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(54) Title: USE OF FERRIC CITRATE IN THE TREATMENT OF CHRONIC KIDNEY DISEASE PATIENTS

(57) Abstract: Methods of administering ferric citrate to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in chronic kidney disease patients, are disclosed.

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USE OF FERRIC CITRATE IN THE TREATMENT OF CHRONIC KIDNEY DISEASE PATIENTS

FIELD

Methods and compositions disclosed herein relate generally to the use of ferric citrate to treat chronic kidney disease (CKD) patients.

BACKGROUND

Chronic kidney disease (CKD) is a gradual and progressive loss of the ability of the kidneys to excrete wastes, concentrate urine, and conserve electrolytes. The U.S. National Kidney Foundation defines chronic kidney disease according to the presence or absence of kidney damage and the level of kidney function, regardless of the type (clinical diagnosis) of kidney disease. The primary measure of kidney function is glomerular filtration rate (GFR), which is often estimated as creatinine clearance from serum and urine creatinine concentrations. Chronic kidney disease or failure is defined as having a GFR less than 60 ml/min for three months or more. The U.S. National Kidney Foundation has suggested a five stage classification of renal dysfunction based on GFR:

Stages of renal dysfunction (adapted from National Kidney Foundation—K/DOQI)

Stage	Description	Creatinine Clearance (~GFR: ml/min/1.73 m^2)	Metabolic consequences
1	Normal or increased GFR—People at increased risk or with early renal damage	>90	-
2	Early renal insufficiency	60-89	Concentration of parathyroid hormone starts to rise (GFR~60-80)
3	Moderate renal failure (chronic renal failure)	30-59	Decrease in calcium absorption (GFR<50) Lipoprotein activity falls Malnutrition Onset of left ventricular hypertrophy Onset of anemia
4	Severe renal failure	15-29	Triglyceride concentrations start to rise Hyperphosphatemia

Stage	Description	Creatinine Clearance (~GFR: ml/min/1.73 m^2)	Metabolic consequences
			Metabolic acidosis Tendency to hyperkalemia
5	End stage renal disease (Uremia)	<15	Azotaemia develops

As indicated in the table above, stage 1 is the least severe and stage 5, or ESRD, the most severe. In the early stages of CKD, *e.g.* stages 1-4, dialysis is typically not required. Therefore, patients experiencing the earlier stages of CKD are described as having non-dialysis dependent chronic kidney disease. Such patients are also commonly referred to as non-dialysis chronic kidney disease (ND-CKD) patients. Anemia typically first appears in CKD Stage 3 when the GFR is less than 60 cc/min, long before dialysis is necessary, although anemia may appear at any stage of CKD. At stage 5, a patient may require dialysis treatment several times per week. Once the degeneration process of the kidney begins, the kidney functions in CKD deteriorate irreversibly toward end stage renal disease (ESRD, stage 5). Patients suffering from ESRD cannot survive without dialysis or kidney transplantation.

According to the U.S. National Kidney Foundation, approximately 26 million American adults have CKD and millions of others are at increased risk. Patients experiencing the earlier stages of CKD typically incur increased medical costs of U.S. $14,000 to U.S. $22,000 per patient per year, compared to the age-matched, non-CKD general population. However, there is growing evidence that some of the increased costs and adverse outcomes associated with CKD can be prevented or delayed by preventive measures, early detection, and early treatment.

Iron deficiency and anemia are common complications of CKD, including ESRD. Anemia is the clinical manifestation of a decrease in circulating red blood cell mass and usually is detected by low blood hemoglobin concentration. The properly functioning kidney produces erythropoietin, a hormone that stimulates proliferation and differentiation of red blood cell precursors, which ultimately leads to erythropoiesis (red blood cell production). In the CKD kidney, erythropoietin production is often impaired, leading to erythropoietin deficiency and the concomitant deficiency in erythropoiesis. Anemia is associated with adverse cardiovascular outcomes, ESRD, mortality and diminished quality of life (Macdougall, *Curr Med Res Opin* (2010) 26:473-482). The prevalence of anemia in CKD increases as kidney function decreases. Approximately 50% of non-dialysis chronic kidney

disease patients are anemic, and by the time CKD patients start dialysis, up to 70% are anemic (Macdougall, *supra*, and McClellan *et al.*, *Curr Med Res Opin* (2004) 20:1501-1510).

Iron deficiency is a significant contributor to anemia in CKD patients. The estimated prevalence ranges from 25 to 70% (Hsu, *et al.*, *J Am Soc Nephrol* (2002) 13: 2783–2786; Gotloib *et al.*, *J Nephrol* (2006) 19: 161–167; Mafra, *et al.*, *J Ren Nutr* (2002) 12: 38–41; Kalantar-Zadeh, *et al.*, *Am J Kidney Dis* (1995) 26: 292–299; and Post, *et al.*, *Int Urol Nephrol* (2006) 38: 719–723). The causes include decreased intake or absorption of iron, iron sequestration as a result of inflammation, blood loss, and increased iron use for red blood cell production in response to erythropoiesis stimulating agents (ESAs) (Fishbane, *et al.*, *Am J Kidney Dis* (1997) 29: 319–333; Kooistra, *et al.*, *Nephrol Dial Transplant* (1998) 13: 82–88; and Akmal, *et al.*, *Clin Nephrol* (1994) 42: 198–202). Depending on CKD stage, 20-70% of CKD patients exhibit low iron indices (Quinbi *et al.*, *Nephrol Dial Transplant* (2011) 26:1599-1607). More than 1 million CKD stage 3 or 4 patients in the U.S. are estimated to suffer from iron deficiency. The presence of either low iron stores ("absolute" iron deficiency) or inadequate iron available to meet the demand for erythropoiesis ("functional" iron deficiency) correlates significantly with reduced hemoglobin levels in CKD patients. Iron deficiency can arise from any one or more factors including, for example, insufficient iron from food intake, increased iron utilization, poor gastrointestinal iron absorption, and generalized malabsorption due to renal failure and bacterial overgrowth, and gastrointestinal bleeding (Macdougall, *supra*).

The current standard of care for anemia and/or iron deficiency in CKD patients is administration of erythropoiesis-stimulating agents (ESAs) and/or iron supplementation. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommend either oral or intravenous iron for patients who have CKD stages 1 to 5 and are not on dialysis (*see* "Using iron agents: KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease," *Am J Kidney Dis* (2006) 47: S58–S70). The ferric form of iron (also known as iron(III) or Fe^{3+}) has long been known to have poor bioavailability when administered orally. Therefore, oral formulations for iron supplementation in CKD patients typically contain the ferrous form of iron (also known as iron(II) or Fe^{2+}). Several ferrous oral iron preparations are available for treatment including ferrous gluconate, ferrous fumarate, and ferrous sulfate. The most common oral iron supplement is ferrous sulfate, which can be given up to three times daily in order to provide an adequate dose for treating iron-deficient CKD patients. However, in some CKD patients, oral iron is poorly tolerated because of adverse side effects, or is ineffective in maintaining

adequate body stores of iron. Side effects typically include gastrointestinal problems, such as diarrhea, nausea, bloating and abdominal discomfort. Additionally, because of the frequency in which they are typically given, oral ferrous forms pose a tablet burden on patients and have significant negative gastrointestinal side effects, which lead to non-compliance with oral treatment regimens (Mehdi *et al.*, *supra*).

An alternative is to administer intravenous iron to CKD patients. Some studies have shown that intravenous iron formulations are more effective than either oral ferric iron supplements or oral ferrous iron supplements for treating iron deficiency and/or anemia in CKD patients (Mehdi *et al.*, *supra*). Effective intravenous formulations for the treatment of CKD patients include ferric carboxymaltose, ferumoxytol, ferric gluconate, iron sucrose, and iron dextran. However, intravenous iron is associated with short-term risks such as anaphylaxis and death, as well as with long-term toxicity, including the development of atherosclerosis, infection, and increased mortality (Quinibi *Arzneimittelforschung* (2010) 60:399-412). Further, many CKD clinics, particularly community sites, are ill-equipped to administer intravenous iron because they lack the infrastructure of a dialysis center. This has left a majority of CKD iron-deficient patients without intravenous iron treatment.

Thus, there is need to develop improved methods for treatment of CKD patients.

SUMMARY

Certain aspects of the disclosure provide clinically safe and effective phosphate binders that can be used to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in CKD patients, including non-dialysis CKD (ND-CKD) patients and end state renal disease (ESRD) patients. In certain aspects, the phosphate binder is clinically safe and effective for long term administration to CKD patients, for example up to and including at least 56 weeks of continuous administration.

In accordance with certain embodiments of the disclosure, a candidate for administrative marketing approval as a phosphate binder is the ferric citrate disclosed herein (also known as KRX-0502 (ferric citrate), see Example 1). Pre-clinical studies have demonstrated the ability of the ferric citrate disclosed herein to bind dietary phosphorus, to decrease intestinal absorption of dietary phosphorus and to reduce serum phosphate levels

(Mathew, *et al.*, *J Am Soc Nephrol* (2006) 17: 357A; Voormolen, et al., *Nephrol Dial Transplant* (2007) 22: 2909–2916; and Tonelli *et al.*, *Circulation* (2005) 112: 2627–2633). Four clinical studies of the ferric citrate disclosed herein (*e.g.*, KRX-0502 (ferric citrate)) in patients with ESRD have been conducted and reported to the U.S. Food and Drug Administration as part of the KRX-0502 (ferric citrate) Investigational New Drug (IND) submission. One of those studies, a Phase 3 long term study (described herein), has confirmed that the ferric citrate disclosed herein (also known as KRX-0502) demonstrates a highly statistically significant change in serum phosphorus versus placebo over a four-week Efficacy Assessment Period and can increase ferritin and transferrin saturation (TSAT) and reduce the use of intravenous iron and erythropoiesis-stimulating agents in ESRD patients when compared to active control agents over a 52-week Safety Assessment Period.

In accordance with the present disclosure, it has been discovered that the ferric citrate disclosed herein can be used as a clinically safe and effective phosphate binder to control and/or reduce serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration, increase iron absorption), maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in CKD patients, including non-dialysis CKD (ND-CKD) patients and end state renal disease (ESRD) patients.

In a one aspect, the present disclosure provides methods of reducing and/or controlling serum phosphorus in a patient in need thereof. In some embodiments, the methods comprise orally administering ferric citrate to a CKD patient, e.g., an end-stage renal disease patient, at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides a mean reduction in serum phosphorus of 2.00 – 2.50 mg/dl. In some embodiments, the ferric citrate is administered in a 1 gram tablet dosage form, each dosage form comprising 210 mg of ferric iron. In some embodiments, the patient is administered up to 18 tablet dosage forms per day. In some embodiments, the patient is administered 6 tablet dosage forms per day. In some embodiments, the ferric citrate is administered within 1 hour of the ingestion of a meal or snack by the patient. In some embodiments, the patient was treated with thrice-weekly hemodialysis or with peritoneal dialysis for at least 3 months prior to administration of the ferric citrate. In some embodiments, the ferric citrate has a BET active surface area greater than about 16 m^2/g. In some embodiments, the BET active surface area ranges from about 16 m^2/g to about 20 m^2/g. In some embodiments, the BET active surface area ranges from about 27.99 m^2/g to about 32.34 m^2/g. In some embodiments, the

BET active surface area is selected from 27.99 m^2/g, 28.87 m^2/g and 32.34 m^2/g. In some embodiments, the ferric citrate has an intrinsic dissolution rate of 1.88 – 4.0 $mg/cm^2/min$.

In another aspect, the present disclosure provides methods of reducing serum phosphorus in a patient in need thereof. In some embodiments, the methods comprise orally administering ferric citrate to a CKD patient, e.g., an end-stage renal disease patient, at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides: a mean reduction in serum phosphorus selected from 1.90, 1.91, 1.92, 1.93, 1.94, 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09 and 2.10 mg/dl when administered for a period of 12 weeks; a mean reduction in serum phosphorus selected from 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24 and 2.25 mg/dl when administered for a period of 24 weeks; a mean reduction in serum phosphorus selected from 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19 and 2.20 mg/dl when administered for a period of 36 weeks; a mean reduction in serum phosphorus selected from 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 2.11, 2.12, 2.13, 2.14 and 2.15 mg/dl when administered for a period of 48 weeks; and a mean reduction in serum phosphorus selected from 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24, 2.25, 2.26, 2.27, 2.28, 2.29 and 2.30 mg/dl when administered for a period of 52 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.00 mg/dl when administered for a period of 12 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.20 mg/dl when administered for a period of 24 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.20 mg/dl when administered for a period of 36 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.10 mg/dl when administered for a period of 48 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.10 mg/dl when administered for a period of 52 weeks.

In yet another aspect, the present disclosure provides methods of increasing serum bicarbonate in a patient in need thereof. In some embodiments, the methods comprise orally administering ferric citrate to a CKD patient, e.g., an end-stage renal disease patient, at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides an increase in serum bicarbonate selected from 0.70, 0.71, 0.72, 0.73, 0.74, 0.75, 0.76, 0.77, 0.78, 0.79 and 0.80 mEq/L when administered for a period of at least 52 weeks. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration of 0.71 mEq/L.

In some embodiments, the ferric citrate is administered in a 1 gram tablet dosage form, each dosage form comprising 210 mg of ferric iron. In some embodiments, the patient is administered up to 18 tablet dosage forms per day. In some embodiments, the patient is administered 6 tablet dosage forms per day. In some embodiments, the ferric citrate is administered within 1 hour of the ingestion of a meal or snack by the patient. In some embodiments, the patient was treated with thrice-weekly hemodialysis or with peritoneal dialysis for at least 3 months prior to administration of the ferric citrate. In some embodiments, the ferric citrate has a BET active surface area greater than about 16 m^2/g. In some embodiments, the BET active surface area ranges from about 16 m^2/g to about 20 m^2/g. In some embodiments, the BET active surface area ranges from about 27.99 m^2/g to about 32.34 m^2/g. In some embodiments, the BET active surface area is selected from 27.99 m^2/g, 28.87 m^2/g and 32.34 m^2/g. In some embodiments, the ferric citrate has an intrinsic dissolution rate of 1.88 – 4.0 $mg/cm^2/min$.

In yet another aspect, the present disclosure provides methods of maintaining iron stores in a patient in need thereof. In some embodiments, the methods comprise orally administering ferric citrate to a CKD patient, e.g., a non-dialysis chronic kidney disease patient or an end stage renal disease patient, in an amount ranging from about 1 g to about 18 g per day. In some embodiments, the ferric citrate in administered in a 1 gram tablet dosage form. In some embodiments, the patient is administered up to 18 tablet dosage forms per day. In some embodiments, the ferric citrate has a BET active surface area greater than about 16 m^2/g. In some embodiments, the BET active surface area ranges from about 16 m^2/g to about 20 m^2/g. In some embodiments, the BET active surface area ranges from about 27.99 m^2/g to about 32.34 m^2/g. In some embodiments, the BET active surface area is selected from 27.99 m^2/g, 28.87 m^2/g and 32.34 m^2/g. In some embodiments, the ferric citrate has an intrinsic dissolution rate of 1.88 – 4.0 $mg/cm^2/min$.

In yet another aspect, the present disclosure provides methods of improving one or more iron storage parameters in a patient in need thereof. In some embodiments, the methods comprise orally administering ferric citrate to a CKD patient, e.g., a non-dialysis chronic kidney disease patient or an end stage renal disease patient, in an amount ranging from about 1 g to about 18 g per day. In some embodiments, the at least one iron storage parameter may be selected from serum ferritin levels, transferrin saturation (TSAT), hemoglobin concentration, hematocrit, total iron-binding capacity, iron absorption levels, serum iron levels, liver iron levels, spleen iron levels, and combinations thereof. In some embodiments, the ferric citrate in administered in a 1 gram tablet dosage form. In some embodiments, the

patient is administered up to 18 tablet dosage forms per day. In some embodiments, the ferric citrate has a BET active surface area greater than about 16 m^2/g. In some embodiments, the BET active surface area ranges from about 16 m^2/g to about 20 m^2/g. In some embodiments, the BET active surface area ranges from about 27.99 m^2/g to about 32.34 m^2/g. In some embodiments, the BET active surface area is selected from 27.99 m^2/g, 28.87 m^2/g and 32.34 m^2/g. In some embodiments, the ferric citrate has an intrinsic dissolution rate of 1.88 – 4.0 $mg/cm^2/min$.

In another embodiment, the at least one iron storage parameter is hematocrit, and improving comprises increasing the hematocrit of the patient. In other embodiments, the at least one iron storage parameter is hemoglobin concentration, and improving comprises increasing the hemoglobin concentration of the patient. In yet other embodiments, the at least one iron storage parameter is total iron-binding capacity, and improving comprises decreasing the total iron-binding capacity of the patient. In yet other embodiments, the at least one iron storage parameter is transferrin saturation, and improving comprises increasing the transferrin saturation of the patient. In yet other embodiments, the at least one iron storage parameter is serum iron levels, and improving comprises increasing the serum iron levels of the patient. In yet other embodiments, the at least one iron storage parameter is liver iron levels, and improving comprises increasing the liver iron levels of the patient. In yet other embodiments, the at least one iron storage parameter is spleen iron levels, and improving comprises increasing the spleen iron levels of the patient. In yet other embodiments, the at least one iron storage parameter is serum ferritin levels, and improving comprises increasing the serum ferritin levels of the patient.

In yet another embodiment, the at least one iron storage parameter is serum ferritin levels, and the present disclosure provides methods of increasing serum ferritin in a patient in need thereof. In some embodiments, the methods comprise orally administering ferric citrate to a CKD patient, e.g., an end-stage renal disease patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides a mean increase in serum ferritin in the patient selected from 150 – 310, 151 – 309, 152 – 308, 153 – 307, 154 – 306, 155 – 306, 155 – 305, 155 – 304, 155 – 303 and 155 – 302 ng/ml when administered for a period of at least 52 weeks. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 150 – 305 ng/ml. In some embodiments, the ferric citrate is administered in a 1 gram tablet dosage form, each dosage form comprising 210 mg of ferric iron. In some embodiments, the patient is administered up to 18 tablet dosage forms per day. In some embodiments, the patient is administered 6 tablet dosage forms per day. In some

embodiments, the ferric citrate is administered within 1 hour of the ingestion of a meal or snack by the patient. In some embodiments, the patient was treated with thrice-weekly hemodialysis or with peritoneal dialysis for at least 3 months prior to administration of the ferric citrate. In some embodiments, the ferric citrate has a BET active surface area greater than about 16 m^2/g. In some embodiments, the BET active surface area ranges from about 16 m^2/g to about 20 m^2/g. In some embodiments, the BET active surface area ranges from about 27.99 m^2/g to about 32.34 m^2/g. In some embodiments, the BET active surface area is selected from 27.99 m^2/g, 28.87 m^2/g and 32.34 m^2/g. In some embodiments, the ferric citrate has an intrinsic dissolution rate of 1.88 – 4.0 $mg/cm^2/min$.

In yet another embodiment, the at least one iron storage parameter is transferrin saturation (TSAT), and the present disclosure provides methods of increasing transferrin saturation (TSAT) in a patient in need thereof. In some embodiments, the methods comprise orally administering ferric citrate to an a CKD patient, e.g., an end stage renal disease patient, at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides a mean increase in TSAT of 5 – 10 % when administered for a period of at least 52 weeks. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) in the patient of 6 – 9 %. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) in the patient of 8%. In some embodiments, the ferric citrate is administered in a 1 gram tablet dosage form, each dosage form comprising 210 mg of ferric iron. In some embodiments, the patient is administered up to 18 tablet dosage forms per day. In some embodiments, the patient is administered 6 tablet dosage forms per day. In some embodiments, the ferric citrate is administered within 1 hour of the ingestion of a meal or snack by the patient. In some embodiments, the ferric citrate has a BET active surface area greater than about 16 m^2/g. In some embodiments, the BET active surface area ranges from about 16 m^2/g to about 20 m^2/g. In some embodiments, the BET active surface area ranges from about 27.99 m^2/g to about 32.34 m^2/g. In some embodiments, the BET active surface area is selected from 27.99 m^2/g, 28.87 m^2/g and 32.34 m^2/g. In some embodiments, the ferric citrate has an intrinsic dissolution rate of 1.88 – 4.0 $mg/cm^2/min$.

