# TRIFERIC DOES NOT INDUCE OXIDATIVE STRESS IN CKD-HD: THE PRIME STUDY

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## ABSTRACT

IV Iron-carbohydrate complexes generate redox-active non-transferrin-bound iron (NTBI) and induce oxidative stress in CKD-HD patients. Oxidative stress is associated with cardiovascular morbidity and mortality.

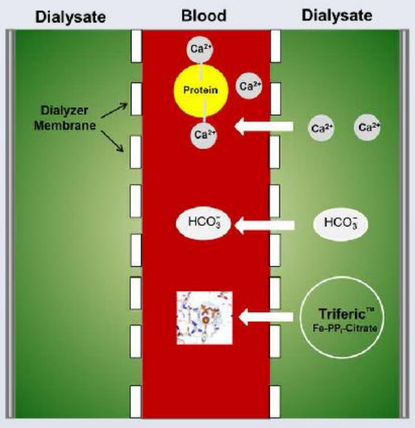
Triferic™ (Soluble Ferric Pyrophosphate or SFP) is a small molecular weight investigational parenteral iron salt devoid of a carbohydrate moiety. In Triferic, pyrophosphate is covalently bonded to iron(III) but promotes rapid iron binding to apotransferrin, thereby minimizing NTBI. The PRIME study randomized 108 iron-replete (baseline ferritin 200-1000 µg/L) CKD-HD patients to Triferic or placebo for up to 36 weeks. ESA could be titrated to maintain a target Hgb level and IV iron could be administered for serum ferritin <200 µg/L. In the Triferic group at the end of treatment, prescribed ESA doses were reduced by 35% (p=0.045) and prescribed IV iron by 51% (p=0.044). Hypo-responders in the Triferic group saw a 74.4% ESA reduction.

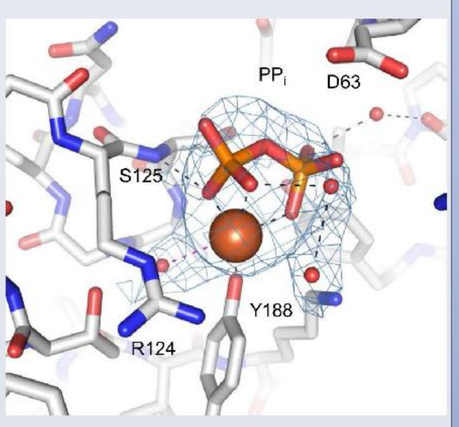
A secondary objective of this study was to compare markers of inflammation (interleukin-6 [IL6]) and oxidative stress (malonydialdehyde [MDA], F2-isoprostanes [F2Iso] and isofurans [IsoF]). Over a single dialysis session, in both treatment groups plasma IL6 statistically significantly increased from pre-dialysis to post-dialysis, whereas MDA and ISoF statistically significantly decreased. F2Iso levels were numerically decreased. Over the 36 weeks of the study (Week 1 *vs* Week 36), there were no statistically significant differences between study groups in pre-dialysis IL6, MDA or ISoF levels . However, F2Iso levels increased 0.001 ng/mL in the placebo group vs decreased 0.003 ng/mL in the SFP group (p = 0.046).

**Conclusions:** Regular administration of Triferic via dialysate does not promote oxidative stress or inflammation either acutely over the course of a single hemodialysis session or after chronic administration for up to 36 weeks.

## INTRODUCTION

- Triferic is a novel, carbohydrate-free, complex iron salt delivered via hemodialysate.
- Crosses the dialyzer membrane during the hemodialysis treatment, binds immediately to apotransferrin and bypasses the RE system.
- Simply replaces the 5-7 mg iron lost with every dialysis treatment.
- Iron concentration of 2 µMol (110 µg/L) maintains iron balance without overloading iron stores.



