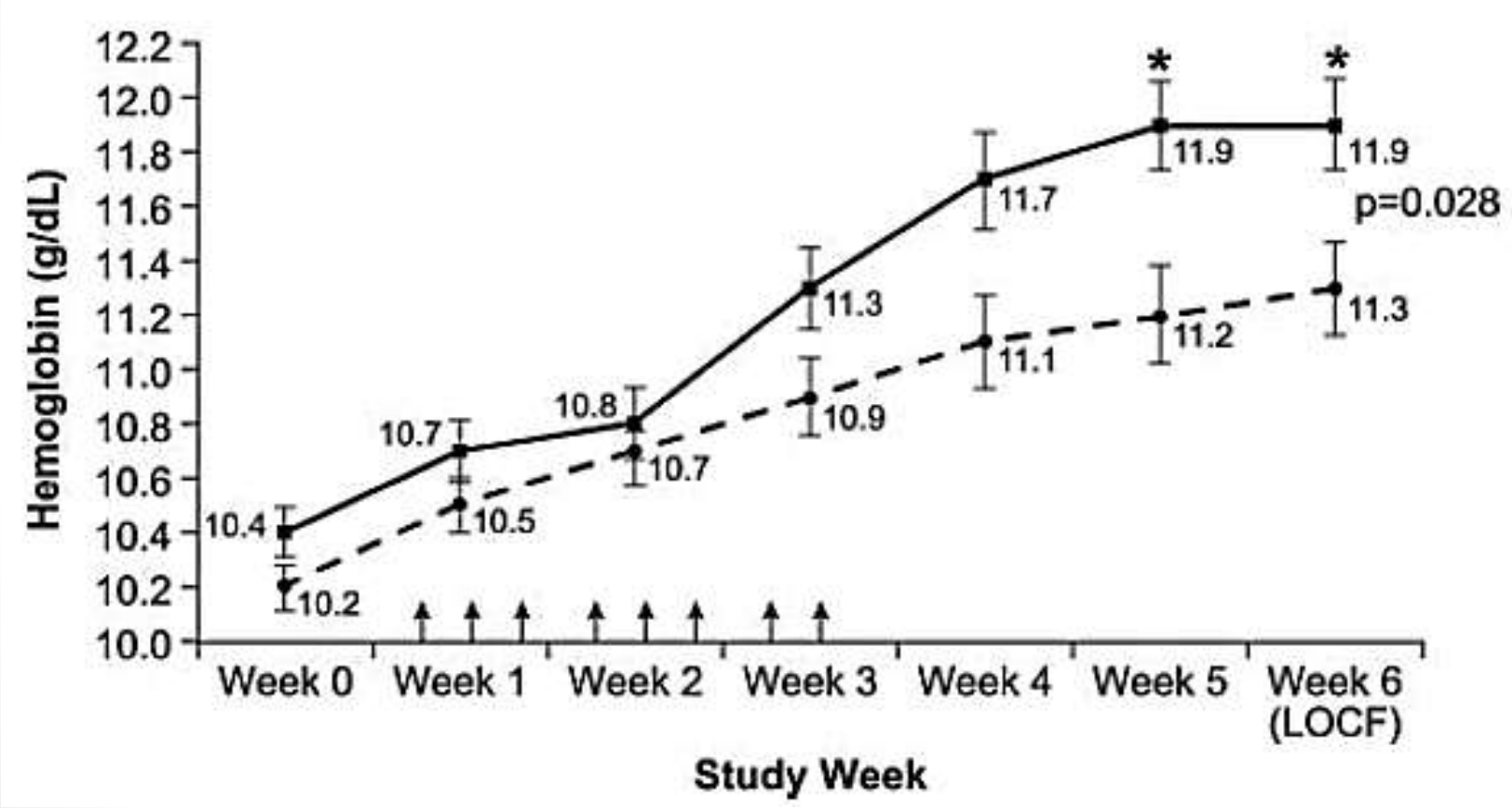
IV Iron RAISES Hgb in High Ferritin Patients

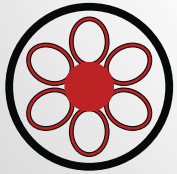


(Coyne, 2007)

Reduced ESA Dose with IV Iron

STUDY	Subjects (N)	IV IRON DOSE	REDUCTION IN EPO DOSE (%)
Fishbane	20	200 mg/wk	46
Sunder-Plassmann	52	100 mg/HD	70
DRIVE-II	118	0–1250mg/6 wks	21

(Kapoian, 2008)



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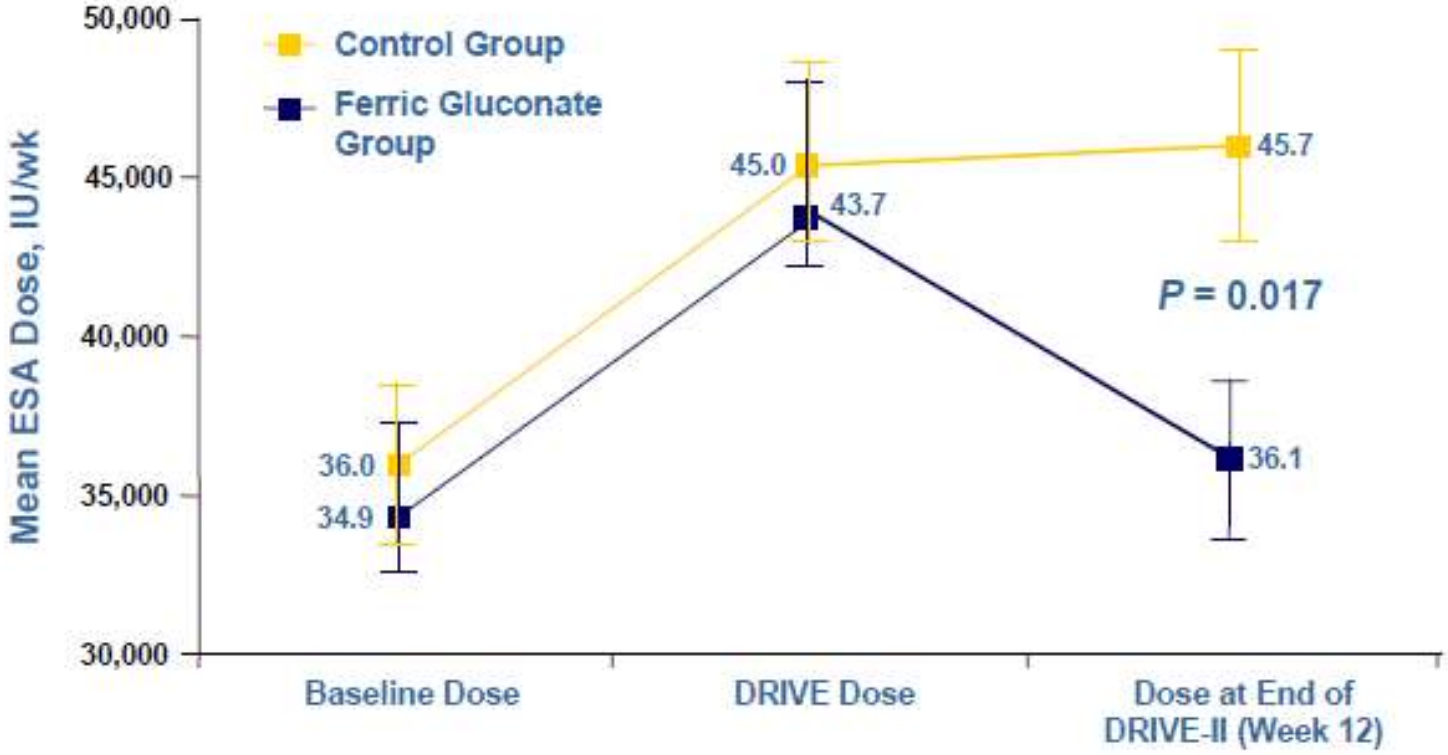
IV Iron Decreases ESA Dose in HD Patients



(Kapoian, 2008)