In yet another embodiment, the at least one iron storage parameter is hemoglobin concentration, and the present disclosure provides methods of increasing hemoglobin concentration in a patient in need thereof. In some embodiments, the methods comprise orally administering ferric citrate to a CKD patient, e.g., an end-stage renal disease patient, at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides a mean increase in hemoglobin concentration in the patient of 0.3 – 0.6 g/dl when administered for a

period of at least 52 weeks. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration in the patient of 0.3 – 0.5 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration of 0.4 g/dl. In some embodiments, the ferric citrate is administered in a 1 gram tablet dosage form, each dosage form comprising 210 mg of ferric iron. In some embodiments, the patient is administered up to 18 tablet dosage forms per day. In some embodiments, the patient is administered 6 tablet dosage forms per day. In some embodiments, the ferric citrate is administered within 1 hour of the ingestion of a meal or snack by the patient. In some embodiments, the ferric citrate has a BET active surface area greater than about 16 m^2/g. In some embodiments, the BET active surface area ranges from about 16 m^2/g to about 20 m^2/g. In some embodiments, the BET active surface area ranges from about 27.99 m^2/g to about 32.34 m^2/g. In some embodiments, the BET active surface area is selected from 27.99 m^2/g, 28.87 m^2/g and 32.34 m^2/g. In some embodiments, the ferric citrate has an intrinsic dissolution rate of 1.88 – 4.0 $mg/cm^2/min$.

In yet another aspect, the present disclosure provides methods of increasing iron absorption in a patient in need thereof. In some embodiments, the methods comprise orally administering ferric citrate to a CKD patient, e.g., a non-dialysis chronic kidney disease patient or an end stage renal disease patient, in an amount ranging from about 1 g to about 18 g per day. In some embodiments, the ferric citrate in administered in a 1 gram tablet dosage form. In some embodiments, the patient is administered up to 18 tablet dosage forms per day. In some embodiments, the ferric citrate has a BET active surface area greater than about 16 m^2/g. In some embodiments, the BET active surface area ranges from about 16 m^2/g to about 20 m^2/g. In some embodiments, the BET active surface area ranges from about 27.99 m^2/g to about 32.34 m^2/g. In some embodiments, the BET active surface area is selected from 27.99 m^2/g, 28.87 m^2/g and 32.34 m^2/g. In some embodiments, the ferric citrate has an intrinsic dissolution rate of 1.88 – 4.0 $mg/cm^2/min$.

In yet another aspect, the present disclosure provides methods of treating iron deficiency in a patient in need thereof. In some embodiments, the methods comprise orally administering ferric citrate to a CKD patient, e.g., a non-dialysis chronic kidney disease patient or an end stage renal disease patient, in an amount ranging from about 1 g to about 18 g per day. In some embodiments, the iron deficiency is anemia. In some embodiments, the treatment provides a hemoglobin level in the patient that is at or above a level selected from 12.0 g/dl and 7.4 mmol/L. In other embodiments, the treatment provides a hemoglobin level in the patient that is at or above a level selected from 13.0 g/dl and 8.1 mmol/L. In yet other embodiments, the treatment provides a hemoglobin level in the patient that is at or above a

level selected from 6.8 mmol/L, 7.1 mmol/L, 7.4 mmol/L, and 8.1 mmol/L. In yet other embodiments, the treatment provides a hemoglobin level in the patient that is at or above a level selected from 11.0 g/dl, 11.5 g/dl, 12.0 g/dl, and 13.0 g/dl. In some embodiments, the treatment reduces at least one symptom of iron deficiency selected from fatigue, dizziness, pallor, hair loss, irritability, weakness, pica, brittle or grooved nails, Plummer-Vinson syndrome, impaired immune function, pagophagia, restless legs syndrome and combinations thereof. In some embodiments, the ferric citrate in administered in a 1 gram tablet dosage form. In some embodiments, the patient is administered up to 18 tablet dosage forms per day. In some embodiments, the ferric citrate has a BET active surface area greater than about 16 m^2/g. In some embodiments, the BET active surface area ranges from about 16 m^2/g to about 20 m^2/g. In some embodiments, the BET active surface area ranges from about 27.99 m^2/g to about 32.34 m^2/g. In some embodiments, the BET active surface area is selected from 27.99 m^2/g, 28.87 m^2/g and 32.34 m^2/g. In some embodiments, the ferric citrate has an intrinsic dissolution rate of 1.88 – 4.0 $mg/cm^2/min$.

In yet another aspect, the present disclosure provides methods of reducing intravenous (IV) iron use in a CKD patient, e.g., an end-stage renal disease patient. In some embodiments, the methods comprise orally administering ferric citrate to the patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate reduces the need for the end-stage renal disease patient to be administered IV iron by an amount selected from 50, 51, 52, 53, 54, 55, 56, 57, 58, 59 and 60 % when administered for a period of at least 52 weeks. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake selected from 51.0, 51.1, 51.2, 51.3, 51.4, 51.5, 51.6, 51.7, 51.9 and 52.0 %. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake of 51.6 %. In some embodiments, the ferric citrate is administered in a 1 gram tablet dosage form, each dosage form comprising 210 mg of ferric iron. In some embodiments, the patient is administered up to 18 tablet dosage forms per day. In some embodiments, the patient is administered 6 tablet dosage forms per day. In some embodiments, the ferric citrate is administered within 1 hour of the ingestion of a meal or snack by the patient. In some embodiments, the patient was treated with thrice-weekly hemodialysis or with peritoneal dialysis for at least 3 months prior to administration of the ferric citrate. In some embodiments, the ferric citrate has a BET active surface area greater than about 16 m^2/g. In some embodiments, the BET active surface area ranges from about 16 m^2/g to about 20 m^2/g. In some embodiments, the BET active surface area ranges from about 27.99 m^2/g to about 32.34 m^2/g. In some embodiments, the BET active surface area is

selected from 27.99 m^2/g, 28.87 m^2/g and 32.34 m^2/g. In some embodiments, the ferric citrate has an intrinsic dissolution rate of 1.88 – 4.0 $mg/cm^2/min$.

In yet another aspect, the present disclosure provides methods of reducing use of erythropoiesis-stimulating agents (ESAs) in a CKD patient, e.g., an end-stage renal disease patient. In some embodiments, the methods comprise orally administering ferric citrate to the patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate reduces the need for the patient to be administered one or more ESAs by an amount selected from 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30 % when administered for a period of at least 52 weeks. In some embodiments, the ferric citrate provides a decrease in median ESA intake selected from 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.9 and 28.0 %. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake of 27.1 %. In some embodiments, the ferric citrate is administered in a 1 gram tablet dosage form, each dosage form comprising 210 mg of ferric iron. In some embodiments, the patient is administered up to 18 tablet dosage forms per day. In some embodiments, the patient is administered 6 tablet dosage forms per day. In some embodiments, the ferric citrate is administered within 1 hour of the ingestion of a meal or snack by the patient. In some embodiments, the patient was treated with thrice-weekly hemodialysis or with peritoneal dialysis for at least 3 months prior to administration of the ferric citrate. In some embodiments, the ferric citrate has a BET active surface area greater than about 16 m^2/g. In some embodiments, the BET active surface area ranges from about 16 m^2/g to about 20 m^2/g. In some embodiments, the BET active surface area ranges from about 27.99 m^2/g to about 32.34 m^2/g. In some embodiments, the BET active surface area is selected from 27.99 m^2/g, 28.87 m^2/g and 32.34 m^2/g. In some embodiments, the ferric citrate has an intrinsic dissolution rate of 1.88 – 4.0 $mg/cm^2/min$.

DETAILED DESCRIPTION

In some aspects, the present disclosure provides methods of using a ferric citrate to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration), increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in chronic kidney disease (CKD) patients. In each instance, the methods comprise administering ferric citrate to a CKD patient, including a non-dialysis CKD (ND-CKD) patient as well as an end stage renal disease

(ESRD) patient. In some aspects, the administration of ferric citrate occurs over a long period of time including, for example, up to and including 52 weeks. In some embodiments, the administration of ferric citrate occurs over a period up to and including 56 weeks.

In each of these disclosed methods, ferric citrate may be administered to the CKD patient over a period of time that is at least 52 weeks and, in some embodiments, up to and including 56 weeks or longer. Additionally, in each of these methods the ferric citrate may be administered to the CKD patient orally, in a 1 g tablet, or caplet, dosage form that contains 210 mg of ferric iron. Up to 18 tablets, or caplets, may be administered over the course of a day.

The present disclosure also provides pharmaceutical compositions, which may also be an iron supplement, which may be administered to CKD patients. The compositions/iron supplements comprise ferric citrate as well as other pharmaceutically acceptable ingredients, as described below. The compositions/iron supplements are formulated to provide iron to CKD patients, and the amount of iron provided by the compositions/iron supplements is sufficient to increase iron absorption, improve one or more iron storage parameters, treat iron deficiency and/or treat anemia in CKD patients. The compositions/iron supplements may be provided in any number of forms, as described below. In particular, the compositions/iron supplements may be provided as oral tablet dosage forms.

Reference is now made in detail to certain embodiments of ferric citrate, dosage forms, compositions, methods of synthesis and methods of use. The disclosed embodiments are not intended to be limiting of the claims. To the contrary, the claims are intended to cover all alternatives, modifications, and equivalents.

Therapeutic Uses of Ferric Citrate

As set forth in greater detail below, disclosed herein are methods and dosage forms that can be used to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in CKD patients, including non-dialysis CKD (ND-CKD) patients and end state renal disease (ESRD) patients.

Therefore, in various aspects, the ferric citrate disclosed herein may be administered to CKD patients to reduce and/or control serum phosphorus. In various aspects, the ferric citrate disclosed herein may be administered to CKD patients to increase serum bicarbonate.

In various aspects, the ferric citrate disclosed herein may be administered to CKD patients to improve one or more iron storage parameters, including to increase serum ferritin, to increase transferrin saturation (TSAT), and to increase hemoglobin concentration. In various aspects, the ferric citrate disclosed herein may be administered to CKD patients to increase iron absorption. In various aspects, the ferric citrate disclosed herein may be administered to CKD patients to maintain iron stores. In various aspects, the ferric citrate disclosed herein may be administered to CKD patients to treat iron deficiency. In various aspects, the ferric citrate disclosed herein may be administered to CKD patients to treat anemia. In various aspects, the ferric citrate disclosed herein may be administered to CKD patients to reduce the need for IV iron and/or erythropoiesis-stimulating agents (ESAs).

Methods of treating CKD patients are also disclosed. In various aspects, the present disclosure provides methods of reducing and/or controlling serum phosphorus, the methods comprising orally administering ferric citrate to a CKD patient, wherein the ferric citrate provides a reduction in serum phosphorus. In various aspects, the present disclosure provides methods of increasing serum bicarbonate, the methods comprising orally administering ferric citrate to a CKD patient, wherein the ferric citrate provides an increase in serum bicarbonate. In various aspects, the present disclosure provides methods of improving one or more iron storage parameters, the methods comprising orally administering ferric citrate to a CKD patient, wherein the ferric citrate provides improvement in one or more iron storage parameters. In various aspects, the present disclosure provides methods of increasing serum ferritin, the methods comprising orally administering ferric citrate to a CKD patient, wherein the ferric citrate provides an increase in serum ferritin. In various aspects, the present disclosure provides methods of increasing transferrin saturation (TSAT), the methods comprising orally administering ferric citrate to a CKD patient, wherein the ferric citrate provides an increase in TSAT. In various aspects, the present disclosure provides methods of increasing hemoglobin concentration, the methods comprising orally administering ferric citrate to a CKD patient, wherein the ferric citrate provides an increase in hemoglobin concentration. In various aspects, the present disclosure provides methods of increasing iron absorption, the methods comprising orally administering ferric citrate to a CKD patient, wherein the ferric citrate provides an increase in iron absorption. In various aspects, the present disclosure provides methods of maintaining iron stores, the methods comprising orally administering ferric citrate to a CKD patient, wherein the ferric citrate provides for maintenance of iron stores. In various aspects, the present disclosure provides methods of treating iron deficiency, the methods comprising orally administering ferric citrate to a CKD

patient, wherein the ferric citrate provides treatment of iron deficiency. In various aspects, the present disclosure provides methods of treating anemia, the methods comprising orally administering ferric citrate to a CKD patient, wherein the ferric citrate provides for treatment of anemia. In various aspects, the present disclosure provides methods of reducing intravenous (IV) iron use in a CKD patient, the methods comprising orally administering ferric citrate to CKD patient, wherein the ferric citrate reduces the need for the CKD to be administered IV iron. In various aspects, the present disclosure provides methods of reducing use of erythropoiesis-stimulating agents (ESAs) in CKD patient, the methods comprising orally administering ferric citrate to the CKD patient, wherein the ferric citrate reduces the need for the CKD patient to be administered one or more ESAs when administered. In each of the methods, the ferric citrate may be administered for a period of time up to and including 52 weeks, including up to and including 56 weeks.

Chronic Kidney Disease Patients

In various aspects, the ferric citrate disclosed herein is administered to any chronic kidney disease (CKD) patients to treat any of the conditions and disorders associated with CKD, such as described herein. All individuals with a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for 3 months are classified as having CKD, irrespective of the presence or absence of kidney damage. Those individuals with CKD who require either dialysis or kidney transplantation are typically referred to as end-stage renal disease (ESRD) patients. Therefore, a patient is traditionally classified as an ESRD patient when he or she reaches the conclusion of the non-dialysis dependent, earlier stages, of CKD. Prior to then, those patients are referred to as non-dialysis dependent CKD patients. However, patients with an advanced stage of CKD, such as stage 5, who have not yet started dialysis or who have not been recommended for transplantation are also typically referred to as non-dialysis dependent CKD patients.

Non-dialysis CKD (ND-CKD) patients are those who have been diagnosed with an early stage of chronic kidney disease and who have not yet been medically directed to undergo dialysis. As noted above, the U.S. National Kidney Foundation has defined 5 stages of chronic kidney disease. Typically, patients progress through stages 1 through 4 before dialysis is medically necessary.

As used herein, ND-CKD is intended to cover all patients who have been diagnosed with chronic kidney disease but who are not undergoing dialysis during the administration of ferric citrate. Such patients can include, for example, patients who have never been subjected

to dialysis and, in some embodiments, patients who have been subjected to dialysis but who are not undergoing dialysis during the administration of ferric citrate.

In various aspects, ESRD patients are typically those who have been diagnosed with a late stage of chronic kidney disease. In some instances the phrase "end-stage renal disease" is used to indicate the fifth stage of CKD. Therefore, as used herein, an ESRD patient is a patient who has an advanced stage of CKD, such as stage 5, and who has begun either hemodialysis or peritoneal dialysis and/or who has been recommended for kidney transplantation by a health care provider.

In some embodiments, CKD patients display one or more of the following characteristics: a serum phosphorus level between 2.5 mg/dL and 8.0 mg/dL; a serum phosphorus level greater than or equal to 6.0 mg/dL when removed from a phosphate binder; are taking 3 to 18 pills/day of calcium acetate, calcium carbonate, lanthanum carbonate, sevelamer (carbonate or hydrochloride or equivalent sevelamer powder), any other agent serving as a phosphate binder, or a combination of any of the foregoing; have a serum ferritin level that is less than 1000 mg/L; have a transferrin saturation level (TSAT) that is less than 50% at screening; have a life expectancy of more than 1 year; or a combination of any of the foregoing.

In addition, CKD patients may be taking phosphorus binding agents other than ferric citrate, though this is not required. The CKD patients can be mammals and, in some embodiments, are humans. In some embodiments, CKD patients are female or male of any age and/or weight. In some embodiments, CKD patients are males or non-pregnant, non-breastfeeding females who are at least 18 years of age and have been on thrice-weekly hemodialysis and/or peritoneal dialysis for at least 3 months.

Serum Phosphorus

Phosphate is critical for a vast array of cellular processes. It is one of the major components of the skeleton and an integral component of the nucleic acids that make up DNA and RNA. In addition, the phosphate bonds of adenosine triphosphate (ATP) carry the energy required for all cellular functions. Phosphate functions as a buffer in bone, serum, and urine and the addition and/or deletion of phosphate groups to/from enzymes and proteins are common mechanisms for the regulation of their activity. Given the breadth of influence phosphate has, its homeostasis is understandably a highly regulated process.

Patients with CKD typically demonstrate elevated levels of serum phosphate. In non-CKD patients, normal serum phosphate levels should be between 0.81 mmol/L and 1.45

mmol/L. In a CKD patient, however, serum phosphate levels are typically markedly increased as kidney function is lost and the body loses its ability to excrete phosphate through the urine. This means that CKD patients typically experience hyperphosphatemia, which is an electrolyte disturbance in which there is an abnormally elevated level of phosphate in the blood. Hyperphosphatemia develops in the majority of CKD patients and is typically associated with progression of secondary hyperparathyroidism and renal osteodystrophy. In addition, hyperphosphatemia has recently been associated with increased cardiovascular mortality among dialysis patients. Adequate control of serum phosphorus is crucial in the clinical management of CKD patients to attenuate the progression of secondary hyperparathyroidism and to reduce the risk of vascular calcification and cardiovascular mortality. Typical measures taken to control serum phosphate levels in CKD patients include dietary phosphorus restriction, dialysis, and oral phosphate binders. Unfortunately, dietary restriction has limited effect in advanced stages of CKD, such as ESRD. Therefore, oral phosphate binders are necessary to limit dietary absorption of phosphorus in CKD patients.

CKD patients treated according to the methods disclosed herein may experience an improvement in serum phosphate levels. In some embodiments, CKD patients treated according to the methods disclosed herein experience a decrease in serum phosphate levels. In some embodiments, the present disclosure provides methods of reducing serum phosphorus in a CKD patient, the methods comprising orally administering ferric citrate to CKD patient, e.g., an end-stage renal disease patient or non-dialysis chronic kidney disease patient, wherein the ferric citrate provides a reduction in serum phosphorus in the patient. In some embodiments, the present disclosure provides methods for treatment of hyperphosphatemia in a CKD patient, the methods comprising orally administering ferric citrate to CKD patient, e.g., an end-stage renal disease patient or non-dialysis chronic kidney disease patient, wherein the ferric citrate provides a reduction in serum phosphorus in the patient. In some embodiments, the present disclosure provides methods of reducing serum phosphorus, the methods comprising orally administering ferric citrate to an end-stage renal disease patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides a reduction in serum phosphorus in the patient. In some embodiments, the ferric citrate is administered for a period of 12 weeks. In some embodiments for a period of 24 weeks, in some embodiments for a period of 36 weeks, in some embodiments for a period of 48 weeks, in some embodiments for a period of 52 weeks, and in some embodiments for a period of up to and including 56 weeks. In some embodiments for a period of 53 weeks. In

some embodiments for a period of 54 weeks, in some embodiments for a period of 55 weeks. In some embodiments for a period of 56 weeks.

In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus from 1.00 – 3.00 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus from 1.10 – 2.90 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus from 1.20 – 2.80 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus from 1.30 – 2.70 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus from 1.40 – 2.60 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus from 1.50 – 2.50 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus from 1.60 – 2.40 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus from 1.70 – 2.30 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus from 1.80 – 2.20 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus from 1.90 – 2.10 mg/dl. The above ranges are disclosed in this format for purposes of efficiency, and any of the above ranges can be combined with any method, formulation, or combination thereof.

In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of from 1.00 – 1.25 mg/dl, 1.00 – 1.50 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of from 1.00 – 1.75 mg/dl . In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of from 1.00 – 2.00 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 2.00 – 2.25 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 2.00 – 2.50 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 2.00 – 2.75 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 2.00 – 3.00 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 1.00 – 2.25 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 1.00 – 2.50 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 1.00 – 2.75 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 1.00 – 3.00 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.00 – 2.50

mg/dl. The above ranges are disclosed in this format for purposes of efficiency, and any of the above ranges can be combined with any method, formulation, or combination thereof.

