Ferric pyrophosphate citrate (Triferic™) administration via the dialysate maintains hemoglobin and iron balance in chronic hemodialysis patients

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ABSTRACT

Background. Administration of ferric pyrophosphate citrate (FPC, Triferic™) via hemodialysate may allow replacement of ongoing uremic and hemodialysis-related iron losses. FPC donates iron directly to transferrin, bypassing the reticuloendothelial system and avoiding iron sequestration.

Methods. Two identical Phase 3, randomized, placebo-controlled trials (CRUISE 1 and 2) were conducted in 599 iron-replete chronic hemodialysis patients. Patients were dialyzed with dialysate containing 2 µM FPC-iron or standard dialysate (placebo) for up to 48 weeks. Oral or intravenous iron supplementation was prohibited, and doses of erythropoiesis-stimulating agents were held constant. The primary efficacy end point was the change in hemoglobin (Hgb) concentration from baseline to end of treatment (EoT). Secondary end points included reticulocyte hemoglobin content (CHr) and serum ferritin.

Results. In both trials, Hgb concentration was maintained from baseline to EoT in the FPC group but decreased by 0.4 g/dL in the placebo group (P < 0.001, combined results; 95% confidence interval [CI] 0.2–0.6). Placebo treatment resulted in significantly larger mean decreases from baseline in CHr (−0.9 pg versus −0.4 pg, P < 0.001) and serum ferritin (−133.1 µg/L versus −69.7 µg/L, P < 0.001) than FPC treatment. The proportions of patients with adverse and serious adverse events were similar in both treatment groups.

Conclusions. FPC delivered via dialysate during hemodialysis replaces iron losses, maintains Hgb concentrations, does not increase iron stores and exhibits a safety profile similar to placebo. FPC administered by hemodialysis via dialysate represents a paradigm shift in delivering maintenance iron therapy to hemodialysis patients.

Keywords: anemia, erythropoiesis-stimulating agent, ferric pyrophosphate citrate, hemodialysis, iron

INTRODUCTION

In patients with hemodialysis-dependent Stage 5 chronic kidney disease (CKD-5HD), iron needs are increased because of elevated erythropoietin requirements resulting from the use of erythropoiesis-stimulating agents (ESAs) and dialysis-associated blood losses, including frequent blood sampling and overt or occult gastrointestinal bleeding [1–3]. At the same time, iron supply is suppressed by the chronic inflammation of renal failure, which stimulates hepatic production of the systemic iron regulatory hormone, hepcidin [3, 4]. To counterbalance increased iron losses and hepcidin-induced sequestration of iron, most hemodialysis patients are currently administered intravenous (IV) iron [5]. Intravenous iron may increase the risks of inflammation, oxidative stress, endothelial dysfunction, cardiovascular disease, immune deficiency and bacterial infections [6] and further exacerbate iron sequestration.

Ferric pyrophosphate citrate (FPC, Triferic™) is a carbohydrate-free, water-soluble, complex iron salt that was first demonstrated to deliver iron via dialysate in 1999, allowing maintenance of hemoglobin (Hgb) concentration and...
iron balance while reducing the need for IV iron by about 80% [7].

FPC is added to liquid bicarbonate concentrate at the clinic. The bicarbonate concentrate with FPC subsequently mixes with acid concentrate and water in the hemodialysis machine to generate dialysate containing 2 µM iron. FPC crosses the dialyzer membrane, enters the blood, donates its iron directly to transferrin and is rapidly cleared from circulation. This provides for iron utilization for erythropoiesis and avoids iron sequestration within reticuloendothelial macrophages [7, 8], thereby avoiding hepcidin-induced iron sequestration.

The Continuous Replacement Using Iron Soluble Equivalents (CRUISE 1 and 2) studies tested the hypothesis that FPC administered via dialysate can sustain iron delivery for erythropoiesis and is more effective than placebo in maintaining Hgb concentration in hemodialysis.

MATERIALS AND METHODS

Two identical, prospective, randomized, single-blind (patients blinded to treatment assignment), placebo-controlled, parallel-group, multicenter, Phase 3 studies were conducted at 88 study locations in the United States and Canada from March 2011 to July 2013.