Target Iron Store Goals Have Increased in Many Dialysis Units

- ESA use limited by reported Adverse Events (Dialysis, CHOIR, TREAT) and bundling costs.
- Increasing iron stores decreases ESA use and increases Hgb
- DOPPS Practice Monitor (DPM) Data[1]
  - 73% of HD patients receive IV Iron
  - 39% of HD patients have ferritin ≥ 800 ng/mL
  - 10% of HD patients have ferritin ≥ 1200 ng/mL
- Dialysis units give IV Iron until TSAT >50% or Ferritin >1200 ng/mL

[1]Fuller DS, Pisoni RL, Bieber BA, Gillespie BW, Robinson BM. The DOPPS Practice Monitor for US Dialysis Care: Trends Through December 2011. American journal of kidney diseases : the official journal of the National Kidney Foundation 2013;61:342-6

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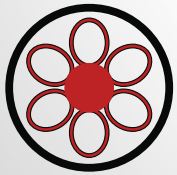
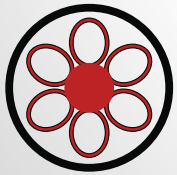


Phosphorus control and iron delivery

THE ORIGINAL HYPOTHESES REGARDING FERRIC CITRATE

The Early Hypotheses for Ferric Citrate

- In 2004, the CSG was contacted to consider the utility of ferric citrate as a phosphate binder in ESRD.
- We hypothesized that FC could bind phosphorus, deliver iron via the gut, and potentially act as a source of alkali.
- Other hypotheses followed as a result of early observations, including improvement in iron stores and reductions in IV Iron/ESA.



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Ferric Citrate as a Phosphate Binder

- Mechanism of Action: Ferric ion dissociates from citrate and binds phosphate forming non-absorbable ferric-phosphate complexes in HD and PD subjects.
- Each 1 gram tablet of ferric citrate contains 210 mg of elemental iron.
- Study dose was 1-12 g/day (210-2520 mg/day elemental iron) given with meals.
- Ferric ion must be converted to ferrous ion for GI absorption.

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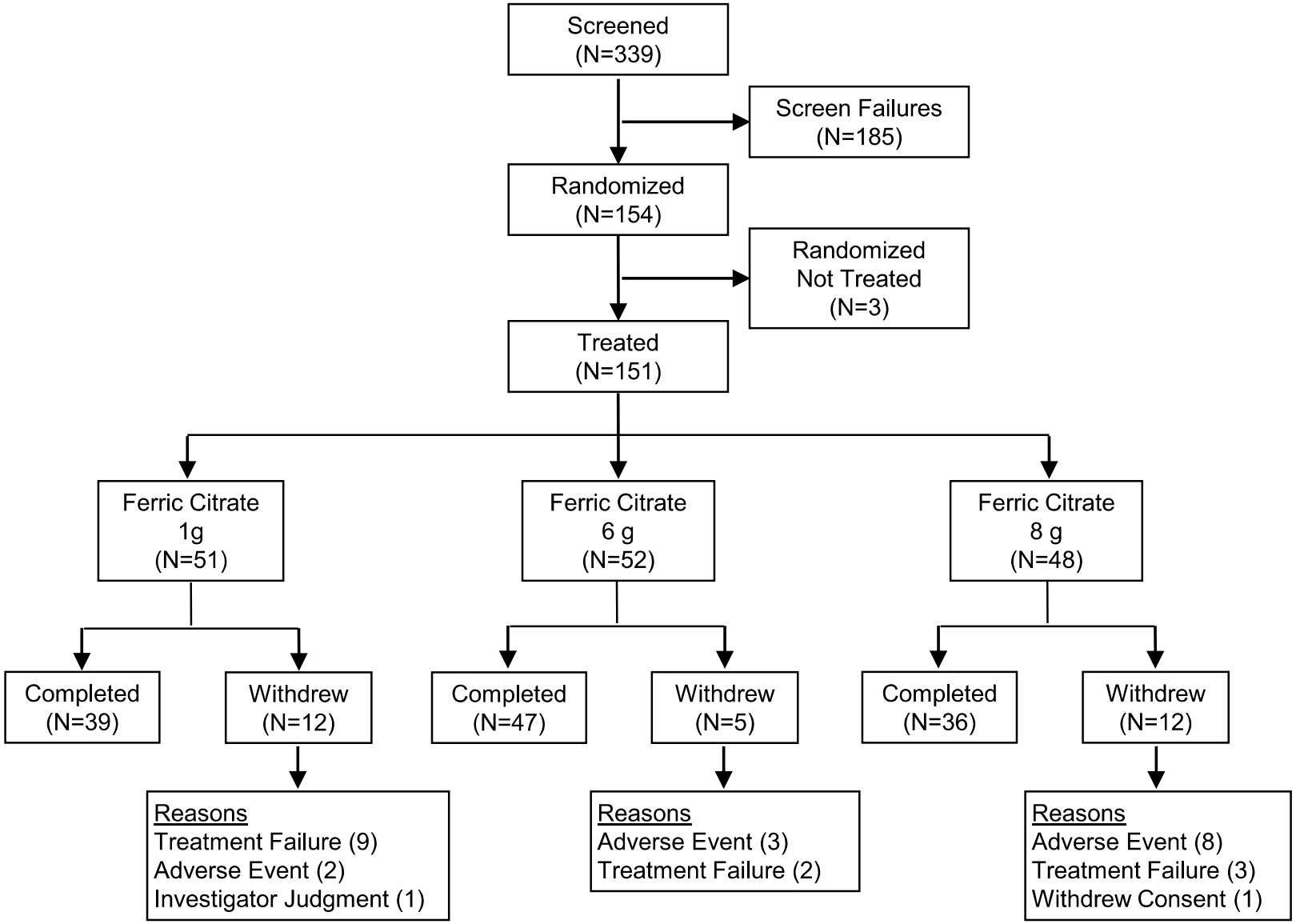
Dose-Ranging and Efficacy

- Fixed dosing generates a dose-response and proves efficacy.

Ferric Citrate Has Predictable Dose Response

- The primary objective of this trial was to determine the dose-response and efficacy of ferric citrate as a phosphate binder in HD patients.
- Design: Prospective, phase 3, multicenter, open-label, RCT
- Subjects: 151 subjects with hyperphosphatemia on maintenance HD randomized 1:1:1 to 1,6, or 8g/day after a 2 week Washout
- Outcomes: Primary: dose-response of ferric citrate on serum phosphorus; Secondary: safety and tolerability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(N=339)
Screen Failures
(N=185)
Randomized
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Randomized
Not Treated
(N=3)
Treated
(N=151)
Ferric Citrate
1g
(N=51)
Ferric Citrate
6 g
(N=52)
Ferric Citrate
8 g
(N=48)
Completed
(N=39)
Withdrew
(N=12)
Completed
(N=47)
Withdrew
(N=5)
Completed
(N=36)
Withdrew
(N=12)
Reasons
Treatment Failure (9)
Adverse Event (2)
Investigator Judgment (1)
Reasons
Adverse Event (3)
Treatment Failure (2)
Reasons
Adverse Event (8)
Treatment Failure (3)
Withdrew Consent (1)