In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 1.00. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 1.10. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is selected from greater than greater than 1.20 . In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 1.30. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 1.40. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 1.50. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 1.60. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 1.70. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 1.80. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 1.90. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 2.00. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 2.10. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 2.20. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 2.30. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 2.40. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 2.50. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 2.60. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 2.70. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 2.80. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is greater than 2.90 mg/dl. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, lower boundary as disclosed below, or combination thereof.

In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 3.00 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 2.90 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 2.80 mg/dl. In

some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 2.70 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 2.60 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 2.50 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 2.40 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 2.30 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 2.20 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 2.10 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 2.00 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 1.90 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 1.80 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 1.70 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 1.60 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 1.50 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 1.40 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 1.30 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 1.20 mg/dl. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is less than 1.10 mg/dl. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, upper boundary disclosed above, or combination thereof.

In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of one of about1.90, 1.91, 1.92, 1.93, 1.94, 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09 and 2.10 mg/dl when administered for a period of 12 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of about 2.00 mg/dl when administered for a period of 12 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of one of about 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24 and 2.25 mg/dl when administered for a period of 24 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of about 2.20 mg/dl when

administered for a period of 24 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of one of about 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19 and 2.20 mg/dl when administered for a period of 36 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of about 2.20 mg/dl when administered for a period of 36 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of one 1.95 mg/dl, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 2.11, 2.12, 2.13, 2.14 and 2.15 mg/dl when administered for a period of 48 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of about 2.10 mg/dl when administered for a period of 48 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of one of about 1.95 mg/dl. , 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24, 2.25, 2.26, 2.27, 2.28, 2.29 and 2.30 mg/dl when administered for a period of 52 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of about 2.10 mg/dl when administered for a period of 52 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of one of about .20, 0.21, 0.22, 0.23, 0.24, 0.25, 0.26, 0.27, 0.28, 0.29, 0.30, 0.31, 0.32, 0.33, 0.34 and 0.35 mg/dl when administered for a period of 56 weeks, as measured from a baseline of 52 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 0.30 mg/dl when administered for a period of 56 weeks, as measured from a baseline of 52 weeks.

In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 20 – 35 %. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 20 – 35 %, 22 – 33 % and 25 – 30 %. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 27 – 28.5 %. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 27 – 28.4 %. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is selected from greater than 20, greater than 21, greater than 22, greater than 23, greater than 24, greater than 25, greater than 26, greater than 27, greater than 28, greater than 29, greater than 30, greater than 31, greater than 32, greater than 33 and greater than 34 %. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus that is selected from less than 35, less than 34, less than 33, less than 32, less than 33, less than 32, less than 31, less than 30, less than 29, less than 28, less than 27, less than 26, less than 25, less than 24, less than 23, less than 22 and less than 21 %.

In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 1.90, 1.91, 1.92, 1.93, 1.94, 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09 and 2.10 mg/dl when administered for a period of 12 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.00 mg/dl when administered for a period of 12 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24 and 2.25 mg/dl when administered for a period of 24 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.20 mg/dl when administered for a period of 24 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19 and 2.20 mg/dl when administered for a period of 36 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.20 mg/dl when administered for a period of 36 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 2.11, 2.12, 2.13, 2.14 and 2.15 mg/dl when administered for a period of 48 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.10 mg/dl when administered for a period of 48 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24, 2.25, 2.26, 2.27, 2.28, 2.29 and 2.30 mg/dl when administered for a period of 52 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.10 mg/dl when administered for a period of 52 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus selected from 0.20, 0.21, 0.22, 0.23, 0.24, 0.25, 0.26, 0.27, 0.28, 0.29, 0.30, 0.31, 0.32, 0.33, 0.34 and 0.35 mg/dl when administered for a period of 56 weeks, as measured from a baseline of 52 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 0.30 mg/dl when administered for a period of 56 weeks, as measured from a baseline of 52 weeks.

In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus as set forth in Table A:

Table A:

Mean Serum Phosphorus (mg/dL)	Placebo (n=91)	Ferric Citrate (n=92)
Baseline (Week 52)	5.3	5.2
End of Treatment[1] (Week 56)	7.2	4.9
Change from Baseline at Week 56	1.9	-0.3
Least Squares (LS) Mean Difference from Placebo[2] p-value[2]		-2.3 p<0.0001

[1] Last observation carried forward was used for missing data.
[2] The LS Mean treatment difference and p-value is created via an ANCOVA model with treatment as the fixed effect and baseline as the covariate.

In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus as set forth in Table B:

Table B:

N=277	Baseline	Week 12	24	36	48	52
Ferric Citrate Mean Serum Phosphorus (mg/dL)[1]	7.4	5.4	5.2	5.2	5.3	5.3
Change from Baseline		-2.0	-2.2	-2.2	-2.1	-2.1
% Change from Baseline		-27%	-30%	-30%	-28%	-28%
p-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

[1] Last observation carried forward was used for missing data.

In some embodiments, CKD patients, such as ESRD patients, treated according to the methods disclosed herein experience maintenance of their serum phosphorus levels such that their serum phosphorus levels remain substantially unchanged during administration of the ferric citrate.

Serum Bicarbonate

Metabolic acidosis is a condition that occurs in CKD patients when the body produces too much acid and/or when the kidneys are not removing enough acid from the body. If unchecked, metabolic acidosis leads to acidemia, where the blood pH drops to less than 7.35, due to increased production of hydrogen by the body and/or the inability of the body to form bicarbonate (HCO_3-) in the kidney. The consequences of metabolic acidosis in CKD patients can be serious, including coma and death. It is therefore important that CKD patients maintain a normal level of bicarbonate in their bloodstream. For non-CKD patients, a typical measure of serum bicarbonate ranges from 22 mEq/L – 28 mEq/L, or from 22 mmol/L to 28

mmol/L, respectively. In a CKD patient, however, the serum bicarbonate concentration can be greatly reduced as the kidneys lose their ability to produce bicarbonate.

CKD patients treated according to the methods disclosed herein may experience an increase in serum bicarbonate concentration. In some embodiments, CKD patients treated according to the methods disclosed herein experience an increase in serum bicarbonate concentration. In some embodiments, the present disclosure provides methods of increasing serum bicarbonate concentration in a CKD patient, such as an ESRD patient or ND-CKD patient, the methods comprising orally administering ferric citrate to a CKD patient, wherein the ferric citrate provides an increase in serum bicarbonate concentration in the patient. In some embodiments, the present disclosure provides methods of increasing serum bicarbonate concentration, the methods comprising orally administering ferric citrate to a CKD patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides an increase in serum bicarbonate concentration in the patient. In some embodiments, the patient is administered up to 18 tablet dosage forms per day. In some embodiments, the ferric citrate is administered for a period of 12 weeks, in some embodiments for a period of 36 weeks, in some embodiments for a period of 52 weeks, and in some embodiments for a period of up to and including 56 weeks.

In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration in the patient of 0.1 – 1.0 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration in the patient selected from 0.70, 0.71, 0.72, 0.73, 0.74, 0.75, 0.76, 0.77, 0.78, 0.79 and 0.80 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration in the patient of 0.71 mEq/L.

In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration greater than 0.70 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration greater than 0.71 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration greater than 0.72 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration greater than 0.73 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration greater than 0.74 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration greater than 0.75 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration greater than 0.76 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration

greater than 0.77 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration greater than 0.78 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration greater than 0.79 mEq/L. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, lower boundary as disclosed below, or combination thereof.

In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration less than 0.80 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration less than 0.79 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration less than 0.78 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration less than 0.77 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration less than 0.76 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration less than 0.75 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration less than 0.74 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration less than 0.73 mEq/L. In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration less than 0.72 mEq/L. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, upper boundary disclosed above, or combination thereof.

In some embodiments, the ferric citrate provides a mean increase in serum bicarbonate concentration of 0.71 mEq/L when administered for a period of 52 weeks.

In some embodiments, CKD patients, such as ESRD patients, treated according to the methods disclosed herein experience maintenance of their serum bicarbonate concentration such that their serum bicarbonate level remains substantially unchanged during administration of the ferric citrate.

Iron Storage Parameters

Patients with CKD may demonstrate low or inadequate markers of systemic iron status. This means that CKD patients may not have sufficient iron stored within their bodies to maintain proper iron levels. Most well-nourished, non-CKD people living in industrialized countries have approximately 4 to 5 grams of iron stored within their bodies. About 2.5 g of this iron is contained in hemoglobin, which carries oxygen through the blood. Most of the

remaining approximately 1.5 to 2.5 grams of iron is contained in iron binding complexes that are present in all cells, but that are more highly concentrated in bone marrow and organs such as the liver and spleen. The liver's stores of iron are the primary physiologic reserve of iron in the non-CKD body. Of the body's total iron content, about 400 mg is utilized in proteins that use iron for cellular processes such as oxygen storage (myoglobin) or performing energy-producing redox reactions (cytochrome proteins). In addition to stored iron, a small amount of iron, typically about 3 to 4 mg, circulates through the blood plasma bound to a protein called transferrin. Because of its toxicity, free soluble ferrous iron (iron(II) or Fe^{2+}) is typically kept at a low concentration in the body.

Iron deficiency first depletes the stored iron in the body. Because most of the iron utilized by the body is required for hemoglobin, iron-deficiency anemia is the primary clinical manifestation of iron deficiency. Oxygen transport to the tissues is so important to human life that severe anemia harms or kills people with CKD, inclusive of ND-CKD patients and ESRD patients, by depriving their organs of oxygen. Iron-deficient CKD patients will suffer, and in some instances may die, from organ damage caused by oxygen depletion well before cells run out of the iron needed for intracellular processes.

There are several markers of systemic iron status that may be measured to determine whether a CKD patient has sufficient iron stores to maintain adequate health. These markers may be of circulating iron stores, iron stored in iron-binding complexes, or both, and are also typically referred to as iron storage parameters. Iron storage parameters can include, for example, hematocrit, hemoglobin concentration (Hb), total iron-binding capacity (TIBC), transferrin saturation (TSAT), serum iron levels, liver iron levels, spleen iron levels, and serum ferritin levels. Of these, the hematocrit, hemoglobin concentration (Hb), total iron-binding capacity (TIBC), transferrin saturation (TSAT) and serum iron levels are commonly known as circulating iron stores. The liver iron levels, spleen iron levels, and serum ferritin levels are commonly referred to as stored iron or iron stored in iron-binding complexes.

In some embodiments, the present disclosure provides methods of improving one or more iron storage parameters in a patient in need thereof. In some embodiments, the methods comprise orally administering ferric citrate to a CKD patient, e.g., a non-dialysis chronic kidney disease patient or an end stage renal disease patient, in an amount ranging from about 1 g to about 18 g per day. In some embodiments, the at least one iron storage parameter may be selected from serum ferritin levels, transferrin saturation (TSAT), hemoglobin concentration, hematocrit, total iron-binding capacity, iron absorption levels, serum iron levels, liver iron levels, spleen iron levels, and combinations thereof. In some embodiments,

the ferric citrate in administered in a 1 gram tablet dosage form. In some embodiments, the patient is administered up to 18 tablet dosage forms per day. In some embodiments, the ferric citrate is administered for a period of 12 weeks, in some embodiments for a period of 36 weeks, in some embodiments for a period of 52 weeks, and in some embodiments for a period of up to and including 56 weeks.

In another embodiment, the at least one iron storage parameter is hematocrit, and improving comprises increasing the hematocrit of the patient. In other embodiments, the at least one iron storage parameter is hemoglobin concentration, and improving comprises increasing the hemoglobin concentration of the patient. In yet other embodiments, the at least one iron storage parameter is total iron-binding capacity, and improving comprises decreasing the total iron-binding capacity of the patient. In yet other embodiments, the at least one iron storage parameter is transferrin saturation, and improving comprises increasing the transferrin saturation of the patient. In yet other embodiments, the at least one iron storage parameter is serum iron levels, and improving comprises increasing the serum iron levels of the patient. In yet other embodiments, the at least one iron storage parameter is liver iron levels, and improving comprises increasing the liver iron levels of the patient. In yet other embodiments, the at least one iron storage parameter is spleen iron levels, and improving comprises increasing the spleen iron levels of the patient. In yet other embodiments, the at least one iron storage parameter is serum ferritin levels, and improving comprises increasing the serum ferritin levels of the patient.

Serum Ferritin

The liver's stores of ferritin are the primary source of stored iron in the body. Ferritin is an intracellular protein that stores iron and releases it in a controlled fashion. Medically, the amount of ferritin present in a blood sample and/or in a sample of liver tissue reflects the amount of iron that is stored in the liver (although ferritin is ubiquitous and can be found in many other tissues within the body in addition to the liver). Ferritin serves to store iron in the liver in a non-toxic form and to transport it to areas where it is required. In non-CKD patients, a normal ferritin blood serum level, sometimes referred to as the reference interval, is usually between 30–300 ng/ml for males, and 15–200 ng/ml for females. In a CKD patient, however, serum ferritin levels are typically markedly reduced as the amount of iron available to be bound by ferritin and stored in the liver is decreased, which occurs as the body loses its ability to absorb and store iron.

In some embodiments, CKD patients treated according to the methods disclosed herein experience an increase in serum ferritin levels. In some embodiments, the present

disclosure provides methods of increasing serum ferritin in a patient in need thereof, the methods comprising orally administering ferric citrate to an CKD patient, e.g., an ESRD patient or ND-CKD patient, wherein the ferric citrate provides an increase in serum ferritin. In some embodiments, the present disclosure provides methods of increasing serum ferritin, the methods comprising orally administering ferric citrate to a CKD patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides an increase in serum ferritin in the patient. In some embodiments, the ferric citrate is administered for a period of 12 weeks, in some embodiments for a period of 24 weeks, in some embodiments for a period of 36 weeks, in some embodiments for a period of 48 weeks, and in some embodiments for a period of 52 weeks.

In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 100 – 400 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 110 – 390 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 120 – 380 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 130 – 370 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of about 140 – 360 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 150 – 350 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 160 – 340 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 170 – 330 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 180 – 320 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 190 – 310 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 200 – 300 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 210 – 290 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 220 – 280 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 230 – 270 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 240 – 260 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 100 – 400 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 100 – 375 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 100 – 350 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 100 – 325 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 100 – 300 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of

from 100 – 275 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 150 – 310 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 151 – 309 ng/ml In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 152 – 308 ng/ml In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 153 – 307 ng/ml In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 154 – 306 ng/ml In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 155 – 306 ng/ml In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 155 – 305 ng/ml In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 155 – 304 ng/ml In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 155 – 303 ng/ml In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 155 – 302 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of from 150 – 305 ng/ml. The above ranges are disclosed in this format for purposes of efficiency, and any of the above ranges can be combined with any method, formulation, or combination thereof.

In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 302 ng/ml when administered over a period of 52 weeks.

In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 100 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 110 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 120 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 130 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 140 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 150 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 160 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 170 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 180 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 190 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 200 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 210 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum

ferritin that is greater than 220 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 230 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 240 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 250 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 260 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 270 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 280 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 290 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 300 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 310 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 320 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 330 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 340 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 350 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 360 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 370 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 380 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 390 ng/ml. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, lower boundary as disclosed below, or combination thereof.

In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is selected from less than 400 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 390 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 380 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 370 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 360 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 350 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 340 ng/ml. In some embodiments, the ferric

citrate provides a mean increase in serum ferritin that is less than 330 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 320 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 310 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 300 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 290 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 280 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 270 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 260 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 250 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 240 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 230 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 220 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 210 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 200 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 190 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 180 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 170 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 160 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 150 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 140 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 130 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 120 ng/ml. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 110 ng/ml. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, upper boundary as disclosed above, or combination thereof.

In some embodiments, the ferric citrate provides a mean increase in serum ferritin selected from about 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309 and 310 mg/dl when administered for a period of 52 weeks. In some embodiments, the ferric citrate

provides a mean increase in serum ferritin of 302 mg/dl when administered for a period of 52 weeks.

In some embodiments, the ferric citrate provides a mean increase in serum ferritin from about 1 – 100 %. In some embodiments, the ferric citrate provides a mean increase in serum ferritin from about10 – 90 %. In some embodiments, the ferric citrate provides a mean increase in serum ferritin from about 20 – 80 %. In some embodiments, the ferric citrate provides a mean increase in serum ferritin from about 30 – 70 %. In some embodiments, the ferric citrate provides a mean increase in serum ferritin from about 40 – 60 %.

In some embodiments, the ferric citrate provides a mean increase in serum ferritin selected from 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59 and 60 %. In some embodiments, the ferric citrate provides a mean increase in serum ferritin selected from 48.0, 48.1, 48.2, 48.3, 48.4, 48.5, 48.6, 48.7, 48.9, 49.0, 49.1, 49.2, 49.3, 49.4, 49.5, 49.6, 49.7, 49.8, 49.9, 50.0, 50.1, 50.2, 50.3, 50.4, 50.5, 50.6, 50.7, 50.8, 50.9 and 50.8 %. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 50.8 %. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 50.8 % when administered over a period of 52 weeks.

In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 1%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 10%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 20%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 30%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 40%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 50%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 60%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 70%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 80%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is greater than 90%. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, lower boundary as disclosed below, or combination thereof.

In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 100%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 90%. In some embodiments, the ferric citrate provides a mean

increase in serum ferritin that is less than 80%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 70%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 60%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 50%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 40%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 30%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 20%. In some embodiments, the ferric citrate provides a mean increase in serum ferritin that is less than 10 %. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, upper boundary disclosed above, or combination thereof.

In some embodiments, the ferric citrate provides a mean increase in serum ferritin selected from 49.0, 49.1, 49.2, 49.3, 49.4, 49.5, 49.6, 39.7, 49.8, 49.9 and 50.0 % when administered for a period of 52 weeks. In some embodiments, the ferric citrate provides a mean increase in serum ferritin of 49.2 % when administered for a period of 52 weeks.

In some embodiments, the ferric citrate provides a mean increase in serum ferritin shown in Table C:

Table C:

Mean Ferritin (ng/mL)[1]	**Active Controls (n=134)**	**Ferric Citrate (n=249)**
Baseline (Day 0)	616	595
Week 12	657	751
Week 24	658	847
Week 36	636	863
Week 48	627	882
Week 52	625	897
Change from Baseline at Week 52 *% Change from Baseline*	9 *1.5%*	302 *50.8%*
LS Mean Difference from Active Control Group at Week 52[2] p-value[2]		286 p<0.0001

[1] Last observation carried forward was used for missing data.
[2] The LS Mean treatment difference and p-value is created via an ANCOVA model with treatment as the fixed effect and baseline as the covariate.

In some embodiments, CKD patients, such as ESRD patients, treated according to the methods disclosed herein experience maintenance of their serum ferritin levels such that their serum ferritin levels remain substantially unchanged during administration of the ferric citrate.

Transferrin Saturation (TSAT)

In addition to stored iron, a small amount of iron, typically about 3 to 4 mg, circulates through the blood plasma bound to a protein called transferrin. Therefore, serum iron levels can be represented by the amount of iron circulating in the blood that is bound to the protein transferrin. Transferrin is a glycoprotein produced by the liver that can bind one or two ferric iron (iron(III) or Fe^{3+}) ions. It is the most prevalent and dynamic carrier of iron in the blood, and therefore is an essential component of the body's ability to transport stored iron for use throughout the body. Transferrin saturation (or TSAT) is measured as a percentage and is calculated as the ratio of serum iron and total iron-binding capacity, multiplied by 100. This value tells a clinician how much serum iron is actually bound to the total amount of transferrin that is available to bind iron. For instance, a TSAT value of 35% means that 35% of the available iron-binding sites of transferrin in a blood sample is occupied by iron. In a non-CKD patient, typical TSAT values are approximately 15–50% for males and 12–45% for females. In a CKD patient, however, TSAT values are typically markedly reduced as the amount of iron available to be bound by transferrin is decreased, which occurs as the body loses its ability to absorb and store iron.