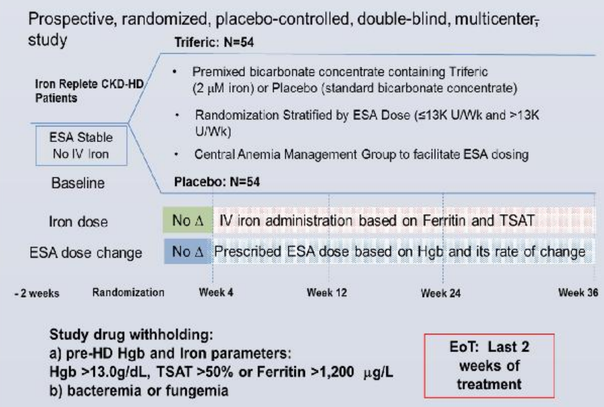




Iron crosses the dialyzer and binds to open sites on transferrin with pyrophosphate.

## OBJECTIVE

- Investigate the effect of administration of Triferic Iron in the dialysate on serum markers of oxidative stress compared to placebo.

## Study Design



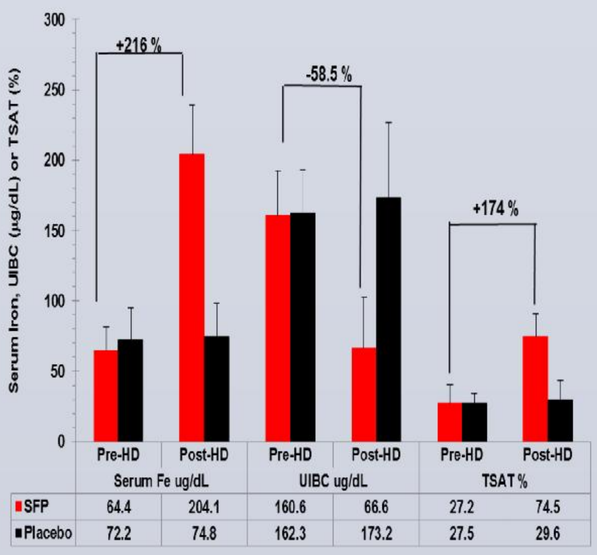

**Study drug withholding:**
**a) pre-HD Hgb and Iron parameters:**
**Hgb >13.0g/dL, TSAT >50% or Ferritin >1,200 µg/L**
**b) bacteremia or fungemia**

**EoT: Last 2 weeks of treatment**

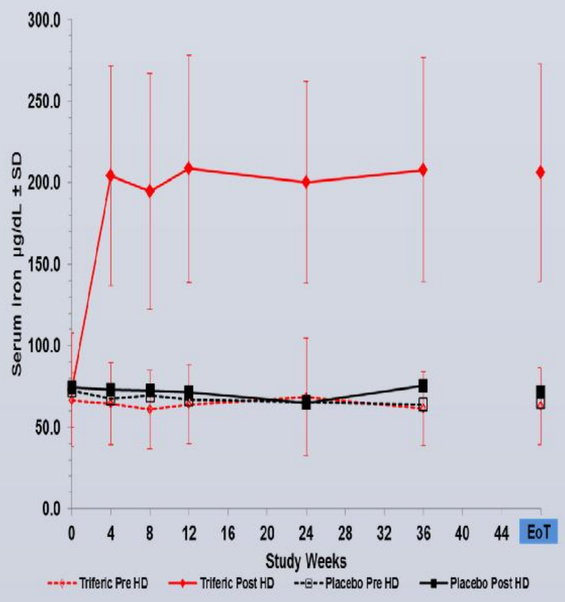
## Measurement of Markers

- C-reactive protein (CRP), and IL-6 concentration were measured as biomarkers of systemic inflammation
- 8-iso PGF2a, Malondialdehyde (MDA) and isofurans were measured as biomarkers of oxidative stress.