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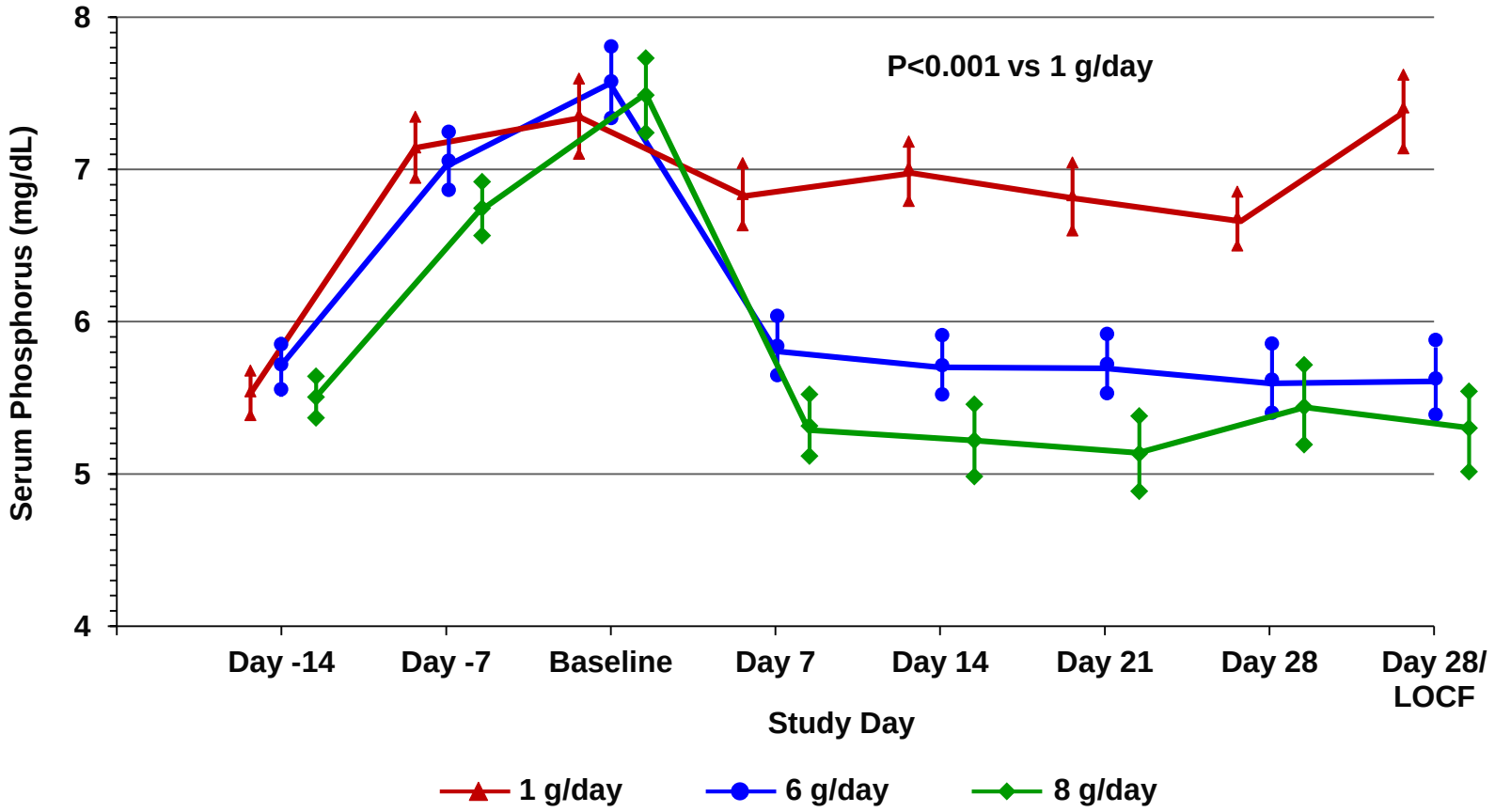
Baseline Characteristics

Parameter	Ferric Citrate Dosage		
	1 g/d (n = 50)	6 g/d (n = 51)	8 g/d (n = 45)
Age (y)	55.9 ± 12.8	56.5 ± 13.0	52.8 ± 11.8
Male sex	32 (64.0)	30 (58.8)	26 (57.8)
Race			
Asian	1 (2.0)	0 (0)	0 (0)
Black or African American	25 (50.0)	31 (60.8)	27 (60.0)
White/Caucasian	21 (42.0)	17 (33.3)	13 (28.9)
Native Hawaiian or Pacific Islander	0 (0)	1 (2.0)	0 (0)
Other	3 (6.0)	2 (3.9)	5 (11.1)
Ethnicity			
Hispanic or Latino	7 (14.0)	4 (7.8)	10 (22.2)
Not Hispanic or Latino	43 (86.0)	47 (92.2)	35 (77.8)
Serum phosphorus (mg/dL)	7.3 ± 1.7	7.6 ± 1.7	7.5 ± 1.6
Calcium (mg/dL)	9.0 ± 0.8	8.9 ± 0.9	8.9 ± 0.8
Ca × P (mg^2/dL^2)	65.6 ± 15.8	67.1 ± 15.5	66.1 ± 14.9
Ferritin (mg/dL)	558.2 ± 290.3	515.2 ± 267.5	527.0 ± 243.41
TSAT (%)	31.9 ± 11.3	33.8 ± 13.6	29.8 ± 9.7
Bicarbonate (mEq/L)	23.0 ± 2.7	22.5 ± 3.2	22.6 ± 3.3

Fixed Dosing of Ferric Citrate Exhibits a Dose-Response Relationship



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Primary Efficacy Outcome

Parameter	Ferric Citrate dose, g/day		
	1 g	**6 g**	**8 g**
Subjects (N)	50	51	45
Phosphorus difference, vs. Baseline (mg/dL)	-0.10 ± 1.3	-1.9 ± 1.7*	-2.1 ± 2.0*

*P<0.001, vs. 1 g/day

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Conclusions of Dose-Response

- Ferric citrate demonstrates a dose-response relationship when given in fixed doses.
- The mean change in Phosphorus is comparable to other phosphate binders given in fixed doses.
- The safety profile exhibits a dose-response as well, also seen with other binders.
- This trial was not long enough to demonstrate long-term safety.

A Three-Period Efficacy and Safety Pivotal Clinical Trial

- Ferric citrate safely controls phosphorus, increases iron stores, and reduces IV Iron and ESA usage, all while maintaining hemoglobin.

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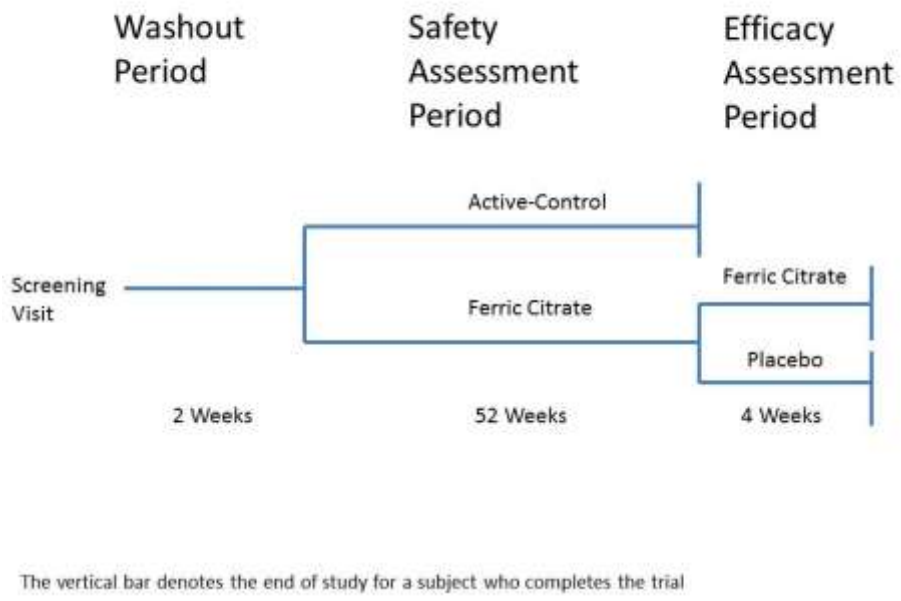
SAFETY AND EFFICACY TRIAL

- 58 week trial with 3 distinct periods
- Primary outcome:
  - Phosphorus control compared to placebo
- Four Secondary Outcomes (compared to active control):
  - Ferritin
  - TSAT
  - IV iron use
  - ESA use



Umanath K et al. Hemodial Int. 2013 Jan;17(1):67-74.