In some embodiments, CKD patients treated according to the methods disclosed herein experience an increase in TSAT values. In some embodiments, the present disclosure provides methods of increasing transferrin saturation (TSAT) in a patient in need thereof, the methods comprising orally administering ferric citrate to CKD patient, e.g., an ESRD patient or a ND-CKD patient, wherein the ferric citrate provides an increase in TSAT in the patient. In some embodiments, the present disclosure provides methods of increasing transferrin saturation (TSAT), the methods comprising orally administering ferric citrate to an end-stage renal disease patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides an increase in TSAT in the patient. In some embodiments, the ferric citrate is administered for a period of 12 weeks, in some embodiments for a period of 24 weeks, in some embodiments for a period of 36 weeks, in some embodiments for a period of 48 weeks, and in some embodiments for a period of 52 weeks.

In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) of 1 – 20 %. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) of 1 – 15 %. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) of 1 – 12 %. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) of 5 – 12 %. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) of 5 – 10 %. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) of 6 – 9 %. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) of 8%.

In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) greater than 1%. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) greater than 2%. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) greater than 3%. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) greater than 4%. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) greater than 5%. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) greater than 6%. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) greater than 7%. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) greater than 8%. In some embodiments, the ferric citrate provides a mean increase in TSAT greater than 9%. In some embodiments, the ferric citrate provides a mean increase in TSAT greater than 10%. In some embodiments, the ferric citrate provides a mean increase in TSAT greater than 11%. In some embodiments, the ferric citrate provides a mean increase in TSAT greater than 12%. In some embodiments, the ferric citrate provides a mean increase in TSAT greater than 13%. In some embodiments, the ferric citrate provides a mean increase in TSAT greater than 14%. In some embodiments, the ferric citrate provides a mean increase in TSAT greater than 15%. In some embodiments, the ferric citrate provides a mean increase in TSAT greater than 16%. In some embodiments, the ferric citrate provides a mean increase in TSAT greater than 17%. In some embodiments, the ferric citrate provides a mean increase in TSAT greater than 18%. In some embodiments, the ferric citrate provides a mean increase in TSAT greater than 19%. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above ranges can be combined with any method, formulation, lower boundary as disclosed below, or combination thereof.

In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) less than 20%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 19%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 18%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 17%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 16%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 15%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 14%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 13%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 12%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 11%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 10%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 9%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 8%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 7%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 6%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 5%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 4%. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 3 %. In some embodiments, the ferric citrate provides a mean increase in TSAT less than 2 %. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above ranges can be combined with any method, formulation, upper boundary disclosed above, or combination thereof.

In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) selected from 5 %, 6 %, 7 %, 8 %, 9 %, 10 %, 11 %, 12 %, 13 %, 14 %, 15 %, 16 %, 17 % and 18 % when administered for a period of 52 weeks. In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) of 8 % when administered for a period of 52 weeks.

In some embodiments, the ferric citrate provides a mean increase in transferrin saturation (TSAT) shown in Table D:

Table D:

Mean TSAT (%)[1]	Active Controls (n=131)	Ferric Citrate (n=244)
Baseline (Day 0)	31	31
Week 12	31	40
Week 24	32	40
Week 36	30	40
Week 48	29	41
Week 52	30	39
Change from Baseline at Week 52 *% Change from Baseline*	-1 *-3.2%*	8 *25.8%*
LS Mean Difference from Active Control Group at Week 52[2] p-value[2]		10 p<0.0001

[1] Last observation carried forward was used for missing data.

[2] The LS Mean treatment difference and p-value is created via an ANCOVA model with treatment as the fixed effect and baseline as the covariate.

In some embodiments, CKD patients, such as ESRD patients, treated according to the methods disclosed herein experience maintenance of their TSAT values such that their transferrin saturation (TSAT) value remains substantially unchanged during administration of the ferric citrate.

Hematocrit

The hematocrit, also referred to as packed cell volume or erythrocyte volume fraction, is the volume percentage of red blood cells in the blood. For non-CKD patients, the hematocrit is typically about 45% of blood volume for men and about 40% of blood volume for women. In CKD patients, however, the hematocrit is often significantly depleted due to poor iron absorption and/or poor iron storage capacity.

The ferric citrate disclosed herein may be administered to CKD patients to increase hematocrit. The exact timing of administration will necessarily vary from patient to patient, depending upon, for example, the severity of CKD experienced by the CKD patient, the level of iron absorption the patient is or is not experiencing, and the judgment of the treating health care professional. In some embodiments, the present disclosure provides methods of increasing hematocrit in a patient in need thereof, the methods comprising orally

administering ferric citrate to a CKD patient, e.g., an ESRD patient or ND-CKD patient, wherein the ferric citrate provides for an increase in the hematocrit of the patient. In some embodiments, the present disclosure provides methods of increasing hematocrit in a CKD patient, the methods comprising orally administering ferric citrate to the patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides for an increase in the hematocrit of the patient. In some embodiments, the ferric citrate is administered for a period of 52 weeks. In some embodiments, the increase is from 1% to 30%. In some embodiments, the increase is from 1% to 20%. In some embodiments, the increase is from 1% to 15%, in some embodiments the increase is from 1% to 12%, in some embodiments the increase is from 1% to 10%, in some embodiments the increase is from 1% to 9%, in some embodiments the increase is from 1% to 8%, in some embodiments the increase is from 1% to 7%, in some embodiments the increase is from 1% to 6%, in some embodiments the increase is from 1% to 5%, in some embodiments the increase is from 1% to 4%, in some embodiments the increase is from 1% to 3%, and in some embodiments the increase is from 1% to 2%.

In some embodiments, CKD patients, such as ESRD patients, treated according to the methods disclosed herein experience maintenance of their hematocrit level such that their overall volume of red blood cells in the blood remains substantially unchanged during administration of the ferric citrate.

Hemoglobin Concentration

Hemoglobin concentration, also referred to as the mean corpuscular hemoglobin concentration or MCHC, is a measure of the concentration of hemoglobin protein in a given volume of packed red blood cells. It is typically calculated by dividing the total amount of hemoglobin protein by the hematocrit. Hemoglobin concentration may also be measured as a mass or weight fraction and presented as a percentage (%). Numerically, however, the mass or molar measure of hemoglobin concentration and the mass or weight fraction (%) are identical, assuming a red blood cell density of 1g/ml and negligible hemoglobin loss in the blood plasma. For non-CKD patients, a typical mass or molar measure of hemoglobin concentration ranges from 32 g/dl – 36 g/dl, or from 4.9 mmol/L to 5.5 mmol/L, respectively. In a CKD patient, however, the hemoglobin concentration can be greatly reduced as the body loses its ability to absorb and store iron.

In some embodiments, CKD patients treated according to the methods disclosed herein experience an increase in hemoglobin concentration. In some embodiments, the

present disclosure provides methods of increasing hemoglobin concentration in a patient in need thereof, the methods comprising orally administering ferric citrate to a CKD patient, e.g., an ESRD patient or ND-CKD patient, wherein the ferric citrate provides an increase in hemoglobin concentration in the patient. In some embodiments, the present disclosure provides methods of increasing hemoglobin concentration, the methods comprising orally administering ferric citrate to a CKD patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides an increase in hemoglobin concentration in the patient. In some embodiments, the ferric citrate is administered for a period of 12 weeks, in some embodiments for a period of 24 weeks, in some embodiments for a period of 36 weeks, in some embodiments for a period of 48 weeks, and in some embodiments for a period of 52 weeks.

In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration of 0.1 – 5.0 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration of 0.1 – 4.0 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration of 0.1 – 3.0 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration of 0.1 – 2.0 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration of 0.1 – 1.0 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration of 0.2 – 0.9 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration of 0.3 – 0.8 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration of 0.3 – 0.7 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration of 0.3 – 0.6 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration of 0.3 – 0.5 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration of 0.4 g/dl.

In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration greater than 0.1 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration greater than 0.2 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration greater than 0.3 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration greater than 0.4 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration greater than 0.5 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration greater than 0.6 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration greater

than 0.7 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration greater than 0.8 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration greater than 0.9 g/dl. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, lower boundary as disclosed below, or combination thereof.

In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration of less than 1.0 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration less than 0.9 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration less than 0.8 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration less than 0.7 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration less than 0.6 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration less than 0.5 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration less than 0.4 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration less than 0.3 g/dl. In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration less than 0.2 g/dl. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, upper boundary disclosed above, or combination thereof.

In some embodiments, the ferric citrate provides a mean increase in hemoglobin concentration shown in Table E:

Table E:

Mean Hemoglobin (g/dL)[1]	Active Controls (n=130)	Ferric Citrate (n=244)
Baseline (Day 0)	11.7	11.6
Week 52	11.1	11.4
Change from Baseline at Week 52	-0.6	-0.2
LS Mean Difference from Active Control Group at Week 52[2] p-value[2]		0.4 p=0.0105

[1] Last observation carried forward was used for missing data.
[2] The LS Mean treatment difference and p-value is created via an ANCOVA model with treatment as the fixed effect and baseline as the covariate.

In some embodiments, CKD patients, such as ESRD patients, treated according to the methods disclosed herein experience maintenance of their hemoglobin concentration such

that their hemoglobin level remains substantially unchanged during administration of the ferric citrate.

Total Iron Binding Capacity (TIBC)

Total iron-binding capacity (TIBC) is a measure of the blood's capacity to bind iron with the protein transferrin. TIBC is typically measured by drawing a blood sample and measuring the maximum amount of iron that the sample can carry. Thus, TIBC indirectly measures transferrin, which is a protein that transports iron in the blood. For non-CKD patients, a typical mass or molar measure of TIBC is in the range of 250–370 μg/dL or 45-66 μmol/L, respectively. In CKD patients, however, the TIBC is typically increased above these levels, as the body must produce more transferrin in an attempt to deliver iron to erythrocyte precursor cells to produce hemoglobin.

In some embodiments, CKD patients treated according to the methods disclosed herein experience a reduction in TIBC. In some embodiments, the present disclosure provides methods of reducing TIBC in patient in need thereof, the methods comprising orally administering ferric citrate to a CKD patient, e.g., an ESRD patient or ND-CKD patient, wherein the ferric citrate provides for a reduction in the TIBC of the patient. In some embodiments, the present disclosure provides methods of reducing TIBC in a CKD patient, the methods comprising orally administering ferric citrate to the patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides for a reduction in the TIBC of the patient. In some embodiments, the ferric citrate is administered for a period of 52 weeks. In some embodiments, the reduction is from 0.1% to 30%, in some embodiments the reduction is from 0.1% to 28%, in some embodiments the reduction is from 0.1% to 26%, in some embodiments the reduction is from 0.1% to 25%, in some embodiments the reduction is from 0.1% to 24%, in some embodiments the reduction is from 0.1% to 23%, in some embodiments the reduction is from 0.1% to 22%, in some embodiments the reduction is from 0.1% to 21%, in some embodiments the reduction is from 0.1% to 20%, in some embodiments the reduction is from 0.1% to 15%, in some embodiments the reduction is from 0.1% to 10%, and in some embodiments the reduction is from 0.1% to 5%.

In some embodiments, CKD patients, such as ESRD patients, treated according to the methods disclosed herein experience maintenance of their TIBC such that their TIBC level remains substantially unchanged during administration of the ferric citrate.

Iron Absorption

CKD patients may suffer from low or inadequate iron absorption that can lead to other health concerns such as iron depletion and anemia. For humans, the majority of iron absorbed from food or supplements is absorbed in the small intestine, particularly in the duodenum, by specialized enterocyte cells present in the duodenal lining. These cells have specialized transporter molecules that allow them to move iron from the intestinal lumen into the body. To be absorbed, dietary iron must be present as part of a protein, such as heme, or it must be in ferrous (iron(II) or Fe^{2+}) form. Enterocytes express a ferric reductase enzyme, Dcytb, which reduces ferric iron (iron(III) or Fe^{3+}) to ferrous iron. A divalent metal transporter protein then transports the iron across the enterocyte's cell membrane and into the cell.

In a non-CKD person, the body regulates iron levels by changing the expression level of the proteins relating to one or more of these steps. For example, in response to iron-deficiency anemia, cells may produce more of the Dcytb enzyme and more of the metal transporter protein in order to increase the amount of iron absorbed from the intestinal lumen. In CKD patients, the body's ability to regulate one or more of these steps is impaired, which in turn leads to reduced or inadequate iron absorption.

CKD patients treated according to the methods disclosed herein may experience increased iron absorption. In some embodiments, the iron that is absorbed is provided by the ferric citrate that is administered to the CKD patients; it is the ferric iron ion that is absorbed into the body from the intestinal lumen. Because the ferric citrate is administered orally, the increased iron absorption occurs through the intestine. While not wishing to be bound by any theory, it is believed that the increased iron absorption may be attributable to the presence of citrate in the ferric citrate administered to the CKD patient. Some studies have shown that administration of iron in combination with citrate (the conjugate base of citric acid) serves to significantly increase (*e.g.*, by several fold) the amount of iron absorbed from dietary sources (*see, e.g.*, Ballot, *et al.*, *Br. J. Nutr.* (1987) 57, 331–343; Gillooly, *et al.*, *Br. J. Nutr.* (1983) 49, 331–342; Zhang, *et al.*, *Eur. J. Nutr.* (2007) 46, 95–102; and Salovaara, *et al.*, *J. Agric. Food Chem.* (2002) 50, 6233–6238).

The ferric citrate disclosed herein may be administered to CKD patients to increase iron absorption. The exact timing of administration will necessarily vary from patient to patient, depending upon, for example, the stage of CKD experienced by the CKD patient, the level of iron absorption the patient is or is not experiencing, and the judgment of the treating health care professional. In some embodiments, the present disclosure provides methods of

increasing iron absorption in an end-stage renal disease patient, the methods comprising orally administering ferric citrate to the patient, wherein the ferric citrate provides for an increase in the amount of iron absorbed by the patient. In some embodiments, the present disclosure provides methods of increasing iron absorption in an end-stage renal disease patient, the methods comprising orally administering ferric citrate to the patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides for an increase in the amount of iron absorbed by the patient. In some embodiments, the ferric citrate is administered for a period of 52 weeks.

Iron Deficiency and Anemia

As stated above, most well-nourished, non-CKD people living in industrialized countries have approximately 4 to 5 grams of iron stored within their bodies in some manner (*e.g.*, as circulating iron or stored iron or both). A decrease in this amount represents an iron deficiency, which is commonly seen in CKD patients. Symptoms of iron deficiency can occur in CKD patients before the condition has progressed to iron-deficiency anemia. Symptoms of iron deficiency can include, for example, fatigue, dizziness, pallor, hair loss, irritability, weakness, pica, brittle or grooved nails, Plummer-Vinson syndrome (painful atrophy of the mucous membrane covering the tongue, pharynx and esophagus), impaired immune function, pagophagia, and restless legs syndrome, among others.

CKD patients treated according to the methods disclosed herein may experience an improvement in iron deficiency. In some embodiments, CKD patients treated according to the methods disclosed herein experience a decrease in iron deficiency. This decrease may occur as the total amount of iron in the body of the CKD patient is increased through the administration of the ferric citrate disclosed herein. In some embodiments, CKD patients treated according to the methods disclosed herein experience a decrease in one or more symptoms of iron deficiency, wherein the symptoms are selected from fatigue, dizziness, pallor, hair loss, irritability, weakness, pica, brittle or grooved nails, Plummer-Vinson syndrome (painful atrophy of the mucous membrane covering the tongue, pharynx and esophagus), impaired immune function, pagophagia, restless legs syndrome and combinations of the foregoing. In some embodiments, CKD patients treated according to the methods disclosed herein experience the elimination of one or more symptoms of iron deficiency, wherein the symptoms are selected from fatigue, dizziness, pallor, hair loss, irritability, weakness, pica, brittle or grooved nails, Plummer-Vinson syndrome (painful atrophy of the

mucous membrane covering the tongue, pharynx and esophagus), impaired immune function, pagophagia, restless legs syndrome and combinations of the foregoing.

In some embodiments, the iron deficiency is anemia. In some embodiments, the iron deficiency is iron-deficiency anemia. Iron-deficiency anemia is characterized by low levels of circulating red blood cells and, in CKD patients, can be caused by insufficient dietary intake, absorption and/or storage of iron. Red blood cells, which contain iron bound in hemoglobin proteins, and are typically not formed when the amount of iron in the body is deficient.

Iron-deficiency anemia is typically characterized by pallor (pale color resulting from reduced oxyhemoglobin in the skin and mucous membranes), fatigue, lightheadedness, and weakness. However, signs of iron-deficiency anemia can vary between CKD patients. Because iron deficiency in CKD patients tends to develop slowly, adaptation to the disease can occur and it can go unrecognized for some time. In some instances, patients with CKD can develop dyspnea (trouble breathing), pica (unusual obsessive food cravings), anxiety often resulting in OCD-type compulsions and obsessions, irritability or sadness, angina, constipation, sleepiness, tinnitus, mouth ulcers, palpitations, hair loss, fainting or feeling faint, depression, breathlessness on exertion, twitching muscles, pale yellow skin, tingling (numbness) or burning sensations, missed menstrual cycle(s), heavy menstrual period(s), slow social development, glossitis (inflammation or infection of the tongue), angular cheilitis (inflammatory lesions at the mouth's corners), koilonychia (spoon-shaped nails) or nails that are weak or brittle, poor appetite, pruritus (generalized itchiness), Plummer-Vinson syndrome (painful atrophy of the mucous membrane covering the tongue, pharynx and esophagus), and restless legs syndrome, among others.

Anemia is typically diagnosed based on a complete blood count measured from a blood sample from a patient. Typically, automatic counters are utilized that report the total number of red blood cells in a sample, the hemoglobin level, and the size of the red blood cells by flow cytometry. However, a stained blood smear on a microscope slide can be examined using a microscope in order to count the total number of red blood cells in a sample and diagnose anemia. In many countries, four parameters (red blood cell count, hemoglobin concentration, mean corpuscular volume and red blood cell distribution width) are measured to determine the presence of anemia. The World Health Organization has set certain threshold values for hemoglobin levels (Hb), such that when an CKD patient's hemoglobin levels fall below those values, a diagnosis of anemia may be made. Those values are: for children 0.5–5.0 yrs of age, Hb = 11.0 g/dL or 6.8 mmol/L; for children 5–12 yrs years of

age, Hb = 11.5 g/ dL or 7.1 mmol/L; for teens 12–15 yrs of age, Hb = 12.0 g/ dL or 7.4 mmol/L; for non-pregnant women 15 years of age and older, Hb = 12.0 g/ dL or 7.4 mmol/L; for pregnant women, Hb = 11.0 g/ dL or 6.8 mmol/L; and for men greater than 15 yrs of age, Hb = 13.0 g/ dL or 8.1 mmol/L.

CKD patients treated according to the methods disclosed herein may experience an improvement in anemia. CKD patients treated according to the methods disclosed herein may experience an improvement in iron-deficiency anemia. In some embodiments, CKD patients treated according to the methods disclosed herein experience a decrease in one or more symptoms of anemia or iron-deficiency anemia. In some embodiments, CKD patients treated according to the methods disclosed herein experience the elimination of one or more symptoms of anemia or iron-deficiency anemia. In some embodiments, the one or more symptoms of anemia or iron-deficiency anemia are selected from pallor, fatigue, lightheadedness, weakness, dyspnea, pica, anxiety, irritability or sadness, angina, constipation, sleepiness, tinnitus, mouth ulcers, palpitations, hair loss, fainting or feeling faint, depression, breathlessness on exertion, twitching muscles, pale yellow skin, tingling (numbness) or burning sensations, missed menstrual cycle(s), heavy menstrual period(s), slow social development, glossitis, angular cheilitis, koilonychia, poor appetite, pruritus, Plummer-Vinson syndrome, restless legs syndrome and combinations of the foregoing.