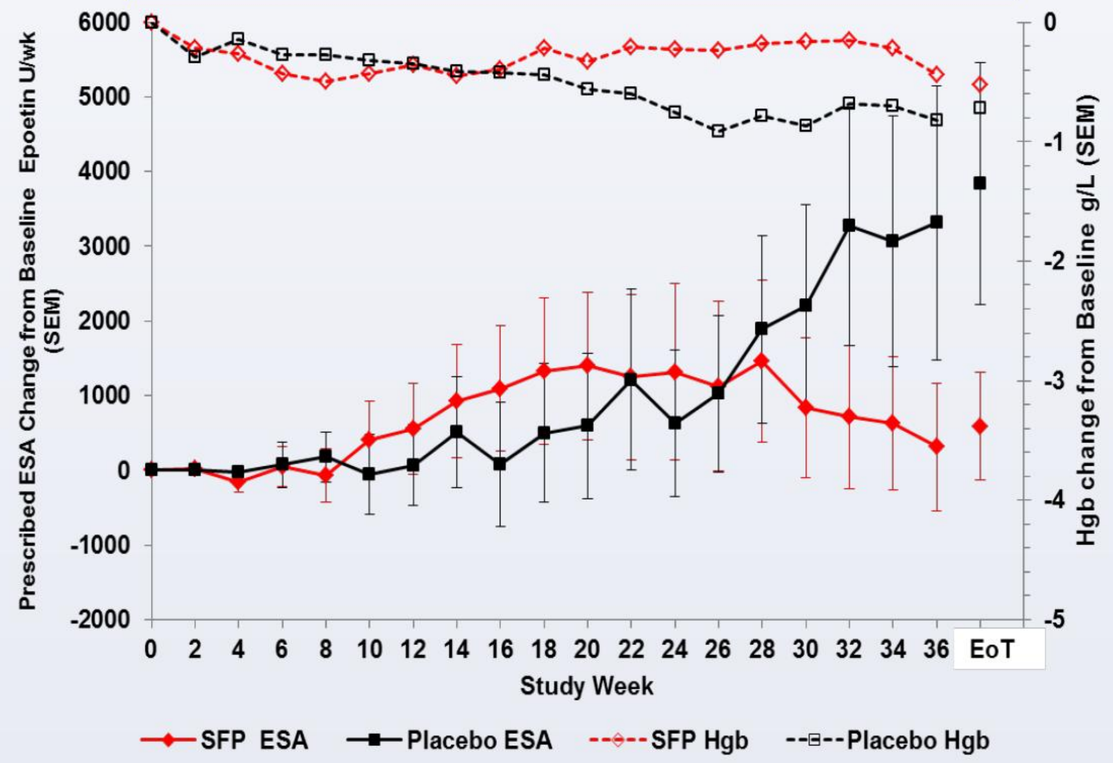
## TRIFERIC RELIABLY DELIVERS IRON AT EACH HD




| | Pre-HD | Post-HD | Pre-HD | Post-HD | Pre-HD | Post-HD |
|---|---|---|---|---|---|---|
| | Serum Fe ug/dL | | UIBC ug/dL | | TSAT % | |
| SFP | 64.4 | 204.1 | 160.6 | 66.6 | 27.2 | 74.5 |
| Placebo | 72.2 | 74.8 | 162.3 | 173.2 | 27.5 | 29.6 |




## TRIFERIC MAINTAINS HGB AND SPARES ESA

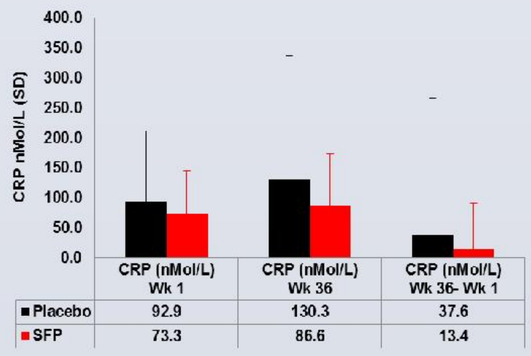



## OXIDATIVE STRESS AND INFLAMMATION ARE NOT DIFFERENT BETWEEN SFP AND PLACEBO AT A SINGLE HD

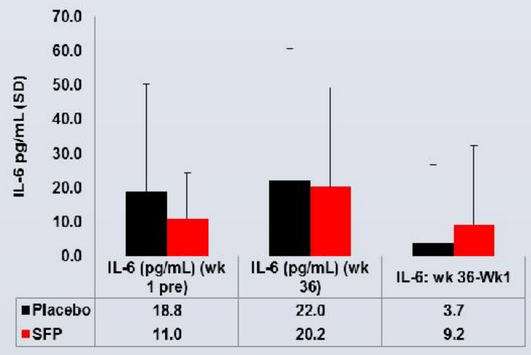
| | Change from Pre to Post HD | | | |
|---|---|---|---|---|
| | Overall N=75 | Placebo N=37 | SFP N=38 | P-value SFP vs Pbo |
| IL-6 pg/mL (SD) | 3.23 (25.69) P=0.002* | 3.65 (36.49) P=0.0095* | 2.85 (7.82) P=0.0082* | NS* |
| MDA µM (SD) | -7.90 (14.38) P<0.001* | -10.01 (14.78) P=0.002* | -5.92 (13.90) P=0.114* | NS* |
| IsoFurans ng/mL (SD) | -0.013 (0.041) P=0.001* | -0.020 (0.041) P<0.001* | -0.006 (0.041) P=0.08* | NS* |
| 8-Iso PGF2a ng/mL (SD) | 0 (0.015) NS* | -0.001 (0.015) NS* | 0.01 (0.015) NS* | NS* |