Study design

The studies consisted of a screening period, followed by three sequential stages (Supplementary data, Figure S1): Stage 1, run-in (1–4 weeks, no study drug treatment); Stage 2, randomized treatment (single-blind treatment for up to 48 weeks; assessment of primary end point) and Stage 3, open-label treatment (long-term safety study; results not reported here).

Patients who met criteria for entry into Stage 2 were randomized in a 1:1 ratio to dialyze during every hemodialysis session with FPC dialysate (2 µmoles [110 µg] iron/liter) or placebo (standard dialysate). Randomization was stratified by pre-randomization Hgb and baseline prescribed ESA dose (see also Supplementary data, Methods).

Oral and IV iron products and changes in ESA product, dose and route of administration were prohibited from screening through the end of Stage 2 (randomized treatment). Patients completed Stage 2 when (i) Hgb became <9.0 or >12.0 g/dL confirmed by a consecutive value obtained within 2 weeks, (ii) ferritin was <100 µg/L confirmed by a consecutive value within 2 weeks, (iii) Hgb was >11.5 g/dL confirmed by a consecutive value within 2 weeks, with an associated Hgb increase of ≥1.0 g/dL over 4 weeks, or (iv) 48 weeks of treatment had elapsed. Patients who completed Stage 2 (randomized treatment) then transitioned to Stage 3 (open-label).

Study population

Patients 18 years or older who had received hemodialysis for ≥4 months using an arteriovenous (AV) fistula or graft or tunneled internal jugular or subclavian catheter were enrolled in Stage 1. Patients had received IV iron between 6 months and 2 weeks before enrollment and had a mean Hgb of 9.5–11.5 g/dL, serum ferritin of 200–800 µg/L and transferrin saturation (TSAT) of 15–40%. ESA doses during the 4 weeks before enrollment were ≤45 000 U/week epoetin or ≤200 µg/week darbe- poetin. For inclusion in Stage 2, patients must have had a mean Hgb of 9.5–11.5 g/dL over the three most recent consecutive weekly measurements, with ≤1.0 g/dL difference between maximum and minimum values.

Exclusion criteria included >800 mg IV iron within 8 weeks or IV iron administration during 2 weeks before enrollment; change in ESA administration route or >35% change in dose during 2 weeks before screening; blood transfusion within 12 weeks before enrollment; serum albumin <3.0 g/dL within 8 weeks before enrollment; low serum folate or vitamin B₁₂ at enrollment; active bleeding or scheduled surgery or concomitant infection or inflammatory disorder other than CKD. Patients who entered Stage 2 were not to have received IV iron in the preceding 4 weeks or had any change in ESA dose during the preceding 6 weeks.

Study procedures

Laboratory evaluations included every-mid-week pre-hemodialysis Hgb; every-other-mid-week pre-hemodialysis ferritin, reticulocyte hemoglobin content (CHR), C-reactive protein (CRP) and serum iron panel; and monthly post-hemodialysis serum iron panel (Supplementary data, Table S1). Treatment-emergent adverse events (TEAEs), transfusions and concomitant medication use were recorded at each visit.

The studies were approved by an institutional review board at each site and written informed consent was obtained from all patients or authorized representatives.

Outcomes

The primary efficacy end point was the mean change in Hgb from baseline to end of treatment (EoT), defined as the last one-sixth of time in the randomized stage (Stage 2) (average of all Hgb values obtained in the window) per patient. The secondary efficacy end points included mean change in Hgb from baseline every 4 weeks; mean change from baseline in ferritin, CHR, serum iron and TSAT every 4 weeks and at EoT; and mean intradialytic change from pre-hemodialysis to post-hemodialysis in serum iron, unsaturated iron-binding capacity (UIBC) and TSAT (see Supplementary data, definition/calculation of selected laboratory end points).

Safety end points included the incidence of intradialytic hypotension (IDH) and incidence and severity of TEAEs.

Statistical analysis

Each trial was designed to detect, with 90% power, a statistically significant treatment difference in Hgb change from baseline between FPC and placebo. The determined sample size of 133 per treatment group per study was increased to 150 per treatment group to allow for early terminations unrelated to iron maintenance or study drug treatment.