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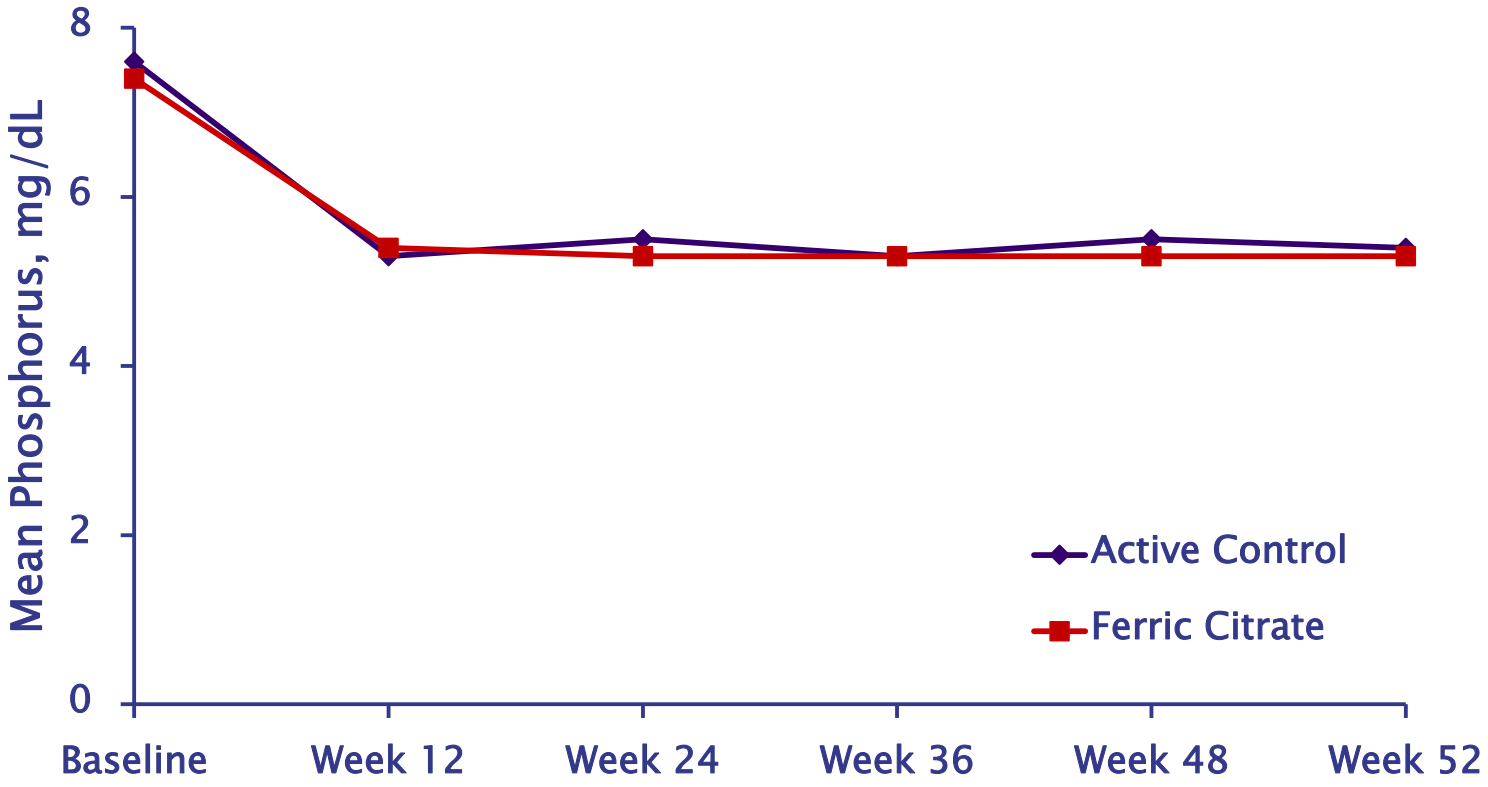
Serum Phosphorus was Controlled Over 52 Weeks



Treatment difference at Week 52 ANCOVA, p = 0.8

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Ferric Citrate Controls Phosphorus

Outcome	Baseline Mean (SEM)		End Of Placebo Control Period Mean (SEM)		ANCOVA Results (Ferric Citrate Vs. Placebo)	
	Ferric Citrate	Placebo	Ferric Citrate	Placebo	Adjusted Mean Difference	P value
Phosphorus (mg/dL)	5.12 (0.12)	5.44 (0.15)	4.86 (0.13)	7.21 (0.19)	-2.18	<0.001

Adapted from Lewis JB et al. J Am Soc Nephrol. 2014 Jul 24. pii: ASN.2014020212

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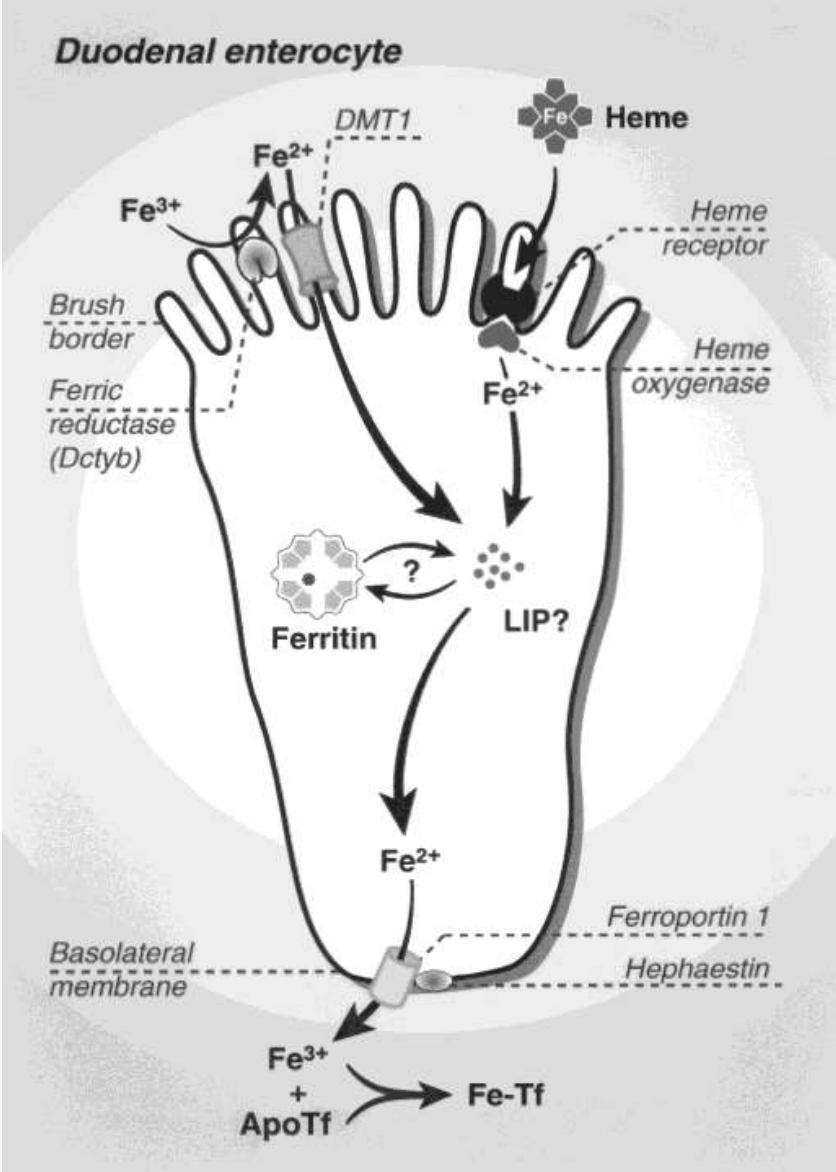
Iron Absorption in Enterocytes

Oral iron absorption is tightly regulated in the GI tract. Ferric iron must first be reduced by ferric reductase (Dctyb). Ferrous iron is then absorbed. Any iron which remains in the enterocyte lost in the daily shedding of enterocytes. The net absorption is ~1mg/day.

Koury & Ponka 2004.