In some embodiments, CKD patients treated according to the methods disclosed herein may experience an improvement in anemia and/or iron-deficiency anemia because hemoglobin levels are raised and/or maintained above a threshold level. In some embodiments, a method of treating anemia in a CKD patient is disclosed, the method comprising orally administering ferric citrate to the CKD patient, wherein the ferric citrate provides a hemoglobin level in the CKD patient that is at or above a level ranging from 11.0 g/dL - 13.0 g/dL, including a level selected from 11.0 g/dL, 11.5 g/dL, 12.0 g/dL, and 13.0 g/dL. In some embodiments, a method of treating anemia in a CKD patient is disclosed, the method comprising orally administering ferric citrate to the CKD patient, wherein the ferric citrate provides a hemoglobin level in the CKD patient that is at or above a level selected from 6.8 mmol/L, 7.1 mmol/L, 7.4 mmol/L, and 8.1 mmol/L. In some embodiments, a method of treating anemia in a male CKD patient is disclosed, the method comprising orally administering ferric citrate to the male CKD patient, wherein the ferric citrate provides a hemoglobin level in the male CKD patient that is at or above a level selected from 13.0 g/dL and 8.1 mmol/L. In some embodiments, a method of treating anemia in a female CKD patient is disclosed, the method comprising orally administering ferric citrate to the female

CKD patient, wherein the ferric citrate provides a hemoglobin level in the female CKD patient that is at or above a level selected from 12.0 g/dL and 7.4 mmol/L.

In some embodiments, ferric citrate for use in a method of treating anemia in a CKD patient is disclosed, wherein the ferric citrate provides a hemoglobin level in the CKD patient that is at or above a level ranging from 11.0 g/dL - 13.0 g/dL, including a level selected from 11.0 g/dL, 11.5 g/dL, 12.0 g/dL, and 13.0 g/dL. In some embodiments, ferric citrate for use in a method of treating anemia in a CKD patient is disclosed, wherein the ferric citrate provides a hemoglobin level in the CKD patient that is at or above a level selected from 6.8 mmol/L, 7.1 mmol/L, 7.4 mmol/L, and 8.1 mmol/L. In some embodiments, ferric citrate for use in a method of treating anemia in a male CKD patient is disclosed, wherein the ferric citrate provides a hemoglobin level in the male CKD patient that is at or above a level selected from 13.0 g/dL and 8.1 mmol/L. In some embodiments, ferric citrate for use in a method of treating anemia in a female CKD patient is disclosed, wherein the ferric citrate provides a hemoglobin level in the female CKD patient that is at or above a level selected from 12.0 g/dL and 7.4 mmol/L.

Intravenous Iron

Patients with CKD may be at risk for, or may suffer from, iron deficiency. Iron deficiency, also referred to as sideropenia or hypoferremia, is a common type of nutritional deficiency, and can occur in a CKD patient as the body loses its ability to absorb iron from the intestinal lumen and/or to store iron for long-term use. When a loss of or decrease in iron in the body is not compensated for by, for example, a sufficient intake of iron from the diet, iron deficiency can develop over time. When a state of iron deficiency is left uncorrected, it can lead to iron-deficiency anemia. Therefore, a direct consequence of untreated, long-term iron deficiency can be iron-deficiency anemia and, in some instances, anemia.

In CKD patients, there are typically three means by which iron-deficiency anemia can be treated. The first approach is by eating foods that are high in iron. If that is insufficient, then a clinician may prescribe oral iron supplements. However, many oral iron supplements cause numerous adverse side effects in CKD patients, which leads to patient non-compliance. In those instances where a CKD patient cannot take oral iron supplements, he or she may have to have intravenous iron supplementation.

Intravenous (IV) iron supplementation is a method of delivering iron by injection with a needle, either through a muscle or into a vein. CKD patients who are receiving IV iron usually do so because they cannot take oral iron. In particular, ESRD patients are on dialysis

and often lose blood during dialysis. These patients are usually also taking an erythropoiesis-stimulating agent (ESA – see below) and may need extra iron because of that as well. Intravenous iron is delivered into the CKD patient's vein through a needle that is attached to an IV bag that contains an iron solution. The procedure takes place in a doctor's office or a clinic and may take up to several hours, depending on which treatment the physician has prescribed. The CKD patient usually receives iron injections over the course of several visits until his or her iron levels are correct. In some instances, an CKD patient may require permanent IV iron supplementation.

The side effects of IV iron supplementation include: gastrointestinal pains, including nausea and cramps; problems breathing; skin problems, including rash; chest pain; low blood pressure; and anaphylaxis, among others.

CKD patients treated according to the methods disclosed herein may experience a decrease in the need for IV iron supplementation. In some embodiments, CKD patients treated according to the methods disclosed herein experience a decrease in cumulative IV iron supplementation. In some embodiments, the present disclosure provides methods of reducing intravenous (IV) iron use in a patient in need thereof, the methods comprising orally administering ferric citrate to a CKD patient, particularly an ESRD patient, wherein the ferric citrate provides for a reduction in IV iron use in the patient. In some embodiments, the present disclosure provides methods of reducing intravenous (IV) iron use in an end-stage renal disease patient, the methods comprising orally administering ferric citrate to the patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides for a reduction in IV iron use in the patient. In some embodiments, the ferric citrate is administered for a period of 52 weeks.

In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake from 1 – 100%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake from 10 – 90 %. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake from 20 – 80 %. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake from 30 – 70 % . The above ranges are disclosed in this format for purposes of efficiency, and any of the above ranges can be combined with any method, formulation, or combination thereof.

In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake from 40 – 60 %. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake selected from 50, 51, 52, 53, 54, 55,

56, 57, 58, 59 and 60 %. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake selected from 51.0, 51.1, 51.2, 51.3, 51.4, 51.5, 51.6, 51.7, 51.9 and 52.0 %. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake of 51.6 %. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake of 51.6 % when administered over a period of 52 weeks.

In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 10%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 20%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 30%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 40%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 50%.

In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is selected from less than 100%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 90%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 80%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 70%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 60%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 50%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 40%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 30%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 20%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 10 %. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, upper boundary as disclosed above, or combination thereof.

In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 60%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 70%. In

some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than %. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 90 %. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, lower boundary as disclosed below, or combination thereof.

In some embodiments, CKD patients, such as ESRD patients, treated according to the methods disclosed herein experience maintenance of the amount of IV iron supplementation needed such that the total amount of IV iron supplementation received by the CKD patient remains substantially unchanged during administration of the ferric citrate.

Erythropoiesis-Stimulating Agents

In addition to the means of controlling iron-deficiency anemia in CKD patients set forth above, CKD patient, particularly an ESRD patient, may also take one or more erythropoiesis-stimulating agents (ESAs) in an effort to control anemia. ESAs work by helping the body to produce red blood cells. These red blood cells are then released from the bone marrow into the bloodstream where they help maintain blood iron levels. Erythropoiesis-stimulating agents, commonly abbreviated as ESAs, are agents that are similar in structure and/or function to the cytokine erythropoietin, which stimulates red blood cell production (erythropoeisis) in the body. Typical ESAs, structurally and biologically, are similar to naturally occurring protein erythropoietin. Examples of commercially available ESAs include Erythropoietin (Epo), Epoetin alfa (Procrit/Epogen), Epoetin beta (NeoRecormon), Darbepoetin alfa (Aranesp), and Methoxy polyethylene glycol-epoetin beta (Mircera). The two ESAs presently approved for marketing in the U.S. are Epoetin alfa (Procrit, Epogen), and Darbepoietin alfa (Aranesp).

ESAs are commonly given to ESRD patients. These patients usually have lower hemoglobin levels because they can't produce enough erythropoietin. The side effects that occur most often with ESA use include: high blood pressure; swelling; fever; dizziness; nausea; and pain at the site of the injection, among others. In addition to these side effects, there are several safety issues that result from ESA use. ESAs increase the risk of venous thromboembolism (blood clots in the veins). ESAs can also cause hemoglobin to rise too high, which puts the patient at higher risk for heart attack, stroke, heart failure, and death.

CKD patients treated according to the methods disclosed herein may experience a decrease in the amount of ESAs needed to maintain hemoglobin levels. In some

embodiments, CKD patients treated according to the methods disclosed herein experience a decrease in ESA use. In some embodiments, the present disclosure provides methods of reducing ESA use in a CKD patient, particularly an ESRD patient, the methods comprising orally administering ferric citrate to the patient, wherein the ferric citrate provides for a reduction in ESA use in the patient. In some embodiments, the present disclosure provides methods of reducing ESA use in an end-stage renal disease patient, the methods comprising orally administering ferric citrate to the patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides for a reduction in ESA use in the patient. In some embodiments, the ferric citrate is administered for a period of 52 weeks.

In some embodiments, the ferric citrate provides a decrease in median ESA intake is from 1 – 50 %. In some embodiments, the ferric citrate provides a decrease in median ESA intake is from 10 – 40 %. In some embodiments, the ferric citrate provides a decrease in median ESA intake is from 20 – 30 %. In some embodiments, the ferric citrate provides a decrease in median ESA intake selected from 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30 %. In some embodiments, the ferric citrate provides a decrease in median ESA intake selected from 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.9 and 28.0 %. In some embodiments, the ferric citrate provides a decrease in median ESA intake of 27.1 %. In some embodiments, the ferric citrate provides a decrease in median ESA intake of 27.1 % when administered over a period of 52 weeks.

In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 20%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 21%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 22%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 23%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 24%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 25%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 26%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 27%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 28 %. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 29 %. The above

boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, lower boundary as disclosed below, or combination thereof.

In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 30%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 29%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 28%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 27%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 26%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 25%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 24%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 23%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 22%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is less than 21 %. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, upper boundary as disclosed above, or combination thereof.

In some embodiments, CKD patients, particularly ESRD patients, treated according to the methods disclosed herein experience maintenance of the amount of ESAs needed to maintain hemoglobin levels such that the total amount of ESA use by the patient remains substantially unchanged during administration of the ferric citrate.

Oral Iron Supplement

In some embodiments, the present disclosure provides an oral iron supplement comprising ferric citrate in an amount effective to increase iron absorption in CKD patients. In some embodiments, the present disclosure provides an oral iron supplement comprising ferric citrate in an amount effective to maintain iron stores in CKD patients. In some embodiments, the present disclosure provides an oral iron supplement comprising ferric citrate in an amount effective to improve one or more iron storage parameters in CKD patients. In some embodiments, the one or more iron storage parameters are selected from hematocrit, hemoglobin concentration (Hb), total iron-binding capacity (TIBC), transferrin

saturation (TSAT), serum iron levels, liver iron levels, spleen iron levels, and serum ferritin levels. In some embodiments, the present disclosure provides an oral iron supplement comprising ferric citrate in an amount effective to treat iron deficiency in CKD patients. In some embodiments, the present disclosure provides an oral iron supplement comprising ferric citrate in an amount effective to treat anemia in CKD patients.

In some embodiments, the present disclosure provides an oral iron supplement comprising ferric citrate having a dose of ferric iron of 210 mg. In some embodiments, the oral iron supplements comprising ferric citrate can be administered so that the dose of ferric iron ranges from 210 mg – 2,520 mg.

In some embodiments, the present disclosure provides ferric citrate for use in the manufacture of an oral iron supplement to increase iron absorption in CKD patients. In some embodiments, the present disclosure provides ferric citrate for use in the manufacture of an oral iron supplement to maintain iron stores in CKD patients. In some embodiments, the present disclosure provides ferric citrate for use in the manufacture of an oral iron supplement to improve one or more iron storage parameters in CKD patients. In some embodiments, the one or more iron storage parameters are selected from hematocrit, hemoglobin concentration (Hb), total iron-binding capacity (TIBC), transferrin saturation (TSAT), serum iron levels, liver iron levels, spleen iron levels, and serum ferritin levels. In some embodiments, the present disclosure provides ferric citrate for use in the manufacture of an oral iron supplement to treat iron deficiency in CKD patients. In some embodiments, the present disclosure provides ferric citrate for use in the manufacture of an oral iron supplement to treat anemia in CKD patients.

In some embodiments, the present disclosure provides ferric citrate for use in the manufacture of an oral iron supplement comprising a dose of ferric iron of 210 mg.

Ferric Citrate

In various aspects, the present disclosure relates to the use of ferric citrate to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in CKD patients. In various aspects, the present disclosure relates to the use of pharmaceutical compositions comprising ferric citrate and a pharmaceutically acceptable binder to reduce and/or control serum phosphorus levels,

increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in CKD patients.

Therefore, disclosed herein are preparations of ferric citrate and pharmaceutical compositions comprising the ferric citrate. In various embodiments, the ferric citrate preparations, and the pharmaceutical compositions comprising the ferric citrate preparations, meet certain dissolution, tableting and disintegration standards. In various aspects, the pharmaceutical compositions can include ferric citrate as the active ingredient and a binder. The pharmaceutical compositions also can include a lubricant and/or a disintegrant (which, in some embodiments, can be the same as the binder).

Certain embodiments of the ferric citrate preparations disclosed for use herein are also disclosed in U.S. Patent Nos. 7,767,851, 8,093,423, 8,299,298 and 8,338,642, and PCT Publication Nos. WO 2004/074444, WO 2007/022435, WO 2007/089571, WO 2007/089577 and WO 2011/011541. Certain embodiments of the ferric citrate preparations, however, are unique to this disclosure. The ferric citrate preparations disclosed herein display an enhanced BET active surface area compared to commercially available or chemical grade forms of ferric citrate. BET theory explains the physical adsorption of gas molecules onto a solid surface. The theory serves as the basis for the measurement of the specific surface area of a material. This theory allows the calculation of surface areas of materials in a very accurate manner and is thus capable of distinguishing differences between separate preparations of what would otherwise appear to be the same material. For example, activated carbon is a form of carbon that has been processed to make it extremely porous and thus to have a very large surface area. Activated carbon has been experimentally determined, using calculations derived from BET theory, to have a surface area of around 3000 $m^2 g^{-1}$. This surface area is significantly higher than the active surface areas of other preparations of carbon even though they are made of the same material.

In some embodiments, the ferric citrate preparations disclosed herein have a BET active surface area exceeding 16 m^2/g. In some embodiments, the high purity ferric citrate preparations disclosed herein have a BET active surface area exceeding 20 m^2/g. In some embodiments, the high purity ferric citrate preparations disclosed herein have a BET active surface area exceeding 25 m^2/g. In some embodiments, the high purity ferric citrate preparations disclosed herein have a BET active surface area exceeding 30 m^2/g. In some

embodiments, the high purity ferric citrate preparations disclosed herein have a BET active surface area exceeding 35 m^2/g. In some embodiments, the high purity ferric citrate preparations disclosed herein have a BET active surface area exceeding 40 m^2/g. In some embodiments, the high purity ferric citrate preparations disclosed herein have a BET active surface area exceeding 45 m^2/g. In some embodiments, the high purity ferric citrate preparations disclosed herein have a BET active surface area exceeding 50 m^2/g. In some embodiments, the ferric citrate preparations disclosed herein have a BET active surface area ranging from 16.17 m^2/g to 19.85 m^2/g. In some embodiments, the ferric citrate preparations disclosed herein have a BET active surface area selected from 16.17 m^2/g and 19.85 m^2/g. In some embodiments, the ferric citrate preparations disclosed herein have a BET active surface area exceeding 27 m^2/g. In some embodiments, the ferric citrate preparations disclosed herein have a BET active surface area ranging from 27.99 m^2/g to 32.34 m^2/g. In some embodiments, the ferric citrate preparations disclosed herein have a BET active surface area ranging from 28.5 m^2/g to 31.5 m^2/g. In some embodiments, the ferric citrate preparations disclosed herein have a BET active surface area selected from 27.99 m^2/g, 28.87 m^2/g and 32.34 m^2/g. In some embodiments, the ferric citrate preparations disclosed herein have a BET active surface area selected from 28.5 m^2/g, 29.1 m^2/g, 30.6 m^2/g and 31.5 m^2/g. This is in sharp contrast to other preparations of ferric citrate such as chemical-grade preparations that are known and commercially available as of the filing date of this disclosure. Commercial grade preparations of ferric citrate have BET active surface areas that are substantially lower than the ferric citrate preparation of the present disclosure. Therefore, the ferric citrate preparations disclosed herein have a significantly larger surface area available for adsorption or chemical reactions, making the preparations of ferric citrate disclosed herein substantially more reactive than commercial preparations.

The BET active surface areas determined for five ferric citrate preparations produced by the methods disclosed in PCT Publication No. WO2004/074444 have been determined. Those BET active surface areas are displayed in Table 1, below, compared to the BET active surface area of commercial-grade preparations of ferric citrate:

Table 1. BET active surface areas of various forms of ferric citrate

Sample	Mean Dissolution Rates (mg/cm2/min)	BET Active Surface Area
RFS-12-1 (sigma / commercially available)	0.76	0.61
RFS-12-2 (sigma / commercially available)		
STM-134-1 (reference material 1)	2.47	16.17
STM-134-2 (reference material 2)		
STM-182-1 (lab-scale 500 g batch 1)	2.61	19.85
STM-182-2 (lab-scale 500 g batch 2)		

The BET active surface areas determined for five ferric citrate preparations produced by the methods disclosed in PCT Publication No. WO2011/011541 have been determined. Those BET active surface areas are displayed in Table 2, below, compared to the BET active surface area of commercial-grade preparations of ferric citrate:

Table 2. BET active surface areas

Sample	BET Active Surface Area (m^2/g)
RFS-12-1 (sigma / commercially available)	0.61
RFS-12-2 (sigma / commercially available)	
Sample #10-1 (Pre-granulation(API+ProSolv))[1]	27.99
Sample #10-2 (Pre-granulation(API+ProSolv))[2]	32.34
Sample #11-1 (Pre-granulation(API+ProSolv))[3]	28.87
Sample #11-2 (Pre-granulation(API+ProSolv))[4]	
Sample #11-3 (Pre-granulation(API+ProSolv))[5]	

The BET active surface areas for four additional ferric citrate preparations produced by methods disclosed herein have also been determined. Those BET active surface areas are displayed in Table 3, below, compared to the BET active surface area of commercial-grade preparations of ferric citrate:

[1] From Example 10 of PCT Publication No. WO 2011/011541.

[2] From Example 10 of PCT Publication No. WO 2011/011541.

[3] From Example 11 of PCT Publication No. WO 2011/011541.

[4] From Example 11 of PCT Publication No. WO 2011/011541.

[5] From Example 11 of PCT Publication No. WO 2011/011541.

Table 3. BET active surface areas

Sample	BET Active Surface Area (m^2/g)
RFS-12-1 (sigma / commercially available)	0.61
RFS-12-2 (sigma / commercially available)	
Batch No. 35102	30.6
Batch No. 35103	29.1
Batch No. 35105	31.5
Batch No. 35106	28.5

The BET active surface areas of the embodiments of ferric citrate preparations disclosed in Tables 1, 2 and 3 are thus significantly higher than those of commercial grade ferric citrate.

Table 4 illustrates the assay content of ferric iron of the ferric citrate disclosed herein. The assay content of ferric iron represents the amount of ferric iron in each of the preparations of ferric citrate shown in Table 4. In some embodiments, the assay content of ferric iron is greater than or exceeds about 20% w/w. In some embodiments, the assay content of ferric iron is 21.2% w/w. In some embodiments, the assay content of ferric iron is 22.1% w/w. In some embodiments, the assay content of ferric iron is 22.4% w/w. In some embodiments, the assay content of ferric iron is between 21% w/w and 23% w/w.

Table 4: Ferric Iron Content

Batch	Material balance	+ Water	Revised Mat Bal. (mat bal+water)	Impurity Content	% Fe(III)
A	94.60	1.9	96.50	3.5	21.2
B	94.40	2.1	96.50	3.5	21.2
C	93.40	2.0	95.40	4.6	22.4
D	92.90	2.2	95.10	4.9	22.1

The ferric citrate disclosed herein is a complex of iron(III) and citric acid. In some aspects, the molar ratio of iron (III) to citric acid is from 1: 0.70 to 1: 0.78. In some aspects, the molar ratio of iron (III) to citric acid is from 1: 0.69 to 1: 0.87. In some aspects, the molar ratio of iron (III) to citric acid is from 1: 0.75 to 1: 1.10. In some aspects, the molar ratio of iron (III) to citric acid is from 1: 0.78 to 1: 0.95. In some aspects, the molar ratio of iron (III) to citric acid is from 1: 0.80 to 1: 0.92. In some aspects, the molar ratio of iron (III) to citric acid is from 1: 0.81 to 1: 0.91. In some aspects, the molar ratio of iron (III) to citric acid is from 1: 0.75 to 1: 1.15. In some aspects, the molar ratio of iron (III) to citric acid is from 1: 0.80 to 1: 1.10.

