Pharmacokinetics of Triferic Administered IV to Healthy Volunteers: No Effect on Hepcidin or Oxidative Stress Markers

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INTRODUCTION

- Triferic is a novel iron salt that is not an iron-carbohydrate complex.
- Triferic replaces the 5-7 mg of iron loss that occurs with each hemodialysis procedure.
- Triferic does not require processing and storage by the reticuloendothelial system to provide active iron for tissue metabolism.
- Triferic is added to the hemodialysate via the bicarbonate concentrate and diffuses across the dialyzer membrane.
- Pharmacokinetic studies in healthy volunteers were conducted to characterize the clinical pharmacology of Triferic iron administered intravenously (IV).

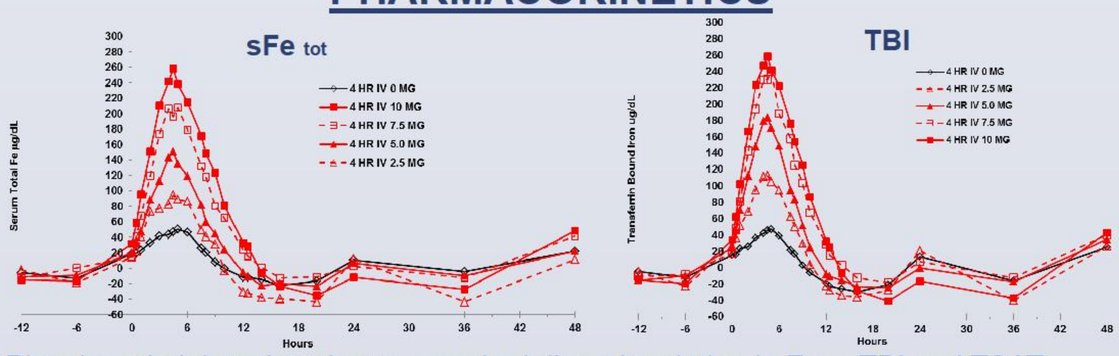
STUDY DESIGN

- Double-blind, single ascending dose, placebo-controlled study of 6 dose levels.
- Infusion times of 4 and 12 hours were chosen to assess the maximal amount of iron that could be safely administered without exceeding total iron binding capacity.
- Each cohort consisted of healthy volunteers (2 placebo and 6 Triferic).
- Triferic was mixed in D5W and administered over 4 or 12 hours via infusion pump.
- Serum total iron (Fe_{tot}) and transferrin-bound iron (TBI) were measured using a validated assay to assess the PK of administered Triferic iron; NTBI was calculated.
- Non-compartmental PK parameters were analyzed.
- Hepcidin-25 was determined by mass spectrometry.
- Soluble transferrin receptor was analyzed by quantitative immunoturbidimetry.
- IL-6 concentration was measured as a biomarker of systemic inflammation.
- 8-iso PGF2α, malondialdehyde (MDA) and isofurans (IsoF) were measured as biomarkers of oxidative stress.

SUBJECT CHARACTERISTICS

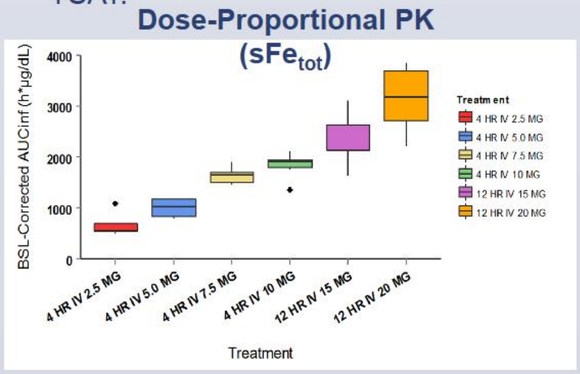
	Triferic	Placebo
Age yrs. [mean (SD)]	29.7 (10.8)	30.5 (10.8)
Sex M/F [n (%)]	17 (47.2)/19 (52.8)	8 (66.7)/4 (33.3)