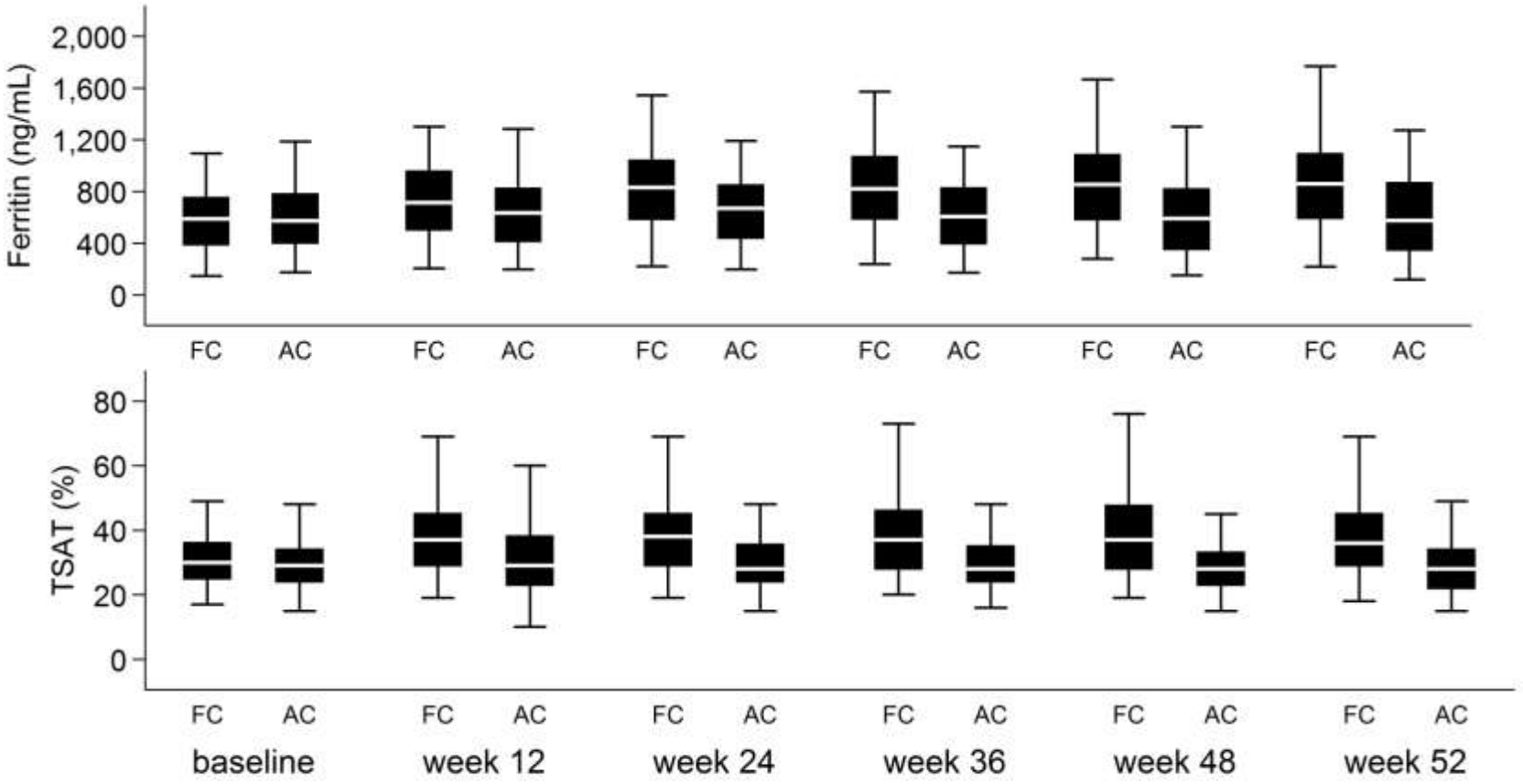


Ferric Citrate Delivers Iron, Reduces IV Iron and ESA Use While Maintaining Hemoglobin

Outcome	Baseline Mean (SEM)		Week 52 Mean (SEM)		ANCOVA or Wilcoxon Results (FC v. AC)	
	FC	AC	FC	AC	Adjusted Mean Difference	P value
Ferritin (ng/mL)	593 (18)	609 (26)	899 (31)	628 (31)	282	<0.001
TSAT (%)	31.3 (0.7)	30.9 (1.0)	39.3 (1.1)	29.7 (1.0)	9.5	<0.001
IV iron (mg/wk)	--	--	--	--	-12.5	<0.001
ESA dose (units/wk)	--	--	--	--	-1191	0.04
Hemoglobin (g/dL)	11.61 (0.08)	11.71 (0.11)	11.42 (0.10)	11.14 (0.12)	0.33	0.02

Adapted from Lewis JB et al. J Am Soc Nephrol. 2014 Jul 24. pii: ASN.2014020212

Ferric Citrate Raises Iron Stores



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Ferric Citrate Decreases IV Iron and ESA Use

	Ferric Citrate	Active Control
Elemental IV Iron (mg/day)*	1.87	3.83
Epoetin equivalent (Units/day)+	756	993

*p-value for treatment difference < 0.0001 (Wilcoxon Rank Sum Test)

+p-value for treatment difference < 0.05 (Wilcoxon Rank Sum Test)

Elemental IV iron intake is calculated as the total IV iron intake divided by the total number of days on study drug

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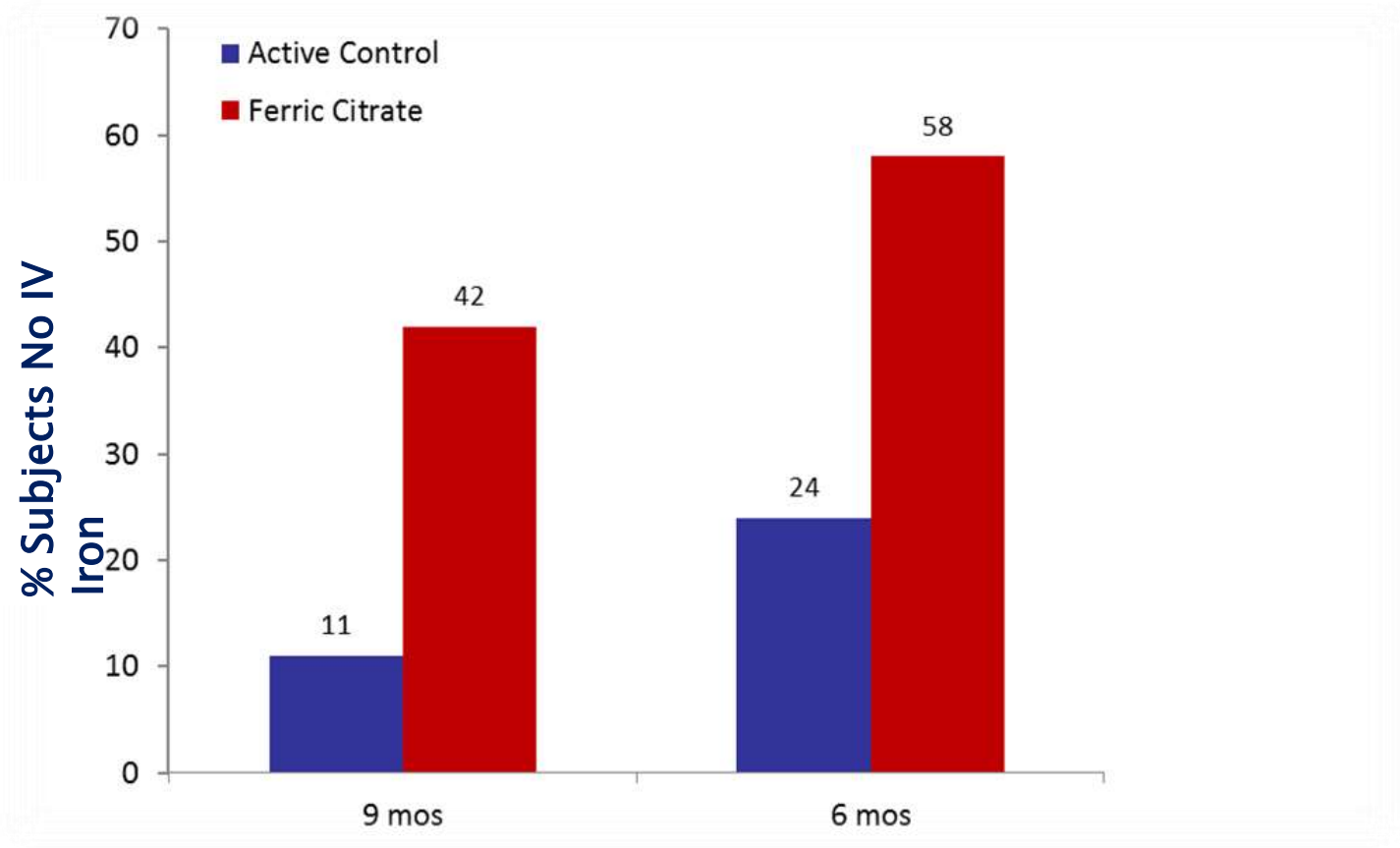
Ferric Citrate Eliminates the Need for IV Iron