In some aspects, the molar ratio of iron (III) to water is from 1: 0.32 to 1: 0.42. In some aspects, the molar ratio of iron (III) to water is from 1: 0.32 to 1: 0.46. In some aspects, the molar ratio of iron (III) to water is from 1: 1.8 to 1: 3.2. In some aspects, the molar ratio of iron (III) to water is from 1: 1.8 to 1: 3.2. In some aspects, the molar ratio of iron (III) to water is from 1: 2.4 to 1: 3.1. In some aspects, the molar ratio of iron (III) to water is from 1: 2.7 to 1: 3.1.

The ferric citrate preparations disclosed herein are more soluble compared to commercially available or chemical grade forms of ferric citrate. In dissolution testing, the percentage of ferric citrate of the present disclosure dissolved within 5 minutes is 91% or more, within 15 minutes is 96% or more, within 30 minutes is 96% or more and within 60 minutes is 95% or more in dissolution testing conducted on the ferric citrate preparations in USP <711> vessels using Apparatus II. Table 5 illustrates dissolution testing data for four exemplary batches of ferric citrate according to the present disclosure. The particular standard used for the dissolution testing establishes a baseline of 100 so to the extent that a batch may have a dissolution greater than 100%, it is a dissolution rate relative to that standard.

Table 5. Dissolution testing data

Batch	5 minutes	15 minutes	30 minutes	60 minutes
A	101%	102%	101%	101%
B	101%	102%	102%	102%
C	97%	97%	97%	97%
D	91%	96%	96%	95%

Thus, in some embodiments, the percentage of ferric citrate dissolved within 15 minutes is 80% or more in dissolution testing conducted in USP <711> vessels using Apparatus II. In some embodiments, the percentage of ferric citrate dissolved within 15 minutes is 85% or more in dissolution testing conducted in USP <711> vessels using Apparatus II. In some embodiments, the percentage of ferric citrate dissolved within 15 minutes is 90% or more in dissolution testing conducted in USP <711> vessels using Apparatus II. In some embodiments, the percentage of ferric citrate dissolved within 15 minutes is 91% or more in dissolution testing conducted in USP <711> vessels using Apparatus II. In some embodiments, the percentage of ferric citrate dissolved within 15 minutes is 95% or more in dissolution testing conducted in USP <711> vessels using Apparatus II. In some embodiments, the percentage of ferric citrate dissolved within 15 minutes is 96% or more in dissolution testing conducted in USP <711> vessels using

Apparatus II. In some embodiments, the percentage of ferric citrate dissolved within 15 minutes is 97% or more in dissolution testing conducted in USP <711> vessels using Apparatus II. In some embodiments, the percentage of ferric citrate dissolved within 15 minutes is 100% or more in dissolution testing conducted in USP <711> vessels using Apparatus II.

The ferric citrate preparations disclosed herein are more soluble compared to commercially available or chemical grade forms of ferric citrate. This increase in solubility of the ferric citrate preparations disclosed herein is believed to be a result of the unique, significantly large active surface area of the ferric citrate preparations disclosed herein. The intrinsic dissolution rate is defined as the dissolution rate of pure substances under the condition of constant surface area. The intrinsic dissolution rate and bioavailability of a drug substance is influenced by its solid state properties including: crystallinity, amorphism, polymorphism, hydration, solvation, particle size and particle surface area. The measured intrinsic dissolution rate is dependent on these solid-state properties and is typically determined by exposing a constant surface area of a material to an appropriate dissolution medium while maintaining constant temperature, stirring rate, and pH.

In some embodiments, the ferric citrate preparations disclosed herein have an intrinsic dissolution rate of greater than 2.28 mg/cm^2/min. In some embodiments, the ferric citrate preparations disclosed herein have an intrinsic dissolution rate exceeding 2.28 mg/cm^2/min. In some embodiments, the ferric citrate preparations disclosed herein have an intrinsic dissolution rate of 2.99 mg/cm^2/min. In some embodiments, the ferric citrate preparations disclosed herein have an intrinsic dissolution rate ranging from 2.28 mg/cm^2/min to 2.99 mg/cm^2/min. In some embodiments, the ferric citrate preparations disclosed herein have an intrinsic dissolution rate selected from 2.28 mg/cm^2/min and 2.99 mg/cm^2/min. This is in sharp contrast to other preparations of ferric citrate such as chemical-grade preparations that are known and commercially available. Commercial grade preparations of ferric citrate have an intrinsic dissolution rate that is substantially lower than the ferric citrate preparation of the present disclosure. Therefore, the ferric citrate preparations disclosed herein have a significantly higher intrinsic dissolution rate, making the preparations of ferric citrate disclosed herein substantially more soluble than commercial preparations.

The intrinsic dissolution rate was determined for a preparation of ferric citrate produced according to the present disclosure. The mean intrinsic dissolution rate is displayed in Table 6, below, compared to the dissolution rate of a commercial-grade preparation of ferric citrate:

Table 6. Intrinsic Dissolution Rates

Sample	Mean Intrinsic Dissolution Rates ($mg/cm^2/min$)
RFS-12 (sigma/commercially available)	0.83
High Purity Ferric Citrate	2.64

The intrinsic dissolution rate of the ferric citrate preparation disclosed in Table 6 is thus significantly higher than that of commercial grade ferric citrate.

Methods of Manufacture

Exemplary methods of manufacture of preparations of ferric citrate provided by this disclosure are disclosed in U.S. Patent Nos. 7,767,851, 8,093,423, 8,299,298 and 8,338,642, and PCT Publication Nos. WO 2004/074444, WO 2007/022435, WO 2007/089571, WO 2007/089577 and WO 2011/011541.

Modes of Administration

The ferric citrate disclosed herein may be advantageously used in human medicine. As disclosed herein, the ferric citrate disclosed herein is useful to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in CKD patients. The ferric citrate disclosed herein may also be advantageously used as an iron supplement. In various aspects, the ferric citrate disclosed herein can be administered orally. In some embodiments, the ferric citrate is administered in an oral dosage form. In some embodiments, the ferric citrate is administered in an oral tablet dosage form. In some embodiments, the tablet is in the form of a caplet.

When used to treat the above diseases and/or conditions, or when used as an iron supplement, the ferric citrate disclosed herein may be administered or applied singly, or in combination with other agents. The ferric citrate disclosed herein may also be administered or applied singly or in combination with other pharmaceutically active agents, including other agents known to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels,

increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in CKD patients.

Methods of treatment are disclosed above and include orally administering ferric citrate to the patient at a dose of ferric iron ranging from 210 mg – 2,520 mg. The ferric citrate disclosed herein can therefore be administered orally. In various aspects, the ferric citrate disclosed herein may be administered in an oral tablet dosage form that comprises 1 gram of ferric citrate and a dose of ferric iron of about 210 mg.

The ferric citrate disclosed herein serves to enhance the absorption of iron from the intestinal lumen and to enhance/maintain the storage of iron after absorption. It is believed that the enhanced absorption and storage of iron may be due to the presence of citrate in the ferric citrate administered to the CKD patient. While not wishing to be bound by any theory, some studies have shown that administration of iron in combination with citrate (the conjugate base of citric acid) serves to significantly increase (*e.g.*, by several fold) the amount of iron absorbed from dietary sources (*see, e.g.*, Ballot, *et al.*, *Br. J. Nutr.* (1987) 57, 331–343; Gillooly, *et al.*, *Br. J. Nutr.* (1983) 49, 331–342; Zhang, *et al.*, *Eur. J. Nutr.* (2007) 46, 95–102; and Salovaara, *et al.*, *J. Agric. Food Chem.* (2002) 50, 6233–6238).

The ferric citrate disclosed herein can be administered in some embodiments once per day, in some embodiments twice per day, in some embodiments three times per day, and in some embodiments more than twice per day. In various aspects, the ferric citrate may be administered in the form of a daily dose that is split up during the course of a single day. By way of example, a single daily dose of ferric citrate may be 6 grams and that 6 grams may be spread out over the course of the day such that 2 grams is taken in the morning, 2 grams in the afternoon, and the final 2 grams in the evening, for a total of 6 grams over the course of a day.

The ferric citrate disclosed herein can be used to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in CKD patients, while also reducing adverse drug effects associated with known forms of oral iron supplements (such as ferrous iron-containing supplements) and/or IV iron supplements.

Pharmaceutical Compositions and Iron Supplements

Disclosed herein are ferric citrate-containing pharmaceutical compositions comprising the ferric citrate preparations disclosed herein and a binder. In some embodiments, the pharmaceutical compositions can be provided to CKD patients as iron supplements. In some embodiments, the pharmaceutical compositions can be provided to CKD patients as phosphate binders and/or to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in CKD patients. In various embodiments, the pharmaceutical compositions meet certain dissolution, tableting and/or disintegration standards. In various aspects, the pharmaceutical compositions can include ferric citrate as the active ingredient and a binder. The pharmaceutical compositions also can include a lubricant and/or a disintegrant (which, in some embodiments, can be the same as the binder). In some embodiments, the pharmaceutical compositions are oral tablet dosage forms.

Certain embodiments of the pharmaceutical compositions and oral tablet dosage forms provided by this disclosure are disclosed in PCT Publication No. WO 2011/011541. Other embodiments, however, are unique to this disclosure.

Oral Tablet Dosage Forms and Oral Iron Supplements

In one aspect, the pharmaceutical compositions are tablets that include ferric citrate and a binder. As is used herein, a "tablet" is a material produced by compression force, such as with a tableting machine. In other embodiments the tablets can include ferric citrate, a binder, a lubricant and a disintegrant. In some embodiments, a single tablet comprises 1 gram of ferric citrate having a 210 mg dose of ferric iron. In some embodiments, the tablets can be used to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in CKD patients. In some embodiments, the tablets can be administered to CKD patients as oral iron supplements.

In some embodiments, the tablets and/or oral iron supplements can be characterized as highly drug loaded with the ferric citrate present in the tablets and/or oral iron supplements

at values of greater than approximately 65% by weight of the formulation, greater than approximately 70% by weight of the formulation, greater than approximately 75% by weight of the formulation, greater than approximately 80% by weight of the formulation, greater than approximately 85% by weight of the formulation, greater than approximately 90% by weight of the formulation and as high as approximately 92% of the formulation. Intermediate values such as approximately 80% by weight ferric citrate, approximately 85% by weight ferric citrate and approximately 90% by weight ferric citrate also can be used in the ferric citrate tablets and/or oral iron supplements. The characteristics of the tablets and/or oral iron supplements produced at these highly loaded weight percentages are controlled by variables such as binder, binder amount, disintegrant, disintegrant amount, formulation method used (*e.g.*, granulation, direct compression), tableting parameters, etc. Thus if a tablet and/or oral iron supplement is made and it has a slight amount of lamination or capping, by varying one or more of the above variables, the lamination or capping can be corrected.

In various embodiments, the tablets and/or oral iron supplements contains one or more components selected from among one or more binders, one or more lubricants, and one or more disintegrants.

The binder can be any binder known in the art. Without limitation, examples of the binder can include one or more of hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), sodium alginate, alginic acid, guar gum, acacia gum, xanthan gum, carbolpol, cellulose gum (carboxy methyl cellulose), ethyl cellulose, maltodextrin, PVP/VA, povidone, microcrystalline cellulose, starch, partially or fully pregelatinized starch, and methyl cellulose. The maltodextrin, PVP/VA, and methyl cellulose function as immediate release binders when used in the ferric citrate tablets and/or oral iron supplements.

It also should be understood that combinations of binders can be used to control and vary the effect of the binder. For example, a binder system can be made up of hydroxypropyl cellulose and polyvinyl pyrrolidone (povidone) with or without microcrystalline cellulose. One or both of the hydroxypropyl cellulose and povidone can be replaced with pregelatinized starch.

In various aspects, the tablets and/or oral iron supplements can include a lubricant. As an example of a lubricant for the ferric citrate tablets and/or oral iron supplements, magnesium stearate, calcium stearate, sodium stearyl fumarate and combinations can be used. Other suitable lubricants include one or more of polyethylene glycol (molecular weight above 3350), sodium lauryl sulfate, talc, mineral oil, leucine, and poloxamer.

In various aspects, the tablets and/or oral iron supplements can include a disintegrant. The disintegrant can be included in the tablets and/or oral iron supplements. The disintegrant can be the same as or different from the binder. By way of example and not limitation, microcrystalline cellulose has both binder and disintegrant properties and microcrystalline cellulose can be used as the sole binder/disintegrant in the tablets and/or oral iron supplements. Examples of other suitable disintegrants include croscarmellose sodium, crospovidone, sodium starch glycolate, and starch.

The binder can be present in the tablets and/or oral iron supplements in an amount ranging from approximately 4.5% by weight to approximately 30% by weight. The disintegrant can be present in the tablets and/or oral iron supplements in an amount ranging from approximately 1.5% by weight to approximately 15% by weight. In various embodiments, some non-starch disintegrants are often used at lower weight percents, e.g., as low as 0.25% and thus the disintegrant present in the tablets and/or oral iron supplements can be as low as 0.25% in some conditions.

The lubricant can be present in the tablets and/or oral iron supplements in an amount ranging from approximately 0.5% by weight to approximately 3% by weight. It should be understood that some components, such as microcrystalline cellulose, can function with both disintegrant and binder properties.

The weight of individual tablets and/or oral iron supplements can depend upon the final dosage to be produced; e.g. 125mg, 250mg, 500mg, 667mg, 750mg and 1,000mg of ferric citrate. In some embodiments, the tablets comprise 1 gram of ferric citrate and therefore a dose of 210 mg of ferric iron.

In various embodiments, tablets and/or oral iron supplements are coated to a weight gain of approximately 2% to 5% using an Opadry suspension or equivalent in a perforated pan coater. Calcium stearate and Opadry purple can be replaced with or used with a different lubricant or coating system, respectively.

In other variations, the tablets and/or oral iron supplements have reduced water content. In one embodiment, the water content of the tablet, as measured by LOD %, is less than 20%. In another embodiment, the water content of the tablet, as measured by LOD %, is less than 19%. In another embodiment, the water content of the tablet, as measured by LOD %, is less than 18%. In another embodiment, the water content of the tablet, as measured by LOD %, is less than 17%. In another embodiment, the water content of the tablet, as measured by LOD %, is less than 16%. In another embodiment, the water content of the tablet, as measured by LOD %, is less than 15%. In another embodiment, the water content

of the tablet, as measured by LOD %, is less than 14%. In another embodiment, the water content of the tablet, as measured by LOD %, is less than 13%. In another embodiment, the water content of the tablet, as measured by LOD % is less than 12%. In another embodiment, the water content as measured by LOD % is less than 11%. In another embodiment, the water content as measured by LOD % is less than 10%. In another embodiment, the water content of the tablet, as measured by LOD %, is less than 9%. In another embodiment, the water content of the tablet, as measured by LOD %, is less than 8%. In another embodiment, the water content of the tablet, as measured by LOD %, is less than 7%. In another embodiment, the water content of the tablet, as measured by LOD %, is less than 6%. In another embodiment, the water content of the tablet, as measured by LOD %, is less than 5%.

LOD (loss on drying) is a method of thermogravimetric moisture determination. In thermogravimetric processes, the moisture of a material includes substances that volatilize during warming, and therefore contribute to the material's loss of mass. Alongside water this may also include alcohol or decomposition products. When using thermogravimetric measurement methods (drying using infrared, halogen, microwaves or ovens) no distinction is made between water and other volatile components.

In some embodiments, the tablets and/or oral iron supplements comprise an amount of ferric citrate selected from approximately 1000 mg, approximately 667 mg, approximately 500 mg, approximately 250 mg and approximately 125 mg. In some embodiments, the tablets and/or oral iron supplements comprise 1 gram (1000mg) of ferric citrate. In some embodiments, the tablets and/or oral iron supplements comprise 1 gram of ferric citrate containing approximately 210 mg of ferric iron.

In some embodiments, the tablets and/or oral iron supplements comprise 1.3 grams of ferric citrate. In some embodiments, the tablets and/or oral iron supplements comprise 1.5 grams of ferric citrate. In some embodiments, the tablets and/or oral iron supplements comprise 1.6 grams of ferric citrate. In some embodiments, the tablets and/or oral iron supplements comprise an amount of ferric citrate selected from 100mg, 125mg, 150mg, 175mg, 200mg, 225mg, 250mg, 275mg, 300mg, 325mg, 350mg, 375mg, 400mg, 425mg, 450mg, 475mg, 500mg, 525mg, 550mg, 575mg, 600mg, 625mg, 650mg, 675mg, 700mg, 725mg, 750mg, 775mg, 800mg, 825mg, 850mg, 875mg, 900mg, 925mg, 950mg, 975mg, 1000mg, 1025mg, 1050mg, 1075mg, 1100mg, 1125mg, 1150mg, 1175mg, 1200mg, 1225mg, 1250mg, 1275mg, 1300mg, 1325mg, 1350mg, 1375mg, 1400mg, 1425mg, 1450mg, 1475mg, 1500mg, 1525mg, 1550mg, 1575mg, 1600mg, 1625mg, 1650mg, 1675mg, 1700mg, 1725mg,

1750mg, 1775mg, 1800mg, 1825mg, 1850mg, 1875mg, 1900mg, 1925mg, 1950mg, 1975mg and 2000mg.

In some embodiments, the tablets and/or oral iron supplements comprise between approximately 65 wt% and 92 wt% ferric citrate; between approximately 4.5 wt% and 30 wt% binder; and between 0.5 wt% and 3 wt% lubricant. In some embodiments, the lubricant is selected from one or more of magnesium stearate, calcium stearate, and sodium stearyl fumarate.

In some embodiments, the tablets and/or oral iron supplements comprise 65 % by weight to 92 % by weight of ferric citrate and 4.5 % by weight to 30 % by weight of a binder, wherein the mean surface area to mass ratio of said tablet is equal to or greater than 1 m^2 per gram, and wherein the LOD % water of the tablet is less than 20% water w/w. In some embodiments, the mean surface area to mass ratio of the tablets and/or oral iron supplements can be equal to or greater than 5 m^2 per gram. In some embodiments, the mean surface area to mass ratio of the tablets and/or oral iron supplements is equal to or greater than 10 m^2 per gram. In some embodiments, the tablets and/or oral iron supplements comprise at least 70 weight percent ferric citrate. In some embodiments, the tablets and/or oral iron supplements comprise at least 80 weight percent ferric citrate. In some embodiments, the tablets and/or oral iron supplements comprise at least 90 weight percent ferric citrate. In some embodiments, the binder comprises one or more of hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), sodium alginate, alginic acid, guar gum, acacia gum, xanthan gum, carbolpol, cellulose gum (carboxymethyl cellulose), ethyl cellulose, maltodextrin, PVP/VA, povidone, microcrystalline cellulose, starch (partially or fully pregelatinized starch) and methyl cellulose. In some embodiments, the LOD % water of the tablets and/or oral iron supplements is less than 15% water w/w. In some embodiments, the LOD % water of the tablets and/or oral iron supplements is less than 10% water w/w. In some embodiments, the tablets and/or oral iron supplements further comprise a disintegrant selected from one or more of microcrystalline cellulose, croscarmellose sodium, crospovidone, sodium starch glycolate, and starch. In some embodiments, the tablets and/or oral iron supplements further comprise a lubricant selected from one or more of magnesium stearate, calcium stearate, and sodium stearyl fumarate. In some embodiments, the tablets and/or oral iron supplements comprise between 0.5% and 3% lubricant. In some embodiments, the binder comprises pregelatinized starch. In some embodiments, the lubricant comprises calcium stearate and sodium stearyl fumarate. In some embodiments, at least 80% of the ferric citrate in the tablets and/or oral iron supplements is dissolved in a time

less than or equal to 60 minutes as measured by test method USP <711>. In some embodiments, the tablets and/or oral iron supplements comprise approximately 1000 mg of ferric citrate. In some embodiments, the tablets and/or oral iron supplements comprise approximately 667 mg of ferric citrate. In some embodiments, the tablets and/or oral iron supplements comprise approximately 500 mg of ferric citrate.