The modified intent-to-treat (MITT) population (randomized patients who received at least one dose of study drug and had at least one post-baseline Hgb value) was used for the efficacy analyses. Safety analyses were conducted on the safety population (all patients who received any randomized study drug).
RESULTS

Patients

A total of 599 patients were enrolled; 290 were randomized to FPC and 295 were randomized to placebo (MITT population; Figure 1). Mean age was 57.1 years and 59.6 years in the FPC and placebo groups, respectively (Table 1). Men constituted the majority in both treatment groups. Most patients (>85%) in both groups had undergone hemodialysis for >1 year. No significant differences were observed between groups in relevant laboratory values, medication histories or other characteristics at baseline.

Patients completed Stage 2 when they met one of the three criteria for a protocol-mandated change in anemia management (primarily high or low Hgb, necessitating ESA dose change), and this accounted for completion of Stage 2 in 137 (45.8%) of FPC-treated patients and 172 (57.3%) of placebo-treated patients (Figure 1 and Supplementary data, Table S2). Fifty-five FPC-treated patients (18.4%) and 49 placebo-treated patients (16.3%) completed Stage 2 by reaching 48 weeks of randomized treatment without meeting criteria for a protocol-mandated change in anemia management (Figure 1). Similar proportions in each group transitioned to Stage 3 (FPC, 66.6%; placebo, 73.7%). In total, 35.8 and 26.3% of FPC-treated and placebo-treated patients discontinued from Stage 2 of the studies; all were included in the intention-to-treat analyses.

The proportions of patients who required protocol-mandated changes in ESA dose were similar in the FPC (43.5%) and placebo (46.0%) groups, but the indications for change differed (Supplementary data, Table S2). Among these patients, an increase in Hgb to >12.0 g/dL led to protocol-mandated decreases in ESA dose in 55.4% of FPC-treated patients as compared with 38.4% of placebo-treated patients (P = 0.007), a difference consistent with improved delivery of iron for erythropoiesis by FPC relative to placebo. A decrease in Hgb to <9.0 g/dL led to protocol-mandated increases in ESA dose in 43.5% of patients receiving placebo compared with 30.0% of those receiving FPC (P = 0.02), a divergence suggesting improved delivery of iron for erythropoiesis by FPC relative to placebo.

Intervention

A total of 292 FPC-treated and 296 placebo-treated patients received at least one dose of study drug. Mean and median durations of exposure to study drug in Stage 2 were 159.4 and 128.0 days, respectively, in the FPC group and 161.4 and 143.0 days, respectively, in the placebo group.

Primary and secondary outcomes

FPC met the primary efficacy endpoint, with a treatment difference of 0.4 g/dL in favor of FPC in the mean change in Hgb from baseline to EoT (P = 0.011 for individual studies, 95% confidence interval [CI] 0.1–0.6; P < 0.001 for combined results, 95% CI 0.2–0.6) (Table 2). During Stage 2, mean Hgb values remained stable in the combined FPC group and decreased in the combined placebo group (Figure 2a). Results were consistent between studies (Supplementary data, Figure S2). An intent-to-treat population analysis (FPC, N = 299; placebo, N = 300) was also performed, and results were similar, with a treatment difference of 0.4 g/dL in favor of FPC for the mean change in Hgb from baseline to EoT (P = 0.010 for individual studies, 95% CI 0.1–0.6; P < 0.001 for combined results, 95% CI 0.2–0.5). Additional sensitivity analyses of the combined study data, which were performed by incorporating all data points via mixed-model repeated-measures analysis, provided similar results (Supplementary data, Table S3), as did an analysis of patients who withdrew for protocol-mandated changes in anemia management (Supplementary data, Table S4).

The mean change from baseline in serum ferritin from EoT was significantly smaller in the combined FPC group (−69.7 µg/L, 95% CI −87.2 to −52.2) than in the combined placebo group (−133.1 µg/L, 95% CI −159.9 to −106.3), as well as significantly smaller in the FPC group than in the placebo group in each of the studies (Supplementary data, Figure S3). The mean difference between the FPC and placebo groups for the combined studies was 63.4 µg/L at EoT (95% CI 31.3–95.5, P < 0.001), with significant differences observed between groups at each time point beginning at week 5 (Figure 2b). Mean differences between FPC and placebo were 70.8 µg/L in CRUISE 1 and 55.6 µg/L in CRUISE 2 at EoT (P < 0.001 for both comparisons), with significant differences observed between groups beginning at week 5 in both studies.