Last 6 and 9 Months with NO IV Iron in the Study

p < 0.0001

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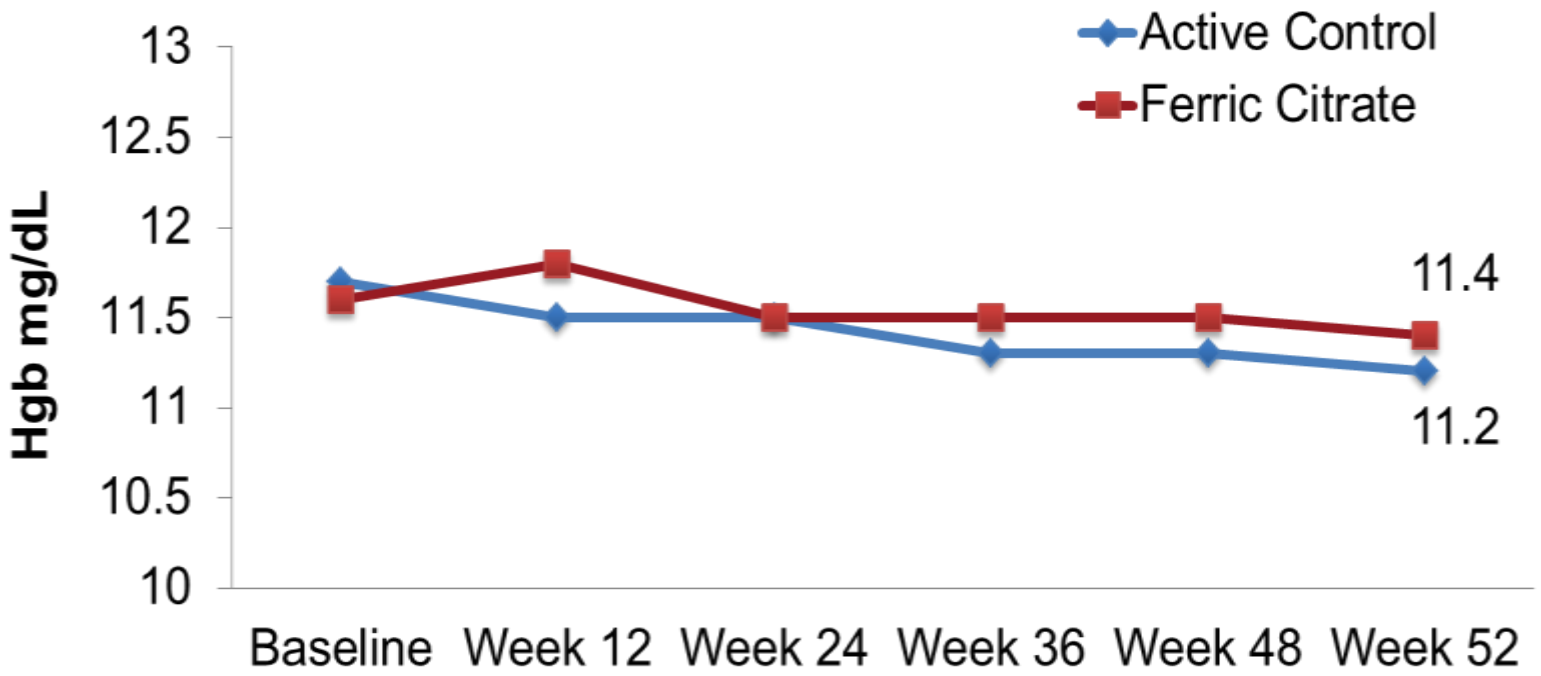
Hemoglobin Remains Stable



p=0.02

Ferric Citrate Safety Profile Similar to Active Control

	Ferric Citrate N = 289	Active Control N = 149
Deaths, (%)	13 (4.5)	8 (5.4)
Subjects with any TEAE, (%)	262 (90.7)	133 (89.3)
Subjects with any SAE, (%)	114 (39.4)	73 (49.0)
Subjects with Infection SAE, (%)	36 (12.5)	27 (18.1)
Subjects with GI SAE, (%)	20 (6.9)	18 (12.1)
Subjects with Cardiac SAE, (%)	20 (6.9)	17 (11.4)

SAE: serious adverse event; TEAE: treatment-emergent adverse event

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PERFECTED-CSG-15 Conclusions

- Ferric Citrate has diverse benefits
- Provides effective phosphorus control compared to placebo and active control
- Raises iron stores
  - TSAT plateaus at 12 weeks, serum ferritin rate of increase decreases
- Decreases IV iron and ESA usage
- Maintains hemoglobin levels
- Saves health care costs through decreasing IV iron and ESA usage

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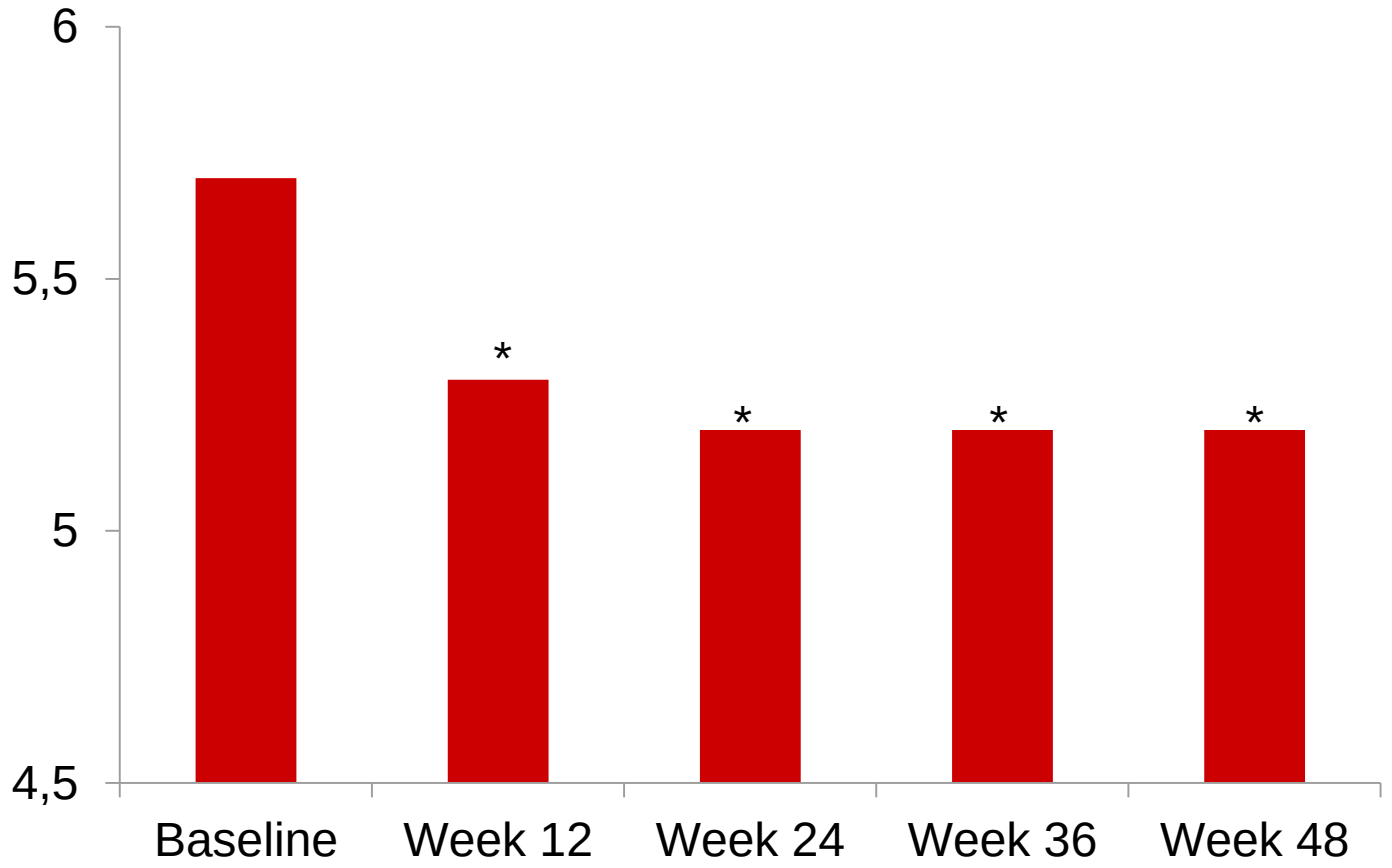
Pragmatic Extension Trial

- Ferric citrate is safe over nearly 2 years of use.