PHARMACOKINETICS

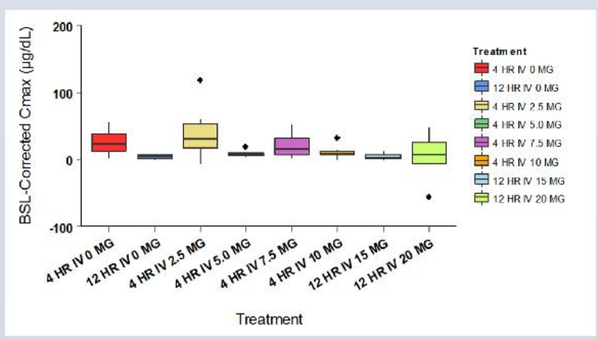


- Placebo administration shows a marked diurnal variation in Fe_{tot}, TBI and TSAT.
- Triferic administered IV demonstrates dose-proportional PK.
- All administered iron is bound to transferrin – no NTBI found at any dose up to 100% TSAT.

Dose-Proportional PK (sFe_{tot})



No Increase in NTBI

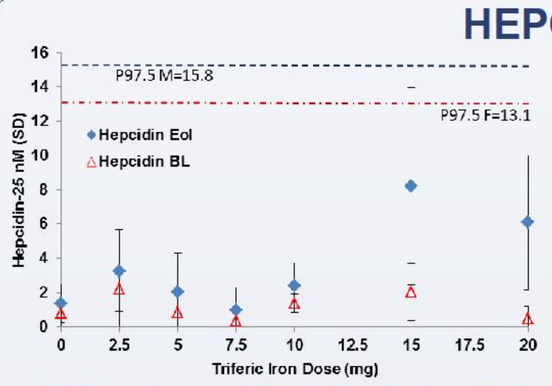


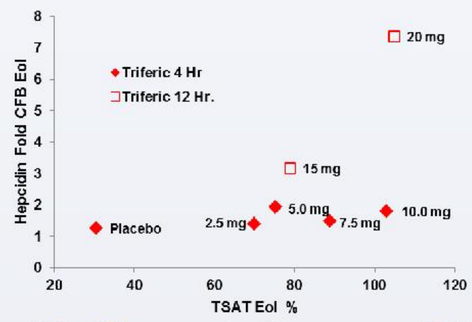
NON-COMPARTMENTAL PK PARAMETERS (sFe_{tot})

Parameter	4-hour Infusion					12-hour Infusion		
Mean (SD)	0 mg	2.5 mg	5.0 mg	7.5 mg	10.0 mg	0 mg	15.0 mg	20.0 mg
λ_z (1/hr)	-	0.544 (0.08)	0.668 (0.28)	0.711 (0.42)	0.917 (0.69)	-	0.475 (0.26)	0.337 (0.11)
$t_{½\ app}$ (hr)	-	1.3 (0.19)	1.19 (0.48)	1.29 (0.72)	1.04 (0.51)	-	1.87 1.08)	2.21 (0.55)
Cl (dL/hr)	-	4.06 (1.2)	5.11 (0.99)	4.59 0.46)	5.56 (0.94)	-	6.72 (1.63)	6.61 (1.50)
T_{max} (hr) median	-	4.5	4.5	4.75	4.5	-	7.5	6
C_{max} (µg/dL)	62.6 (32.4)	113 (44.5)	151 (33.9)	228 (19.7)	261 (30.3)	44.3 (34.8)	177 (38.2)	251 (51.7)
$AUC_{0-\infty}$ (hr*µg/dL)	-	675 (270)	1010 (190)	1650 (172)	1840 (263)	-	2340 (565)	3150 (657)

- Triferic iron is rapidly cleared from the circulation with $t_{½\ app} \cong 1.2$ hr

