TRIFERIC HAS A SAFETY PROFILE SIMILAR TO PLACEBO: AN INTEGRATED SAFETY ANALYSIS OF PHASE 2 AND 3 STUDIES

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INTRODUCTION

- Triferic™ (FPC) is a novel, carbohydrate-free, complex iron salt delivered via hemodialysate
- Ferric pyrophosphate citrate
- MW 1313 Da, similar to vitamin B_{12}
- Crosses the dialyzer during hemodialysis and binds immediately to apotransferrin, bypassing the RE system
- Replaces the 5-7 mg iron/treatment lost by trapping of blood in dialysis circuit and blood draws
- Dialysate iron concentration of 2 µMol (110 µg/L) maintains iron balance without overloading iron stores
- Reduces ESA requirements by 35% (PRIME study)
- Maintains Hgb in absence of IV iron (CRUISE 1 and 2 pivotal studies)

TRIFERIC CLINICAL DEVELOPMENT PROGRAM

- The Phase 2-3 clinical development program for Triferic in CKD 5HD patients included:
  - **Placebo-Controlled Clinical Studies: CONTROLLED and ALLTriferic**
    - CRUISE 1 and 2: N=588
    - PRIME: N=103
  - **Other Controlled and Open-Label Studies: ALL**
    - SFP-1,-2,-3 and NIH-1 Prelim: N=195
    - SFP-6 Crossover: N= 703
  - **Uncontrolled OL Extension Studies: ALL**
    - CRUISE 1 (OL EXT): N=205
    - CRUISE 2 (OL EXT): N=214
    - SFP-6 (OL EXT): N=309
  - **Unique Triferic patients in Phase 2 and 3 studies: N=1411**
- Safety in all studies was assessed by collection of adverse events (AE), serious adverse events (primarily hospitalizations), laboratory assessments and vital sign data.
- The safety analysis examined the crude incidence of AE, and AE of special interest. Exposure-adjusted event rates and incidences of adverse events were also calculated, as were ratios of AE

DEMOGRAPHICS

	CONTROLLED Triferic N=346	CONTROLLED Placebo N=345	ALL Triferic N=1411
Age (mean SD)	57.5 (12.6)	59.5 (13.7)	58.8 (13.3)
Min, Max	20, 93	21, 89	19, 96
<65: n (%)	247 (71.4)	223 (64.6)	967 (68.5)
≥65: n (%)	99 (28.6)	122 (35.4)	444 (31.5)
Gender: n (%)			
M	210 (60.7)	228 (66.1)	871 (61.7%)
F	136 (39.3)	117 (33.9)	540 (38.3)
Race Group: n (%)			
White	185 (53.5)	198 (57.4)	717 (50.8)
Non-white	161 (46.5)	147 (42.6)	694 (49.2)

DISPOSITION

	CONTROLLED Triferic N=346 n (%)	CONTROLLED Placebo N=345 n (%)	ALL Triferic N=1411† n (%)
Completed study	235 (67.9)	259 (75.1)	982 (82.5)*
Protocol-directed change in anemia management	137 (39.6)	172 (49.9)	
ESA dose change	130 (37.6)	138 (40.0)	
IV Iron requirement	7 (2.0)	35 (10.1)	
Other	98 (28.3)	87 (25.2)	
Discontinued	111 (32.1)	86 (24.9)	209 (17.5)*
Entered OL extension	199 (57.5)	221 (64.1)	
Reason for Discontinuation			
Death	12 (3.5)	8 (2.3)	45 (3.2)
Adverse Event	13 (3.8)	6 (1.7)	45 (3.2)
Protocol Violation	11 (3.2)	6 (1.7)	23 (1.6)
Withdrew Consent	14 (4.0)	12 (3.5)	50 (3.5)
Lost to Followup	1 (0.3)	0	8 (0.6)
Sponsor or Investigator Request	8 (2.3)	4 (1.2)	84 (6.0)
Non-Protocol Change in Anemia Mgmt	16 (4.6)	20 (5.8)	
Transfusion	6 (1.7)	11 (3.2)	
Study Drug Suspended for >12 weeks	0	1 (0.3)	
Other	30 (8.7)	18 (5.2)	267 (18.9)

† Received Triferic at any time
* Denominator is 1191, the number of patients who entered any randomized, controlled treatment period.
^ For the ALL Triferic group, numbers are across both randomized and open-label treatment periods.