Safety Profile Similar in Extension Trial

	Ferric Citrate in Extension Trial N=166	Ferric Citrate group in PERFECTED N=289	Active Control group in PERFECTED N=149
Deaths, n (%)	6 (3.6%)	13 (4.5%)	8 (5.4%)
Subjects with any TEAE, n (%)	142 (85.5%)	262 (90.7%)	133 (89.3%)
Subjects with any SAE, n (%)	75 (45.2%)	114 (39.4%)	73 (49.0%)
Subjects with Infection SAE, n (%)	30 (18.1%)	36 (12.5%)	27 (18.1%)
Subjects with GI SAE, n (%)	9 (5.4%)	20 (6.9%)	18 (12.1%)
Subjects with Cardiac SAE, n (%)	18 (10.8%)	20 (6.9%)	17 (11.4%)

Ferric Citrate Controls Phosphorus for Additional 48 Weeks



*p<0.05, compared to baseline

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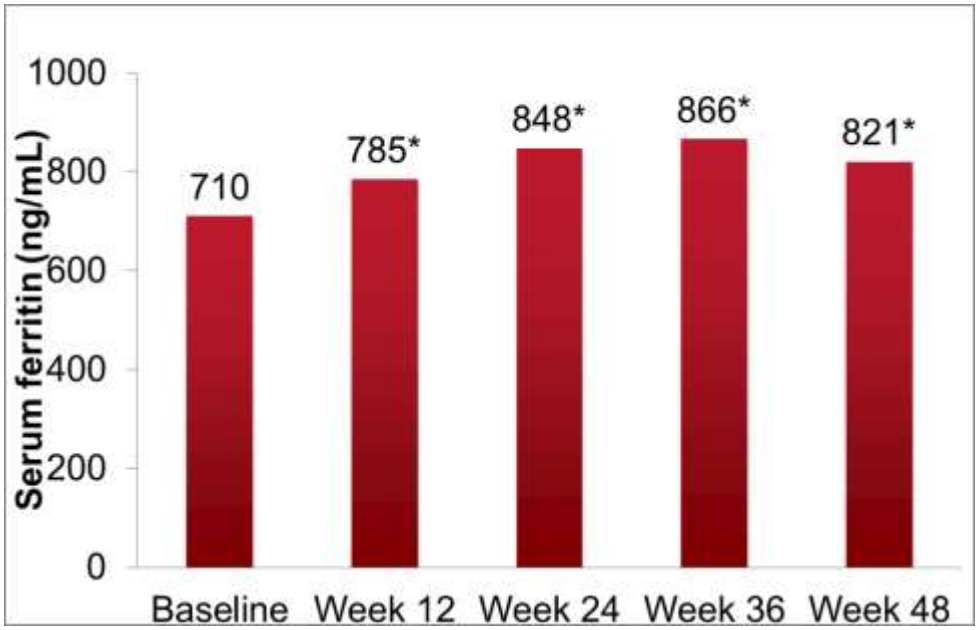
Ferric Citrate has Positive Effects on Iron Stores, IV Iron and ESA Usage

- Iron stores increase
- Ferritin and TSAT levels plateau
- IV Iron use reduced
- ESA use reduced

*p<0.05, compared to Baseline



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CKD-MBD and Anemia in ESRD

- Two domains of therapy in the ESRD patient
- Well nourished patient will require phosphate binders to maintain serum phosphorus levels as dialysis and dietary restrictions rarely suffice
- Dialysis patients develop anemia as a result of diminished EPO production and iron deficiency
  - 70-80% require therapy with iron and ESAs (DOPPS data)
- Ferric citrate can provide therapy across both domains

Ferric Citrate is an Effective Phosphate Binder

- Dose response and efficacy compared to placebo over 4 weeks
- Long term safety and efficacy compared to active control
  - PERFECTED- CSG-15
- Safety extended a further 48 weeks for 100 weeks total
- Ferric citrate effectively controls serum PO_4 in the CKD-MBD domain

Anemia Therapy In ESRD

- Many ESRD patients are iron deficient
  - Absolute and functional
- Kidneys are responsible for EPO production
- Require adequate iron stores to maintain responsiveness to ESAs
- Protocols in dialysis units for IV iron use to target "adequate" iron stores (80% target serum ferritin 1200 ng/mL)
- ESA dosing protocol to maintain hemoglobin level 10-12 g/dL
- Monitored with routine lab work done at least on a monthly basis

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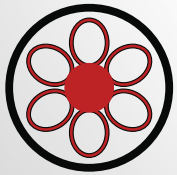
We Have Come Full Circle…

- Historically oral iron (as ferrous sulfate given in the fasting state) could not deliver sufficient iron to maintain Hgb and reduce EPO use. This resulted in the widespread use of IV iron.

- Higher iron stores are now being targeted to reduce EPO use and sustain Hgb.

- The recently completed clinical trial demonstrated that oral ferric citrate, a phosphate binder, given with meals raises iron stores, reduces IV iron use, reduces ESA use, and sustains Hgb.



Oral Ferric Citrate vs. Ferrous Sulfate in Dialysis Patients

ORAL FERRIC CITRATE	ORAL FERROUS SULFATE
Given with meals	Given in fasting state
Much higher tolerability of daily elemental iron dose (2520 mg/day)	Lower tolerability of daily elemental iron dose (200 mg/day)
Increases iron stores; Decreases ESA use; Sustains hemoglobin	Unable to sustain adequate iron stores over time

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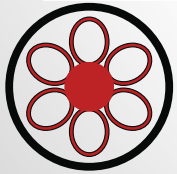
Oral Ferric Citrate vs. IV Iron in Dialysis Patients

ORAL FERRIC CITRATE	IV IRON
Absorption is tightly regulated in the GI tract; Minor GI symptoms	Delivery not regulated; No GI symptoms
Avoids IV Iron administration and its attendant risks (introduction of infection, allergic reactions)	Risks of introduction of infection and allergic reactions
Phosphate binder	Not a phosphate binder
Lower cost	Higher cost
Staff time saving	Staff time consuming