The mean (±SD) change from baseline in CHr from baseline at EoT was significantly smaller in the combined FPC group than in the combined placebo group (−0.4 ± 1.3 pg versus −0.9 ± 1.4 pg, P < 0.001) (Figure 2c). Results were consistent between studies (Supplementary data, Figure S4). Similarly, the mean change from baseline in pre-hemodialysis serum iron at EoT was significantly smaller in the combined FPC group than in the combined placebo group (−1.3 ± 23.1 µg/dL versus −6.7 ± 19.7 µg/dL, P = 0.008) (Figure 2d). The mean change from baseline in pre-hemodialysis TSAT at EoT was also significantly smaller in the combined FPC group than in the combined placebo group (−1.0 ± 8.4% versus −3.2 ± 7.8%, P = 0.002) (Figure 2e).

The mean change in serum iron from pre-hemodialysis to post-hemodialysis was larger in the combined FPC group (+104.6 ± 41.6 µg/dL) than in the combined placebo group (+4.6 ± 17.4 µg/dL) (Figure 3). Likewise, a marked increase in mean TSAT from pre-hemodialysis to post-hemodialysis (+35.4 ± 13.4%) was observed in the combined FPC group but not in the combined placebo group (−0.4 ± 5.2%). Mean
UIBC decreased (by −71.2 ± 31.6 µg/dL) from pre-hemodialysis to post-hemodialysis in the combined FPC group to a post-hemodialysis value of 102.3 ± 39.8 µg/dL but did not change significantly in the combined placebo group (+14.9 ± 17.9 µg/dL). Post-dialysis serum iron, TSAT and UIBC values returned to baseline by the time of the next hemodialysis session.

A minority of patients received transfusions (prohibited during randomized stage), leading to study withdrawal. Fewer patients in the combined FPC group (9 patients, 20 units) than in the combined placebo group (23 patients, 48 units) received transfusions (P < 0.02) (Supplementary data, Table S5). This result is consistent with better maintenance of Hgb in the FPC group.

Adverse events

The majority of patients in both groups experienced at least one TEAE (combined FPC, 78.4%; combined placebo, 75.3%; Supplementary data, Table S6). Drug-related TEAEs were reported in 7.5 and 4.1% of the combined FPC and combined placebo groups, respectively. None of the serious TEAEs (reported
in 27.7 and 27.4% of patients in combined FPC and combined placebo groups, respectively) was considered related to study drug. Among patients with TEAEs leading to study discontinuation (combined FPC, 13; combined placebo, 7), events were considered treatment-related in 7 and 0 of the FPC-treated and placebo-treated patients, respectively. Sixteen deaths (combined FPC, 10; combined placebo, 6) led to study discontinuation (Figure 1); none was considered related to study drug.

The most common TEAEs in the combined FPC group were experienced by similar proportions of FPC-treated and placebo-treated patients (Supplementary data, Table S7). The most frequently reported TEAE in both groups was procedural hypotension (primarily IDH, Supplementary data, Table S8), which occurred in 21.6% of FPC-treated patients and 19.3% of placebo-treated patients. Other frequently reported events were AV fistula site complication, muscle spasms, headache and diarrhea. One non-serious case of suspected hypersensitivity was reported (as IDH) in one FPC-treated patient (see Supplementary data, brief summary of case of suspected hypersensitivity); review of the case suggested that the event was likely due to hypovolemia. No clinically meaningful differences were observed between groups in the incidence of TEAEs of special interest [data not shown].

### Table 1. Baseline demographics, Stage 2 (MITT population)

| Variable | CRUISE 1 | Combined |
|----------|----------|----------|
|          | FPC (N = 290) | Placebo (N = 295) | FPC (N = 290) | Placebo (N = 295) |
| Age (years) | 57.1 ± 12.5 | 59.6 ± 13.7 | 57.1 ± 12.5 | 59.6 ± 13.7 |
| Sex | Male | 177 (61.0%) | 195 (66.1%) | 177 (61.0%) | 195 (66.1%) |
| | Female | 113 (39.0%) | 100 (33.9%) | 113 (39.0%) | 100 (33.9%) |
| Race | White | 153 (52.8%) | 165 (55.9%) | 153 (52.8%) | 165 (55.9%) |
| | Black | 111 (38.3%) | 99 (33.6%) | 111 (38.3%) | 99 (33.6%) |
| | Other | 26 (9.0%) | 31 (10.5%) | 26 (9.0%) | 31 (10.5%) |