Table 7 provides a formulation for a ferric citrate tablet and/or oral iron supplement according to one embodiment of the present disclosure:

Table 7. Formulation for a Ferric Citrate Tablet and/or Oral Iron Supplement

Material Description	Theoretical kg/Batch	% w/w
Ferric Citrate	14.89	87.6
Pregelatinized Starch	1.70	10.0
Calcium Stearate	0.406	2.4
Purified Water	15.30*	N/A*
Core Tablet Total	17.00	100.0
Opadry Purple 03K100000	0.51	15.0
Purified Water	2.89*	85.0*
Coated Tablet Total	17.5	100.0

* – Purified water is removed during a drying phase in the manufacturing process

Table 8 provides a formulation for a ferric citrate tablet and/or oral iron supplement according to one embodiment of the present disclosure:

Table 8:

Material Description	Target kg/Batch	Theoretical 100 kg/Lot	% w/w Individual	% w/w Coated Tablet
Ferric Citrate	14.9	80.0 - 90.0	80.0 - 90.0	76.2 - 88.2
Pregelatinized Starch	1.7	8.0 – 15.0	8.0 – 15.0	7.6 – 14.7
Calcium Stearate (1)	0.4	1.0 – 3.0	1.0 – 3.0	0.9 – 2.9
OR – Sodium Stearyl Fumarate (1)	0.4	2.0 – 3.0	2.0 – 3.0	1.9 – 2.9
Purified Water	15.3*	72.0-135.0*	*	*
Core Tablet Total	17. 0	100.0	100.0	N/A*
Opadry Purple	0.9	5.3	15.0	2.0 – 5.0
Purified Water	5.1*	30.0*	85.0*	N/A*
Coated Tablet Total	17.5 to 17.9	35.3	100.0	100.0

(1) – use either calcium stearate or sodium stearyl fumarate as lubricant
* – Purified water is removed

Table 9 provides a formulation for a ferric citrate tablet and/or oral iron supplement according to one embodiment of the present disclosure:

Table 9:

Material Description	Target kg/Batch	% w/w Individual
Ferric Citrate	14.89	87.6
Pregelatinized Starch	1.70	10.0
Calcium Stearate (1)	0.406	2.4
Purified Water	15.30	N/A
Core Tablet Total	17. 00	100.0
Opadry Purple	0.51	15.0
Purified Water	2.89	85.0
Coated Tablet Total	17.5	100.0

Table 10 provides a formulation for a ferric citrate tablet and/or oral iron supplement according to one embodiment of the present disclosure:

Table 10:

Material / Component	Formula Composition % w/w
Ferric Citrate	70.0 to 99.0
Starch	0.0 to 30.0
Microcrystalline Cellulose	0.0 to 30.0
Polyvinylpyrrolidone	0.0 to 30.0
Calcium Stearate	0.0 to 3.0
Sodium Stearyl Fumarate	0.0 to 3.0
Purified Water	N/A*
Core Caplet Total	100.0
Film coating	0.0 to 5.0
Purified Water	N/A*
Coated Caplet Total	100.0

* The purified water is removed.

Table 11 provides a formulation for a ferric citrate tablet and/or oral iron supplement according to one embodiment of the present disclosure:

Table 11:

Material	Weight mg ± 10%
Ferric Citrate	1,500
Starch	150
Microcrystalline Celluose	0
Polyvinylpyrrolidone	0
Calcium Stearate	16
Sodium Stearyl Fumarate	0
Purified Water	N/A*
Core Caplet Total - mg	1,666
Film coating	50
Purified Water	N/A*
Coated Caplet Total - mg	1,766

* The purified water is removed.

Dosing

The tablets and/or oral iron supplements disclosed herein can be made to accommodate a number of doses of ferric citrate. The weight of individual tablets and/or oral iron supplements can depend upon the final dosage to be produced; e.g., 125mg, 250mg, 500mg, 667mg, 750mg and 1,000mg of ferric citrate per tablet. In various aspects, the ferric citrate is provided in a tablet dosage form comprising 1 gram of ferric citrate containing approximately 210 mg of ferric iron. The number of tablets and/or oral iron supplements administered can be adjusted to conform to the desired amount of ferric citrate to be administered. For example, if a CKD patient is directed to take 4 grams of ferric citrate daily in a single dose, the CKD patient may take 4 tablets and/or oral iron supplements, each comprising 1 gram of ferric citrate, or may take 8 tablets and/or oral iron supplements, each comprising 500mg of ferric citrate.

In some embodiments, a daily dose of ferric citrate administered to CKD patients can be from 1 gram – 18 grams, at a dose of ferric iron ranging from 210 mg – 3,780 mg. In some embodiments, one or more tablets comprising 1 gram of ferric citrate, each tablet having a dose of ferric iron of 210 mg, is/are administered to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in CKD patients.

In some embodiments, the ferric citrate is administered at a daily dose of 1 tablet per day, the tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 1 gram of ferric citrate and 210 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 2 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 2 grams of ferric citrate and 420 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 3 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 3 grams of ferric citrate and 630 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 4 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 4 grams of ferric citrate and 840 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 5 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 5 grams of ferric citrate and 1,050 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 6 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 6 grams of ferric citrate and 1,260 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 7 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 7 grams of ferric citrate and 1,470 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 8 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 8 grams of ferric citrate and 1,680 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 9 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 9 grams of ferric citrate and 1,890 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 10 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 10 grams of ferric citrate and 2,100 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 11 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 11 grams of ferric citrate and 2,310 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 12 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 12 grams of ferric citrate and 2,520 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 13 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total

daily dose of 13 grams of ferric citrate and 2,730 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 14 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 14 grams of ferric citrate and 2,940 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 15 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 15 grams of ferric citrate and 3,150 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 16 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 16 grams of ferric citrate and 3,360 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 17 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 17 grams of ferric citrate and 3,570 mg ferric iron. In some embodiments, the ferric citrate is administered at a daily dose of 18 tablets per day, each tablet comprising 1 gram of ferric citrate containing 210 mg of ferric iron, for a total daily dose of 18 grams of ferric citrate and 3,780 mg ferric iron.

EXAMPLES

The following example describes in detail the use of the ferric citrate disclosed herein. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the disclosure.

Example 1

A Three-Period, 58-Week Trial Of Ferric Citrate As A Phosphate Binder In Patients With End-Stage Renal Disease (ESRD) On Dialysis

The primary objectives of this trial were as follows:

1. To determine the long-term safety over 52 weeks of up to twelve (12) caplets/day of KRX-0502 (ferric citrate) in patients with end-stage renal disease undergoing either hemodialysis or peritoneal dialysis.
2. To determine the efficacy of KRX-0502 (ferric citrate) in a four-week, randomized, open-label, placebo-controlled Efficacy Assessment Period.

Study Rationale

Previous clinical trials have demonstrated the ability of ferric citrate to lower serum phosphorus levels in patients with ESRD who are on thrice-weekly hemodialysis. These trials used a maximum of approximately 12 g/day of ferric citrate for four weeks.

This clinical trial determined the long-term safety of ferric citrate in controlling and managing serum phosphorus levels over a 56-week treatment period when compared to an active control for 52 weeks in the Safety Assessment Period and to placebo in a randomized, open-label, placebo-controlled four-week Efficacy Assessment Period.

Study Design

This trial was a three-period, multicenter, safety and efficacy clinical trial. The first period was a two-week washout (the Washout Period), the second period was a 52-week randomized, open-label, active control safety assessment (the Safety Assessment Period), and the third period was a four-week, randomized, open-label, placebo-controlled, efficacy assessment (the Efficacy Assessment Period) in only patients randomized to treatment with ferric citrate during the Safety Assessment Period.

Period 1 (Washout Period). Patients were washed out from their current phosphate binder for up to approximately two weeks. Only patients who achieve a serum phosphorus ≥6.0 mg/dL during the Washout Period were moved into the Safety Assessment Period. Patients who did not achieve a serum phosphorus ≥6.0 mg/dL during washout were screen failures.

Period 2 (Safety Assessment Period). Following washout, patients were randomized 2:1 to either the ferric citrate group or an active-control group of either calcium acetate, sevelamer carbonate, or any combination of calcium acetate and sevelamer carbonate at the discretion of the PI and/or patient. Both ferric citrate and the active-control medications were provided by the sponsor. Patients were followed on their randomized assignment for safety assessments over 52 weeks. If a patient was ≥ 80% compliant with 12 caplets/day of ferric citrate or 12 pills/day of calcium acetate and/or sevelamer carbonate at least 2 visits in a row, and had a serum phosphorus > 8.0 mg/dL, the patient was considered a treatment failure and stopped study drug but continued to complete all trial visits. The ferric citrate or active-control drug was stopped and the patient returned to the care of their primary nephrologist, but continued to be followed for all trial visits and outcomes.

Period 3 (Efficacy Assessment Period). Following the Safety Assessment Period, those patients randomized to treatment with ferric citrate entered a four-week, randomized, open-label, placebo-controlled Efficacy Assessment Period. Patients entering the Efficacy Assessment Period were re-randomized 1:1 to treatment with ferric citrate or placebo.

A Dietician provided a study-supplied list of Vitamin D-rich foods to the patient either during the Washout Period or at the Randomization Visit and instructed the patient to keep their diet consistent in Vitamin D-rich food throughout the trial as much as possible.

Within 30 days before the start of the Efficacy Assessment Period, the Dietician again reviewed the list of Vitamin D-rich foods with the patient and reminded the patient to try to keep their diet consistent in terms of Vitamin D-rich foods until the end of the trial, if possible. The Dietician was blinded as to assignment to ferric citrate or placebo during the Efficacy Assessment Period.

Laboratory measurements were conducted throughout the study to assess safety and efficacy. The dose and specific IV iron preparation administered (if necessary) were at the discretion of the PI. Oral iron therapy was not permitted. Calcium-containing drugs were not permitted if given within two hours of food ingestion (calcium-containing drugs were permitted two hours or more prior to or following food ingestion or at bedtime for the purpose of raising the serum calcium). No Vitamin C supplements were permitted. Patients were allowed to take daily water soluble vitamins that include a small amount of Vitamin C (e.g., Centrum, Nephrocaps, Renaphro), but those patients were instructed to take them two hours or more prior to or following food ingestion or at bedtime. IV iron therapy was not permitted if the ferritin level is > 1000 micrograms/L or the TSAT is > 30%. If it was deemed in the patient's best interest to receive IV iron outside these parameters, the Clinical Coordinating Center (CCC) was consulted, and when approved and documented, was not considered a protocol exception.

Study Duration

The duration of the trial was approximately 18 to 24 months, with approximately six to eight months allocated for patient Screening, Washout Period, and Randomization, 12 months for the Safety Assessment Period, and one (1) month for the Efficacy Assessment Period.

Study Population

ESRD patients on thrice-weekly hemodialysis or on peritoneal dialysis for at least three months prior to the Screening Visit (Visit 0) who were currently taking ≥3 and ≤18 pills/day of calcium acetate, calcium carbonate, lanthanum carbonate, and/or sevelamer (carbonate or hydrochloride or sevelamer powder equivalent to sevelamer tablets), or any other agent serving as a phosphate binder, or any combination of these agents were eligible for enrollment. It was anticipated that there would be approximately 20 to 40 centers in the United States and approximately 5 to 10 centers in Israel. Up to approximately 775 patients were screened to randomize approximately 350 patients to the ferric citrate group or active-control group. Each of approximately 25 to 50 sites were asked to randomize no more than approximately 35 patients.

Inclusion criteria:

- Males or non-pregnant, non-breast-feeding females
- Age ≥ 18 years
- On thrice-weekly hemodialysis or on peritoneal dialysis for at least the previous three months prior to Screening Visit (Visit 0)
- Serum phosphorus levels ≥2.5 mg/dL and ≤8.0 mg/dL at Screening Visit (Visit 0)
- Serum phosphorus ≥6.0 mg/dL during the Washout Period (Visits 2 or 3)
- Taking 3 to 18 pills/day of calcium acetate, calcium carbonate, lanthanum carbonate, and/or sevelamer (carbonate or hydrochloride or equivalent sevelamer powder) or any other agent serving as a phosphate binder, or any combination of these agents as reported by the patient at Screening Visit (Visit 0)
- Serum ferritin <1000 micrograms/L and TSAT < 50% at the Screening Visit (Visit 0)
- Willing to be discontinued from current phosphate binder and randomized to ferric citrate or active-control group
- Willing and able to give informed consent
- Life expectancy >1 year

Exclusion Criteria:

- Parathyroidectomy within six months prior to Screening Visit (Visit 0)
- Actively symptomatic gastrointestinal bleeding or inflammatory bowel disease
- Serum phosphorus levels ≥10.0 mg/dL documented in all of the three monthly laboratories (done routinely in the dialysis unit) in the 3 months prior to the Screening Visit (Visit 0)
- History of malignancy in the last five years (treated cervical or non-melanomatous skin cancer may be permitted if approved by the CCC)
- Absolute requirement for oral iron therapy
- Absolute requirement for Vitamin C (multivitamins [Nephrocaps, Renaphro, etc.] allowed)
- Absolute requirement for calcium-, magnesium-, or aluminum-containing drugs with meals
- Intolerance to oral iron-containing products
- Intolerance to orally administered calcium acetate and sevelamer carbonate

Study Drug

KRX-0502 (ferric citrate) was the drug under investigation in this study. The drug was administered as caplets, each caplet comprising 1 gram (1,000 mg) of ferric citrate containing approximately 210 mg of ferric iron.

Study Drug Administration

The target goal for serum phosphorus was 3.5 to 5.5 mg/dL.

Ferric citrate, active control, and placebo were considered study drugs. Eligible patients with a serum phosphorus level ≥6.0mg/dL after the Washout Period were randomized in a 2:1 ratio to the ferric citrate group or the active-control group. For patients randomized to ferric citrate, the starting dose was 6 caplets/day. For patients randomized to the active-control group, the starting dose of phosphate binder was the last dose that was administered immediately prior to the start of the Washout Period (if the patient remained on the same phosphate binder) or at the discretion of the PI, guided by the package insert, if the patient changed binders. However, for patients whose previous dose of phosphate binder exceeded 12 pills/day, if randomized to the active-control group, their starting dose of active-control drug was at the discretion of the PI, but will not exceed 12 pills/day. Calcium acetate 667 mg capsules and sevelamer carbonate 800 mg tablets were used and were supplied by Keryx Biopharmaceuticals, Inc. (Keryx) for the duration of the trial.

Serum phosphorus and calcium were checked at Visit 5 (Week 1), and every two weeks during the first 12 weeks after Visit 4 (Randomization Visit), and monthly for the rest of the Safety Assessment Period. During the Efficacy Assessment Period, serum phosphorus and calcium were drawn weekly. These values guided study drug administration. While on study drug, the use of other phosphate binders was not permitted. Dose adjustments in ferric citrate were guided by a titration schedule. The titration of calcium acetate and sevelamer carbonate throughout the 52-week Safety Assessment Period were according to the current package inserts for these agents and/or at the discretion of the site PI.

Patients took study drug orally with or within one hour of meals or snacks. Patients were instructed not to take the study drug if greater than one hour has passed since the ingestion of their meals or snacks. The PI or designee at each site dispensed the study drug to the patient and instructed the patient on how to administer it. It was recognized that some patients required a different distribution in pills in a given day due to snacks or missed meals. If the patient was receiving the total number of pills per day required by protocol in any distribution with meals, there was no need for approval by the CCC (for example, a patient on

a starting dose of ferric citrate 6 g/day may take 1 caplet with breakfast, 1 with a snack, 2 with lunch, and 2 with dinner).

Laboratory Assessments

For patients on hemodialysis, blood samples were obtained pre-dialysis on the second or third dialysis session of the week, if possible. For patients who are on hemodialysis who dialyze on Monday, Wednesday or Friday, all blood samples were drawn pre-dialysis on Wednesday or Friday, if possible. For patients who dialyze on Tuesday, Thursday or Saturday, all blood samples were drawn pre-dialysis on Thursday or Saturday, if possible. These collection methods were allowed to be different for sites in Israel. The total amount of blood collected from each patient for trial-related analyses was approximately 15 ml per visit.

For patients who were on peritoneal dialysis, blood samples were collected either at the dialysis unit or the clinic as per the study protocols.

Serum phosphorus and calcium were performed at Screening (Visit 0); weekly during the Washout Period after Visit 1 (Week -2); at Visit 4 (Randomization Visit); at Visits 5 (Week 1), 6 (Week 2), 7 (Week 4), 8 (Week 6), 9 (Week 8), 10 (Week 10), 11 (Week 12), 12 (Week 16), 13 (Week 20), 14 (Week 24), 15 (Week 28), 16 (Week 32), 17 (Week 36), 18 (Week 40), 19 (Week 44), 20 (Week 48), and 21 (Week 52) of the 52-week Safety Assessment Period; and at Visits 22 (Week 53), 23 (Week 54), 24 (Week 55) and 25 (Week 56) of the Efficacy Assessment Period.

Complete Blood Count (CBC) (white blood cell [WBC] count, white blood cell types [WBC differential], red blood cell [RBC] count, hematocrit [HCT], hemoglobin [Hgb], red blood cell indices, platelet [thrombocyte] count) was done at the Randomization Visit (Visit 4); at Visits 11 (Week 12), 14 (Week 24), 17 (Week 36), 20 (Week 48), and 21 (Week 52) of the 52-week Safety Assessment Period; and at Visit 25 (Week 56) of the Efficacy Assessment Period.

Complete Chemistry Profile (sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose [random], aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphate [ALP], total bilirubin, total protein, albumin, and albumin-adjusted calcium) was done at the Randomization Visit (Visit 4); at Visits 11 (Week 12), 14 (Week 24), 17 (Week 36), 20 (Week 48), and 21 (Week 52) of the 52-week Safety Assessment Period; and at Visit 25 (Week 56) of the Efficacy Assessment Period.

Iron studies including serum iron, ferritin, TSAT, and total iron-binding capacity were done at Screening (Visit 0); at the Randomization Visit (Visit 4); at Visits 7 (Week 4), 9 (Week 8), 11 (Week 12), 12 (Week 16), 13 (Week 20), 14 (Week 24), 15 (Week 28), 16

(Week 32), 17 (Week 36), 18 (Week 40), 19 (Week 44), 20 (Week 48), and 21 (Week 52) of the 52-week Safety Assessment Period; and at Visit 25 (Week 56) of the Efficacy Assessment Period.

Intact parathyroid hormone (iPTH) levels were done at the Randomization Visit (Visit 4); at Visits 11 (Week 12), 17 (Week 36), and 21 (Week 52) during the Safety Assessment Period; and at Visit 25 (Week 56) of the Efficacy Assessment Period.

Serum vitamins (25-dihydroxy-vitamin D3, vitamin A, vitamin B-12, vitamin E, vitamin K, and folic acid) were done at the Randomization Visit (Visit 4,); and at Visits 11 (Week 12), 17 (Week 36), and 21 (Week 52) during the Safety Assessment Period.

A lipid profile (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides) was done at the Randomization Visit (Visit 4); at Visits 11 (Week 12), 17 (Week 36), and 21 (Week 52) during the Safety Assessment Period.

Serum aluminum was done at the Randomization Visit (Visit 4) and at Visit 21 (Week 52).

Serum bicarbonate was performed at a local laboratory and was done at the Randomization Visit (Visit 4); at Visits 11 (Week 12), 14 (Week 24), 17 (Week 36), 20 (Week 48) and 21 (Week 52) during the Safety Assessment Period; and at Visit 25 (Week 56) of the Efficacy Assessment Period.

Except for serum bicarbonate, which was collected and measured locally, all labs were performed by Spectra Clinical Research, Rockleigh, NJ, USA.

Statistical Considerations: Efficacy

Unless otherwise stated, all hypotheses were tested at a 2-sided significance level of 0.05 and the 95% confidence interval was two-sided. All analyses were performed using SAS Version 9.

Prior to the database lock, a detailed Statistical Analysis Plan (SAP) was completed and placed on file. The Data Analysis Plan contained a more comprehensive explanation than described below of the methodology used in the statistical analyses. The Data Analysis Plan also contained the rules and data handling conventions used to perform the analyses, and the procedure used for accounting for missing data.