*Wilcoxen Signed Rank

## TRIFERIC DOES NOT INCREASE MARKERS OF SYSTEMIC INFLAMMATION OVER 36 WEEKS

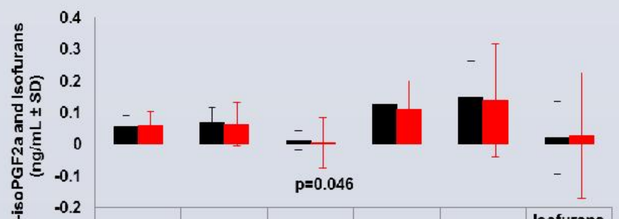



| | CRP (nMol/L) Wk 1 | CRP (nMol/L) Wk 36 | CRP (nMol/L) Wk 36- Wk 1 |
|---|---|---|---|
| Placebo | 92.9 | 130.3 | 37.6 |
| SFP | 73.3 | 86.6 | 13.4 |

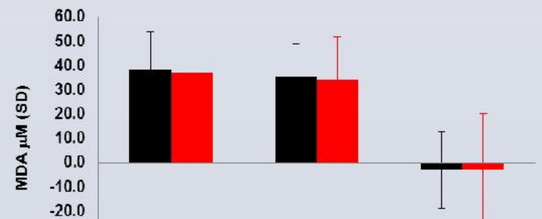



| | IL-6 (pg/mL) (wk 1 pre) | IL-6 (pg/mL) (wk 36) | IL-6: wk 36-Wk1 |
|---|---|---|---|
| Placebo | 18.8 | 22.0 | 3.7 |
| SFP | 11.0 | 20.2 | 9.2 |

## TRIFERIC DOES NOT INCREASE MARKERS OF OXIDATIVE STRESS




| | 8-iso PGF2a (ng/mL) (wk 1) | 8-iso PGF2a (ng/mL) (wk 36) | 8-iso PGF2a: wk 36 – pre wk 1 | Isofurans (ng/mL) (wk 1) | Isofurans (ng/mL) (wk 36) | Isofurans (ng/mL) wk 36 pre – wk 1 |
|---|---|---|---|---|---|---|
| Placebo | 0.056 | 0.068 | 0.0124 | 0.126 | 0.146 | 0.021 |
| SFP | 0.059 | 0.063 | 0.0043 | 0.109 | 0.137 | 0.0283 |




| | MDA (µM) (wk 1 pre) | MDA (µM) (wk 36) | MDA: wk 36 pre – wk 1 |
|---|---|---|---|
| Placebo | 38.0 | 35.0 | -3.1 |
| SFP | 37.0 | 34.0 | -3.0 |

## CONCLUSIONS

- **Triferic reliably delivers iron at each HD treatment**
- **Triferic maintains Hgb and reduces ESA requirements compared to placebo**
- **During a single HD treatment with SFP, the inflammatory response and oxidative stress burden is not different compared to Placebo treatment.**
- **36 weeks of SFP administration decreased pre-dialysis F2Isoprostane levels compared to placebo. The clinical significance of the difference is small.**
- **36 weeks of SFP administration did not influence pre-dialysis IL6, MDA or Isofuran levels compared to placebo**

***Triferic maintains iron stores and Hgb by replacing iron losses that occur at each HD treatment. Triferic bypasses RES processing found in IV iron products and does not increase markers of inflammation or oxidative stress acutely or after 36 weeks administration.***

**Triferic represents a new paradigm for iron replacement in CKD-HD patients.**



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