#### Primary cause of CKD
- Diabetes: 148 (51.0%) vs 145 (49.2%)
- Hypertension: 164 (56.6%) vs 145 (49.2%)
- Received hemodialysis for >1 year: 253 (87.2%) vs 259 (87.7%)

#### History of cardiovascular risk factors and inflammatory conditions
- Heart failure: 90/290 (30.7%) vs 71/295 (24.1%)
- Diabetes: 183/290 (62.8%) vs 180/295 (61.0%)
- Coronary artery disease: 104/290 (35.9%) vs 116/295 (39.3%)
- Cerebrovascular accident: 34/290 (11.7%) vs 45/295 (15.3%)
-Peripheral vascular disease: 44/152 (25.0%) vs 44 (14.9%)

#### Table 2. Change from baseline in Hgb at EoT in Stage 2 (MITT population)

| Variable | CRUISE 1 | CRUISE 2 | Combined |
|----------|----------|----------|----------|
|          | FPC (N = 148) | Placebo (N = 151) | FPC (N = 142) | Placebo (N = 144) | FPC (N = 290) | Placebo (N = 295) |
| Baseline Hgb (g/dL), mean ± SD | 11.0 ± 0.6 | 10.9 ± 0.6 | 11.0 ± 0.6 | 10.9 ± 0.6 | 11.0 ± 0.6 | 10.9 ± 0.6 |
| Change from baseline (g/dL), mean ± SD | 0.0 ± 1.2 | 0.4 ± 1.3 | 0.0 ± 1.2 | 0.4 ± 1.3 | 0.0 ± 1.2 | 0.4 ± 1.3 |

#### DISCUSSION

The primary objective of these studies was to demonstrate that FPC administered via dialysate is more effective than placebo in maintaining Hgb concentration in chronic hemodialysis patients. FPC maintained Hgb from baseline to EoT, and the primary efficacy end point of the mean change in Hgb from baseline to EoT favored FPC by 0.4 g/dL (P < 0.001). This observed magnitude of difference in Hgb concentrations between the two groups was constrained by the study design, which limited changes in Hgb in all patients to within predefined safe upper and lower limits. Since the ESA dose was clamped and iron supplementation was prohibited during the randomized treatment stage, the CRUISE study design allowed completion of the randomized treatment stage and transition to the open-label stage if a patient required a protocol-mandated change in anemia management (Hgb < 9.0 g/dL or ferritin <100 µg/L).

The study population was iron-replete at the time of enrollment as reflected by an average serum ferritin level of about 500 µg/L. In hemodialysis patients, serum ferritin concentrations reflect the magnitude of body iron stores and the effects of chronic inflammation and associated with renal failure.
Because neither group had evidence of significant changes in inflammation based on lack of significant change in CRP during the course of the study, changes in serum ferritin most likely reflected changes in body iron stores. The placebo group experienced decline in serum ferritin due to depletion of iron stores, as a consequence of ongoing uremic- and hemodialysis-associated losses. FPC generally conserved serum ferritin (Figure 2b), indicating that FPC effectively replaced the uremic and gastrointestinal losses that average about 5–7 mg iron per hemodialysis treatment. Fewer FPC-treated patients than placebo-treated patients required a protocol-mandated change in anemia management for a serum ferritin <100 µg/L (3 versus 13% respectively; P < 0.001; Supplementary data, Table S2), indicating that, in actual clinical practice, only a small proportion of patients receiving FPC are likely to experience iron losses that exceed the supply from FPC-iron and will require occasional additional supplementation with IV iron. Notably, with regular administration of FPC, the average serum ferritin level did not exceed baseline values, demonstrating that patients did not develop iron overload. Therefore, maintenance of iron therapy using FPC prevents depletion of iron stores, without causing iron overload, in iron-replete hemodialysis patients.