ADVERSE EVENTS >5% IN CONTROLLED TRIFERIC

Preferred Term	Controlled Triferic N=346 PYE=158.9 Subjects n (%)	Controlled Triferic N=346 PYE=158.9 Subjects/100 SYE	Controlled Placebo N=345 PYE=161.1 Subjects n (%)	Controlled Placebo N=345 PYE=161.1 Subjects/100 SYE	ALL Triferic N=1411 PYE=780.0 Subjects n (%)	ALL Triferic N=1411 PYE=780.0 Subjects/100 SYE
Procedural Hypotension	81(23.4)	50.98	77(22.3)	47.80	287(20.3)	36.79
Arteriovenous Fistula Site Complication	36(10.4)	22.66	45(13.0)	27.93	172(12.2)	22.05
Diarrhoea	34(9.8)	21.40	37(10.7)	22.97	177(12.5)	22.69
Headache	34(9.8)	21.40	24(7.0)	14.90	163(11.6)	20.90
Cough	33(9.5)	20.77	27(7.8)	16.76	102(7.2)	13.08
Nausea	30(8.7)	18.88	36(10.4)	22.35	184(13.0)	23.59
Haemodialysis-Induced Symptom	29(8.4)	18.25	20(5.8)	12.41	179(12.7)	22.95
Dizziness	26(7.5)	16.36	27(7.8)	16.76	136(9.6)	17.44
Dyspnoea	25(7.2)	15.73	18(5.2)	11.17	120(8.5)	15.38
Pain in Extremity	24(6.9)	15.10	25(7.2)	15.52	99(7.0)	12.69
Oedema Peripheral	23(6.6)	14.47	10(2.9)	6.21	102(7.2)	13.08
Vomiting	22(6.4)	13.85	32(9.3)	19.86	125(8.9)	16.03
Fluid Overload	22(6.4)	13.85	27(7.8)	16.76	89(6.3)	11.41
Muscle Spasms	18(5.2)	11.33	21(6.1)	13.04	77(5.5)	9.87
Upper Respiratory Tract Infection	18(5.2)	11.33	19(5.5)	11.79	70(5.0)	8.97
Asthenia	18(5.2)	11.33	12(3.5)	7.45	58(4.1)	7.44

ADVERSE EVENTS OF SPECIAL INTEREST

	Controlled Triferic N=346	Controlled Placebo N=345	ALL Triferic N=1411
Patient-Years of Exposure	158.9	161.1	779.97
Total N of TEAE	2089	2081	10771
N of Patients With At Least One TEAE, n (%)	278 (80.3)	268 (77.7)	1020 (72.3)
Total N of TEAE of Special Interest	550	588	2367
N of Patients With At Least One TEAE of Special Interest, n (%)	138(39.9)	137(39.7)	526 (37.3)
IDH, n (%)	80 (23.1)	77 (22.3)	262 (18.6)
Symptomatic	37 (46.3)	32 (41.6)	141 (53.8)
Requiring Intervention	52 (65.0)	53 (68.8)	208 (79.4)
Suspected Hypersensitivity Reactions, n (%)	2 (0.6)	1 (0.3)	6 (0.4)
Composite Cardiovascular Events, n (%)	30 (8.7)	35 (10.1)	139 (9.9)
HD Vascular Access Thrombotic Events, n (%)	21 (6.1)	15 (4.3)	121 (8.6)
Arteriovenous Fistula or Graft Thrombosis	19 (5.5)	14 (4.1)	113 (93.4)
HD Catheter Thrombosis	2 (0.6)	2 (0.6)	10 (8.3)
Other Thrombotic Events, n (%)	3 (0.9)	8 (2.3)	43 (3.0)
Systemic/Serious Infections, n (%)	28 (8.1)	32 (9.3)	143 (10.1)

OTHER SAFETY FINDINGS

- Serious adverse events were similar in Triferic and Placebo groups in controlled studies
- Serious adverse events in OL studies were similar to Triferic in controlled studies
- No SAE was considered related to Triferic by the investigators
- Exposure-adjusted mortality in Triferic was 7.9/100 PYE and in Placebo 7.2/100 PYE (controlled studies including SFP-6 crossover)
- Exposure-adjusted mortality in OL Triferic was 6.5/100 PYE
- No death occurred during Triferic administration on hemodialysis
- No death attributed to Triferic by investigators
- No anaphylaxis reported in controlled or open-label studies
- No ECG findings attributed to Triferic
- Triferic reliably delivers iron with each hemodialysis but is rapidly cleared such that serum iron returns to baseline by the next session
  - Pre-dialysis serum iron remained at baseline levels throughout treatment
  - Pre-dialysis ferritin declined by 14% from baseline to EoT
- No laboratory abnormalities attributed to Triferic

CONCLUSIONS

- ***Triferic has a safety profile similar to placebo in controlled studies***
- ***Long term administration of Triferic shows no new safety findings compared to controlled studies***
- ***No anaphylaxis reported in over 100,000 administrations***
- ***When coupled with efficacy data, Triferic demonstrates a positive benefit-to-risk profile***

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J4) Chronic Kidney Disease. Anaemia.
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