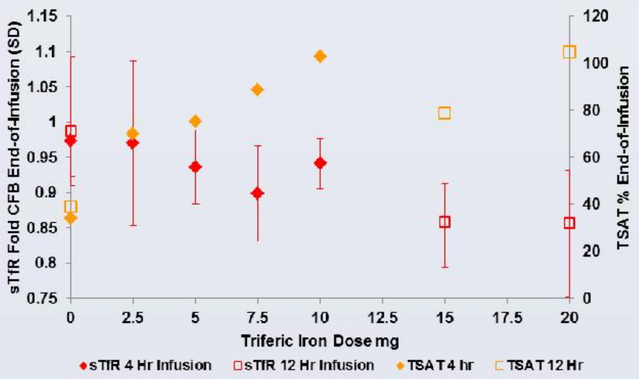
HEPCIDIN-25





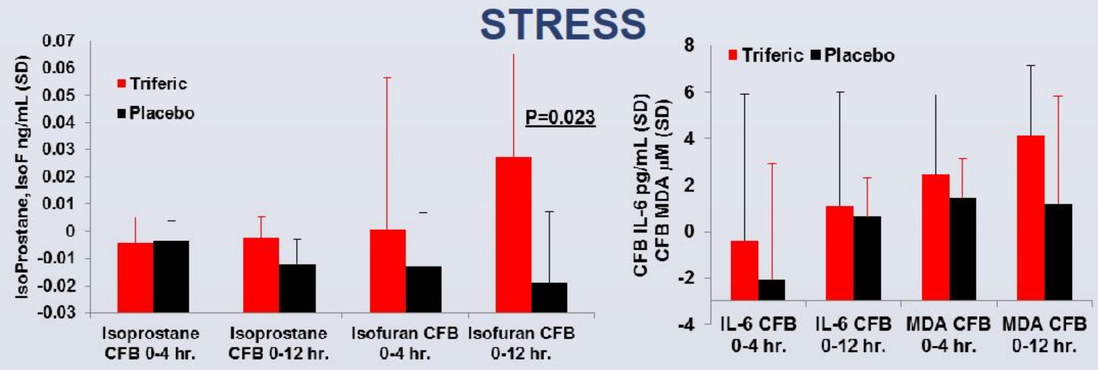
- At Baseline and End-of-Infusion (EoI) all hepcidin-25 concentrations were within published ranges for age and sex.
- No change in hepcidin-25 concentrations at the end of the 4-hour Triferic infusion (EoI).
- There was an increase in hepcidin-25 concentration at EoI with the 12-hour infusion (15 mg 3.2-fold and 20 mg 7.4-fold).
- All hepcidin-25 values returned to baseline concentration by 24 hours.
- The increase in hepcidin-25 with the 15 and 20 mg/12-hour infusion may be related to the 8 hour longer infusion time allowing iron to enter stores and upregulate hepcidin as the iron store regulator.

SOLUBLE TRANSFERRIN RECEPTOR (sTfR)



- Soluble transferrin receptor concentrations declined in a dose-related manner.
- Maximal decline was observed at the two highest doses (15 mg and 20 mg).
- sTfR levels correlate with increased levels of TSAT (diferric Tf).

BIOMARKERS OF INFLAMMATION AND OXIDATIVE STRESS



- There is no consistent effect of Triferic on markers of oxidative stress or inflammation.
- The statistically significant difference between placebo and Triferic on the CFB isofurans at 12 hours is not consistent with the isoprostane results.

SAFETY ASSESSMENT

- TEAE were mild to moderate in intensity and were similar to placebo in number and type.
- No significant safety concerns were noted in the results of the clinical laboratory tests or vital signs values.

CONCLUSIONS

- Triferic was well-tolerated at doses of 2.5 to 10 mg administered over 4 hours and 15 and 20 mg administered over 12 hours.
- IV Triferic demonstrated dose-proportional increase in Fe_{tot} and TBI for C_{max} and AUC across the dose range studied.
- Clearance of Triferic iron, above basal levels, was rapid with an average $t_{½app}$ of ~1.2 hours.
- Administered Triferic iron was completely bound to transferrin as shown by the concordance of total iron and TBI values.
- There was no NTBI observed across the doses of Triferic studied.
- Hepcidin-25 concentrations increased above baseline with the 15 and 20 mg Triferic doses, but returned to baseline by 12 hours post End-of-Infusion.
- Soluble transferrin receptor concentrations decreased at the End-of-Infusion consistent with the increase in TSAT (diferric transferrin) from Triferic.
- Triferic did not induce changes in biomarkers of oxidative stress or inflammation.
- ***Parenteral Triferic iron is rapidly bound to transferrin, rapidly cleared from the circulation and does not significantly increase hepcidin, inflammation or oxidative stress.***
- ***Triferic represents a new paradigm for iron therapy in CKD 5HD patients.***

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