**FIGURE 2:** Mean change in Hgb concentration (A), ferritin concentration (B), CHr (C), serum iron concentration (D) and TSAT (E) from baseline during Stage 2-CRUISE 1 and 2 studies combined (MITT population). Values other than EoT are based on an LOCF analysis. Bars indicate SEM. For Hgb, P-value is from an analysis of covariance with baseline Hgb as the covariate. For all other parameters, P-value is from a Wilcoxon rank-sum test. CHr, reticulocyte Hgb content; EoT, end of treatment; Fe, iron; FPC, ferric pyrophosphate citrate; Hgb, hemoglobin; LOCF, last post-baseline observation carried forward; MITT, modified intent to treat (FPC, N = 290; placebo, N = 295); TSAT, transferrin saturation.
The intradialytic increase in serum iron and concomitant decrease in UIBC (Figure 3) indicate uptake of FPC-iron by available binding sites on transferrin. The substantial elevation in TSAT during dialysis indicates a greatly increased proportion of diferric transferrin. Diferric transferrin transports twice as much iron as the monoferric form and has a higher affinity for the transferrin receptor, thereby enhancing the efficiency of iron delivery to erythroid precursors [9]. The FPC-iron bound to transferrin is cleared rapidly from the circulation, with TSAT returning to baseline by the next dialysis [7]. This is in contrast to IV iron, which is approved for periodic repletion of iron stores in iron-deficient hemodialysis patients. Intravenous iron in 50–100 mg doses is often infused over a few minutes, generating non-transferrin-bound iron, oxidative stress and endothelial dysfunction [10, 11].

TEAEs, including serious TEAEs, were similar in the groups (Supplementary data, Table S7) and were consistent with those anticipated in CKD-5HD patients. Measurement of indicators of inflammation (CRP) and nutrition (albumin, transferrin) showed no significant changes in the FPC group. The numerical imbalance in the number of deaths in the FPC and placebo groups (Figure 1) is likely secondary to a relatively small sample size since the mortality rate for FPC (6.5 deaths/100 patient-years of exposure [PYE]) in the pooled phase 2 and 3 studies (>1400 patients, representing 780 patient-years of exposure) is similar to the placebo rate (7.2/100 PYE) from recent controlled studies [12]. Neither anaphylaxis nor an increase in the frequency or severity of IDH was observed with FPC. Other IV iron complexes have been rarely associated with hypersensitivity reactions, including anaphylaxis, anaphylactoid reaction and angioedema, which may be associated with the carbohydrate moiety [13]. FPC is a carbohydrate-free iron salt, which may account for the lack of anaphylactic reactions to date.

Although demonstrating that FPC-iron administered via dialysate is able to maintain Hgb concentration, our studies have limitations. Our data may not be generalizable to all types of patients on maintenance hemodialysis. For example, patients with larger blood losses may develop iron deficiency and require supplemental administration of IV iron for repletion of stores. Furthermore, this study did not reflect current clinical practice, which is characterized by frequent ESA dose adjustments and supplemental IV iron to maintain Hgb. These changes had to be prohibited in this study to isolate the effects of FPC on Hgb and demonstrate that the placebo group could develop iron-restricted erythropoiesis while FPC maintained Hgb concentrations.

In conclusion, our studies demonstrate that regular administration of FPC during hemodialysis by addition to the hemodialysis solution is well tolerated and effectively replaces ongoing dialytic and uremic iron losses, thereby maintaining iron balance and Hgb concentration. Maintenance iron therapy using FPC represents a paradigm shift in management of anemia in chronic hemodialysis patients.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

Drs Gupta, Lin and Pratt and Ms Guss are employees of Rockwell Medical, Inc., the sponsor of the studies. Drs Gupta and Pratt hold stock in and serve on the advisory board for Rockwell Medical. Dr Gupta holds the rights to the patent on parenteral delivery of FPC, including via dialysis solutions.

Drs Fishbane, Singh, Cournoyer, Jindal and Fanti received research grants from Rockwell Medical during the conduct of the studies.

Dr Fishbane is a consultant for Rockwell Medical and Keryx. Dr Singh serves on the advisory board for Rockwell Medical and has received research grants from GSK and Sandoz.

Dr Cournoyer has participated on advisory boards for Otsuka, Takeda, Valeant and Sanofi and has received research grants from Amgen, Jansen, Pfizer and Merck.

The results presented in this manuscript have not been published in whole or part, except in abstract form.

(See related article by Fell et al. Ferric pyrophosphate: good things come to those who wait? Nephrol Dial Transplant 2015; 30: 1942–1944.)

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