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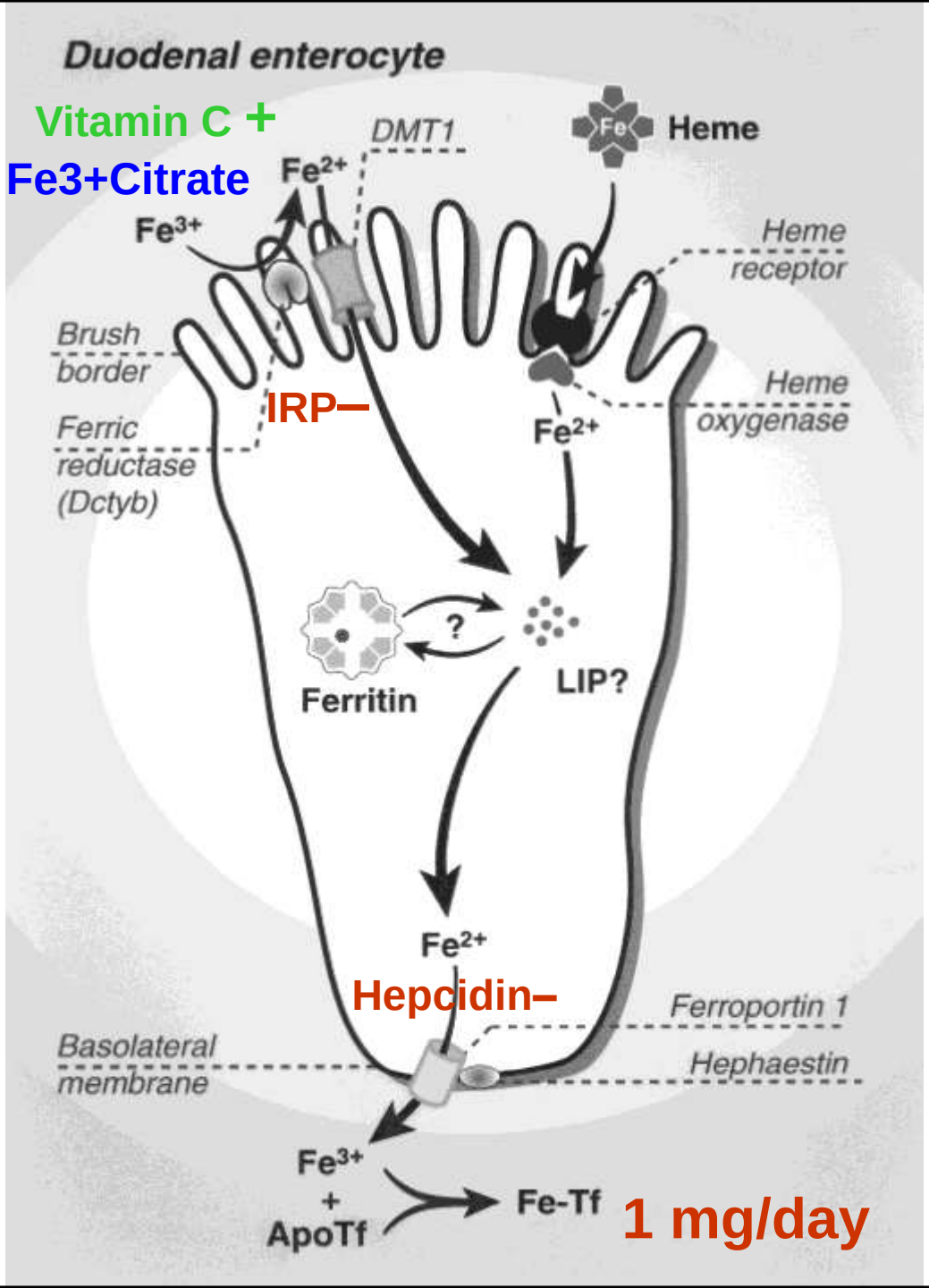
Oral Iron Absorption is Tightly Regulated in the GI Tract



(Koury and Ponka, 2004)

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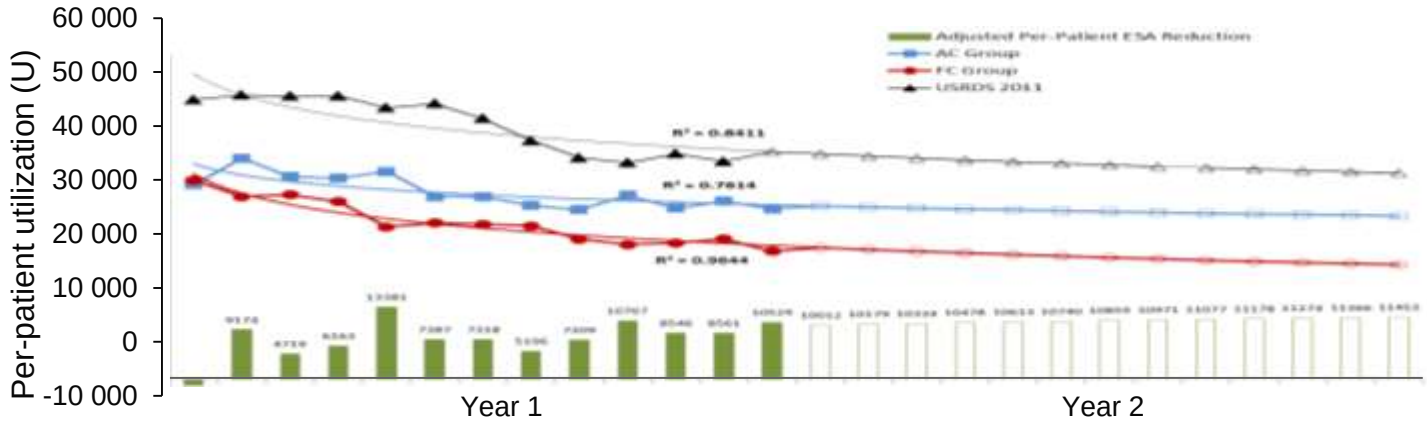
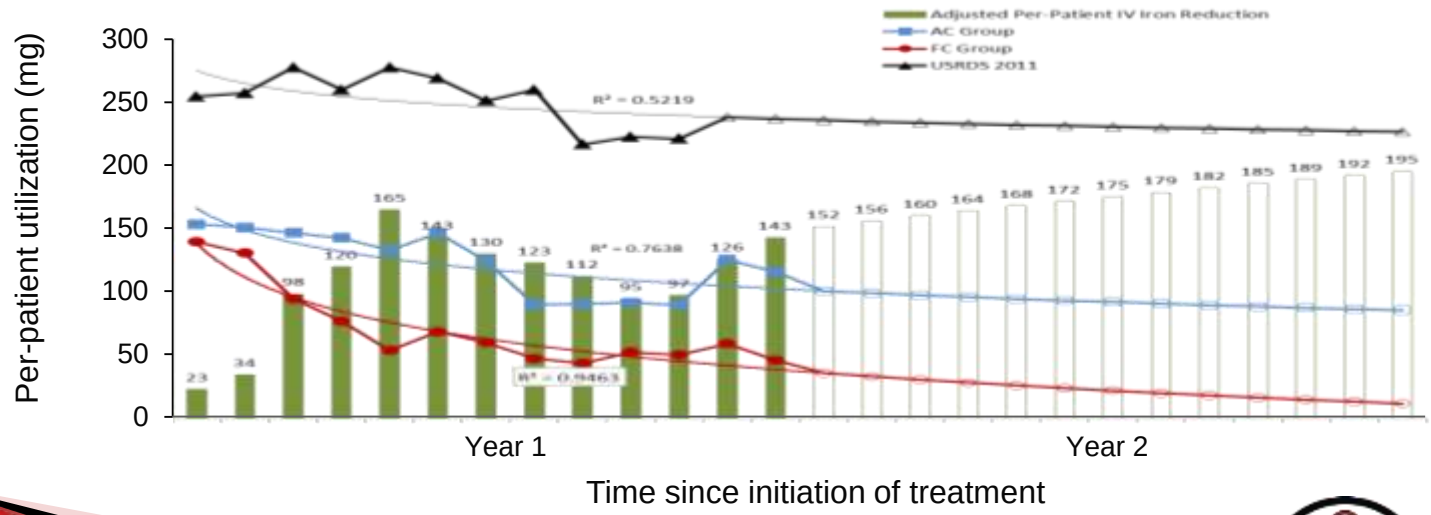
IF IV IRON IS USED IT IS THE NEPHROLOGIST WHO MUST ACT AS HEPSIDIN

Ferric Citrate Provides Cost Savings Based on Reduced IV Iron and ESA Usage

ESA



IV Iron



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How Does Ferric Citrate Fit in the Treatment of ESRD Patients?

- Ferric Citrate will likely become binder of first choice
  - Patients and physicians would like more choices in effective binders
  - It is an effective phosphate binder
- Decreased costs will influence those choices
  - Saved health care dollars can be utilized for other patient needs (fixed sum under bundled ESRD reimbursement)
- Reduced IV administration (Iron and/or ESA) will save personnel time in dialysis units
- Reduced hospitalizations benefits patients and health care system

THANKS FOR YOUR ATTENTION!!