Summary tabulations displayed the number of observations, mean, standard deviation, median, minimum, maximum, and appropriate percentiles for continuous variables, and the number and percentage by category for categorical data. Summaries present data by treatment arm and overall, if appropriate. The data listings include all available efficacy and safety data.

The efficacy analyses were based on Full Analysis (FA) population that consisted of all patients who took at least one dose of study medication and provided baseline and at least one post-baseline efficacy assessment. The safety analyses were based on safety population that was consistent of all patients who took at least one dose of study medication.

There were two unique and distinct baseline assessments. The baseline for the Safety Assessment Period was the Randomization Visit (Visit 4) and was defined as "Week-0-baseline." The baseline for the Efficacy Assessment Period was the last visit of the Safety Assessment Period (Visit 21, Week 52) and was defined as "study-baseline."

The primary efficacy outcome of this trial was the effect of ferric citrate vs. placebo on the change in serum phosphorus from study-baseline (Visit 21, Week 52) to end of the Efficacy Assessment Period (Visit 25, Week 56). The primary efficacy variable was analyzed via an ANCOVA model with treatment as the fixed effect and study-baseline as the covariate. Between-treatment differences were estimated and two-sided 95% confidence intervals for the differences were presented.

The secondary endpoints for this trial include the following:

1. CHANGE FROM BASELINE IN FERRITIN AT WEEK 52

Change from baseline in ferritin at Week 52 as compared to baseline (Visit 4). This variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate). A sensitivity analysis will be performed using MMRM method.

2. CHANGE FROM BASELINE IN TSAT AT WEEK 52

Change from baseline in TSAT at Week 52 as compared to baseline (Visit 4). This variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate). A sensitivity analysis will be performed using MMRM method.

3. CUMULATIVE USE OF IV IRON OVER 52 WEEKS

The cumulative IV iron intake from randomization to Week 52 will be compared between treatment groups. This variable will be similarly analyzed as the primary efficacy variable using ANCOVA method. The two-sided 95% confidence intervals of treatment differences for all above comparisons will be presented.

4. CUMULATIVE USE OF EPO (ESA) OVER 52 WEEKS

The cumulative EPO (ESA) administrated from randomization to Week 52 will be compared between treatment groups. This variable will be similarly analyzed as the primary

efficacy variable using ANCOVA method. The two-sided 95% confidence intervals of treatment differences for all above comparisons will be presented.

Treatment differences between ferric citrate and all active control binders as well as the differences between ferric citrate and sevelamer carbonate as a single agent at Week 12 (Visit 11) in terms of change from Visit-4 baseline in serum phosphorus, phosphorus times calcium product, and in serum calcium will be analyzed. These variables will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and Visit-4 baseline (covariate). An analysis using MMRM method will be conducted as a sensitivity analysis. The least square mean estimates of the treatment effects as well as the 2-sided 95% confidence intervals (CI) of the treatment effects will be derived. Non-inferiority will be claimed if the lower-bound of the two-sided 95% confidence interval of the treatment difference is within 20% of least square mean of the control.

5. PERCENTAGE OF PATIENTS ACHIEVING PHOSPHORUS GOAL

1. Percentage of patients achieving phosphorus goal (≤5.5mg/dL) at Weeks 12, 24, 36, 48, 52 and 56 – These variables will be analyzed via chi-square tests. Between-treatment differences in the percentages will be estimated and two-sided 95% confidence intervals for the differences will be calculated using normal approximation without continuity correction.
2. Percentage of patients achieving the phosphorus goal (≤5.5mg/dL) at Week 56 for patients remaining on study medication during the four-week Efficacy Assessment Period – These variables will be analyzed via chi-square tests. Between-treatment differences in the percentages will be estimated and two-sided 95% confidence intervals for the differences will be calculated using normal approximation without continuity correction.
3. Percentage of patients obtaining a serum phosphorus ≥ 9.0mg/dL at any time during the four-week Efficacy Assessment Period – These variables will be analyzed via chi-square tests. Between-treatment differences in the percentages will be estimated and two-sided 95% confidence intervals for the differences will be calculated using normal approximation without continuity correction.

6. CHANGE IN SERUM PHOSPHORUS CONCENTRATION

1. Change in serum phosphorus concentration at Weeks 12, 24, 36, 48, and 52 as compared to baseline (Visit 4). This variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate).

7. CHANGE IN OTHER LABORATORY MEASURES

1. Change in serum calcium concentration at Weeks 12, 24, 36, 48, and 52 as compared to baseline (Visit 4). This variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate).
2. Change in ferritin, and TSAT at Weeks 12, 24, 36 and 48 as compared to baseline (Visit 4). This variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate).
3. Change in serum iron and TIBC at Weeks 12, 24, 36, 48, and 52 as compared to baseline (Visit 4). This variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate).
4. Change in Ca x P product at Weeks 12, 24, 36, 48, and 52 as compared to baseline (Visit 4). This variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate).
5. Change in iPTH at Weeks 12, 36, 52, and 56 as compared to baseline (Visit 4). This variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate).
6. Change in serum 25-dihydroxy-vitamin D3, vitamin A, vitamin B-12, vitamin E, vitamin K and folic acid at Weeks 12, 36, and 52 as compared to baseline (Visit 4). This variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate).
7. Change in serum bicarbonate concentration at Weeks 12, 36, and 52 as compared to baseline (Visit 4). This variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate).
8. Change in IV iron intake at Weeks 12, 24, 36, 48, and 52 as compared to baseline (Visit 4). This variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate).
9. Change in the use of EPO (ESA) administered at Weeks 12, 24, 36, 48, and 52 as compared to baseline (Visit 4). This variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate).
10. Change in the use of Vitamin D supplementation (and its analogs) and Sensipar (cinacalcet) at Weeks 12, 24, 36, 48, and 52 as compared to baseline (Visit 4). This

variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate).

11. Change in LDL, HDL, and triglycerides at Weeks 12, 36, and 52 as compared to baseline (Visit 4). This variable will be analyzed using LOCF methodology. ANCOVA will be employed. The model will include treatment (fixed effect), and baseline (covariate).

Statistical Considerations: Safety

Safety was assessed by recording and monitoring adverse events, concomitant medication use, physical examinations, and sequential blood by treatment assignment. Rates of adverse events were summarized overall and by organ system class, preferred term, severity, and suspected relationship to study drug by treatment assignment. AEs were summarized for the Washout Period, Safety Assessment Period, and Efficacy Assessment Period separately by treatment assignment. The changes from baseline in laboratory parameters over time were summarized by treatment assignment.

Statistical Considerations: Power

Approximately 434 patients were randomized in a 2:1 ratio to either ferric citrate (approximately 288 patients) or active-control (approximately 146 patients), to be treated during the Safety Assessment Period. This sample size provided at least 90% power to detect a treatment difference between ferric citrate and placebo at a 5% significance level, assuming that the treatment difference is 1.2 and the common standard deviation is 2.

Results

Summary of Treatment Differences in Serum Phosphorus, Phosphorus times Calcium Product and Serum Calcium Change from Study-baseline at Week 12 between Ferric Citrate and Sevelamer Carbonate as a Single Agent (ANCOVA Method), Full Analysis Population – shown in Table 12:

Table 12:

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Sevelamer Carbonate in Safety Assessment Period (N=73)	Treatment Differences[1]
Phosphorus (MG/DL)			
Baseline			
N	277	72	
Mean (SD)	7.39 (1.557)	7.51 (1.633)	
Median	7.20	7.40	
(Min, Max)	(2.7, 12.3)	(4.3, 12.9)	
Week 12			
N	277	72	
Mean (SD)	5.38 (1.374)	5.23 (1.713)	
Median	5.10	5.00	
(Min, Max)	(2.4, 9.9)	(2.5, 14.1)	

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Sevelamer Carbonate in Safety Assessment Period (N=73)	Treatment Differences[1]
Week 12 Change from Baseline			
N	277	72	
Mean (SD)	-2.01 (1.887)	-2.28 (2.169)	
Median	-2.00	-2.45	
(Min, Max)	(-7.6, 4.6)	(-8.9, 6.7)	
95% CI	(5.21, 5.55)	(4.89, 5.55)	(-0.21, 0.54)
LS Mean (SE)	5.38 (0.09)	5.22 (0.17)	0.16 (0.19)
p-value			0.3900
Product Of Calcium And Phosphorus			
Baseline			
N	277	72	
Mean (SD)	65.4075 (15.47697)	68.0872 (16.29263)	
Median	62.7000	66.2700	
(Min, Max)	(25.920, 123.210)	(36.660, 123.840)	
Week 12			
N	277	72	
Mean (SD)	48.8440 (12.93765)	48.0251 (14.36518)	
Median	47.5000	46.2800	
(Min, Max)	(20.440, 92.650)	(22.500, 109.980)	
Week 12 Change from Baseline			
N	277	72	
Mean (SD)	-16.5635 (16.97535)	-20.0621 (19.17393)	
Median	-16.7400	-19.8500	
(Min, Max)	(-78.660, 42.700)	(-86.200, 46.340)	
95% CI	(47.47, 50.48)	(44.57, 50.48)	(-1.87, 4.77)
LS Mean (SE)	48.97 (0.77)	47.52 (1.50)	1.45 (1.69)
p-value			0.3903
Calcium (MG/DL)			
Baseline			
N	278	72	
Mean (SD)	8.843 (0.8048)	9.056 (0.7291)	
Median	8.900	9.150	
(Min, Max)	(6.30, 11.10)	(6.70, 10.30)	
Week 12			
N	278	72	
Mean (SD)	9.089 (0.7568)	9.231 (0.7210)	
Median	9.100	9.400	
(Min, Max)	(6.30, 12.00)	(7.00, 10.60)	
Week 12 Change from Baseline			
N	278	72	
Mean (SD)	0.245 (0.7486)	0.175 (0.7509)	
Median	0.200	0.100	
(Min, Max)	(-2.80, 3.00)	(-1.50, 2.30)	
95% CI	(9.04, 9.19)	(9.00, 9.29)	(-0.20, 0.13)
LS Mean (SE)	9.11 (0.04)	9.15 (0.08)	-0.04 (0.08)
p-value			0.6765

Note: [1].The LS Mean treatment difference and p-value for the change in Serum Phosphorus, Ca x P and Ca is created via an ANCOVA model with treatment as the fixed effect and Day-0 baseline as the covariate. Between-treatment differences are calculated as the LS Mean (KRX-0502) - LS Mean (Control). Only subjects with both a baseline and post baseline observations for the parameter of interest were included.

Summary of Mean Serum Phosphorus Values at Weeks 12, 24, 36, 48, and 52 and Change from Study-baseline by Treatment (ANCOVA Method), Full Analysis Population – shown in Table 13:

Table 13:

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Control in Safety Assessment Period (N=146)	Treatment Differences[1]
Day 0 Baseline			
N	277	144	
Mean (SD)	7.39 (1.557)	7.55 (1.750)	
Median	7.20	7.40	
(Min, Max)	(2.7, 12.3)	(4.3, 12.9)	
Week 12			
N	277	144	
Mean (SD)	5.38 (1.374)	5.34 (1.652)	
Median	5.10	5.05	
(Min, Max)	(2.4, 9.9)	(2.5, 14.1)	
Week 12 Change from Baseline			
N	277	144	
Mean (SD)	-2.01 (1.887)	-2.21 (2.086)	
Median	-2.00	-2.25	
(Min, Max)	(-7.6, 4.6)	(-8.9, 6.7)	
95% CI	(5.22, 5.56)	(5.08, 5.56)	(-0.23, 0.36)
LS Mean (SE)	5.39 (0.09)	5.32 (0.12)	0.07 (0.15)
p-value			0.6594
Week 24			
N	277	144	
Mean (SD)	5.24 (1.455)	5.49 (1.536)	
Median	5.10	5.30	
(Min, Max)	(1.3, 10.7)	(2.0, 14.1)	
Week 24 Change from Baseline			
N	277	144	
Mean (SD)	-2.14 (1.844)	-2.06 (2.125)	
Median	-2.10	-2.00	
(Min, Max)	(-7.5, 3.9)	(-8.4, 6.7)	
95% CI	(5.08, 5.43)	(5.23, 5.71)	(-0.51, 0.08)
LS Mean (SE)	5.26 (0.09)	5.47 (0.12)	-0.21 (0.15)
p-value			0.1510
Week 36			
N	277	144	
Mean (SD)	5.22 (1.348)	5.32 (1.557)	
Median	5.10	5.10	
(Min, Max)	(1.1, 9.5)	(2.2, 14.1)	
Week 36 Change from Baseline			
N	277	144	
Mean (SD)	-2.16 (1.748)	-2.24 (2.037)	
Median	-2.10	-2.10	
(Min, Max)	(-7.4, 3.2)	(-8.1, 6.7)	
95% CI	(5.08, 5.40)	(5.07, 5.52)	(-0.33, 0.22)
LS Mean (SE)	5.24 (0.08)	5.29 (0.11)	-0.05 (0.14)
p-value			0.7075
Week 48			
N	277	144	
Mean (SD)	5.32 (1.468)	5.48 (1.563)	
Median	5.20	5.35	
(Min, Max)	(2.2, 10.8)	(2.2, 14.1)	
Week 48 Change from Baseline			
N	277	144	
Mean (SD)	-2.07 (1.828)	-2.07 (2.036)	
Median	-2.10	-1.90	
(Min, Max)	(-8.4, 4.6)	(-7.8, 6.7)	
95% CI	(5.16, 5.50)	(5.22, 5.69)	(-0.42, 0.17)
LS Mean (SE)	5.33 (0.09)	5.46 (0.12)	-0.12 (0.15)
p-value			0.4086
Week 52			
N	277	144	
Mean (SD)	5.32 (1.437)	5.36 (1.572)	
Median	5.20	5.10	

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Control in Safety Assessment Period (N=146)	Treatment Differences[1]
(Min, Max)	(1.1, 10.7)	(2.6, 14.1)	
Week 52 Change from Baseline			
N	277	144	
Mean (SD)	-2.06 (1.834)	-2.19 (2.220)	
Median	-2.20	-2.10	
(Min, Max)	(-7.1, 3.7)	(-9.8, 6.7)	
95% CI	(5.16, 5.51)	(5.10, 5.58)	(-0.30, 0.29)
LS Mean (SE)	5.33 (0.09)	5.34 (0.12)	-0.01 (0.15)
p-value			0.9696

Note: [1]. The LS Mean treatment difference and p-value for the change in Ferritin is created via an ANCOVA model with treatment as the fixed effect and Day-0 baseline as the covariate. Between-treatment differences are calculated as the LS Mean (KRX-0502) – LS Mean (control).

Only subjects with both a baseline and post baseline observations for the parameter of interest were included.

Summary of Mean Serum Phosphorus Values and Change from Week-52-baseline by Treatment and Visit during the Efficacy Assessment Period (ANCOVA Method), Full Analysis Population – shown in Table 14:

Table 14:

Statistics	KRX-0502 in Efficacy Assessment Period (N=92)	Placebo in Efficacy Assessment Period (N=91)	Treatment Differences[1]
Week 52 Baseline			
N	85	82	
Mean (SD)	5.16 (1.259)	5.25 (1.475)	
Median	5.10	5.30	
(Min, Max)	(2.2, 8.7)	(1.1, 8.8)	
Week 53			
N	76	79	
Mean (SD)	4.90 (1.152)	6.66 (1.611)	
Median	4.95	6.50	
(Min, Max)	(2.0, 7.7)	(2.4, 10.6)	
Week 53 Change from Baseline			
N	76	79	
Mean (SD)	-0.31 (1.432)	1.39 (1.626)	
Median	-0.30	1.30	
(Min, Max)	(-4.6, 2.9)	(-2.1, 5.5)	
95% CI	(4.62, 5.21)	(6.36, 6.94)	(-2.15, -1.32)
LS Mean (SE)	4.92 (0.15)	6.65 (0.15)	-1.73 (0.21)
p-value			<0.0001
Week 54			
N	84	81	
Mean (SD)	4.78 (1.309)	6.91 (1.724)	
Median	4.70	6.80	
(Min, Max)	(2.1, 8.9)	(3.4, 10.6)	
Week 54 Change from Baseline			
N	84	81	
Mean (SD)	-0.36 (1.404)	1.65 (1.847)	
Median	-0.40	1.60	
(Min, Max)	(-3.9, 3.8)	(-2.3, 6.5)	
95% CI	(4.50, 5.11)	(6.57, 7.20)	(-2.52, -1.64)
LS Mean (SE)	4.80 (0.16)	6.88 (0.16)	-2.08 (0.22)
p-value			<0.0001
Week 55			
N	85	82	

Statistics	KRX-0502 in Efficacy Assessment Period (N=92)	Placebo in Efficacy Assessment Period (N=91)	Treatment Differences[1]
Mean (SD)	4.75 (1.237)	6.96 (1.808)	
Median	4.60	7.00	
(Min, Max)	(2.8, 9.5)	(2.7, 10.6)	
Week 55 Change from Baseline			
N	85	82	
Mean (SD)	-0.41 (1.444)	1.71 (1.967)	
Median	-0.50	1.85	
(Min, Max)	(-3.2, 4.6)	(-2.6, 6.5)	
95% CI	(4.45, 5.08)	(6.62, 7.26)	(-2.63, -1.73)
LS Mean (SE)	4.76 (0.16)	6.94 (0.16)	-2.18 (0.23)
p-value			<0.0001
Week 56			
N	85	82	
Mean (SD)	4.92 (1.323)	7.24 (1.812)	
Median	4.60	7.25	
(Min, Max)	(2.3, 9.5)	(3.0, 10.6)	
Week 56 Change from Baseline			
N	85	82	
Mean (SD)	-0.23 (1.484)	1.99 (1.979)	
Median	-0.50	2.20	
(Min, Max)	(-2.9, 4.6)	(-2.7, 6.5)	
95% CI	(4.62, 5.26)	(6.89, 7.55)	(-2.74, -1.82)
LS Mean (SE)	4.94 (0.16)	7.22 (0.17)	-2.28 (0.23)
p-value			<0.0001

Note: [1]. The LS Mean treatment difference and p-value for the change in Serum Phosphorus is created via an ANCOVA model with treatment as the fixed effect and Week-52 baseline as the covariate. Between-treatment differences are calculated as the LS Mean (KRX-0502) - LS Mean (Placebo). Only subjects with both a baseline and post baseline observations for the parameter of interest were included.

Summary of Mean Ferritin at Weeks 12, 24, 36, 48, and 52 and Change from Study-baseline by Treatment (ANCOVA Method), Full Analysis Population – shown in Table 15:

Table 15:

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Control in Safety Assessment Period (N=146)	Treatment Differences[1]
Day 0 Baseline			
N	249	134	
Mean (SD)	595.00 (293.896)	615.76 (307.842)	
Median	587.00	574.00	
(Min, Max)	(22.0, 1612.0)	(11.0, 1548.0)	
Week 12			
N	243	134	
Mean (SD)	751.19 (379.766)	656.68 (321.518)	
Median	718.00	646.50	
(Min, Max)	(25.0, 2691.0)	(13.0, 1664.0)	
Week 12 Change from Baseline			
N	243	134	
Mean (SD)	158.88 (283.314)	40.92 (273.201)	
Median	123.00	26.50	
(Min, Max)	(-882.0, 1660.0)	(-794.0, 920.0)	
95% CI	(723.34, 792.15)	(598.46, 691.14)	(55.22, 170.68)
LS Mean (SE)	757.75 (17.50)	644.80 (23.57)	112.95 (29.36)
p-value			0.0001
Week 24			
N	247	134	

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Control in Safety Assessment Period (N=146)	Treatment Differences[1]
Mean (SD)	846.90 (414.672)	658.44 (301.698)	
Median	830.00	675.00	
(Min, Max)	(91.0, 2413.0)	(11.0, 1525.0)	
Week 24 Change from Baseline			
N	247	134	
Mean (SD)	252.49 (326.299)	42.68 (291.868)	
Median	220.00	35.50	
(Min, Max)	(-628.0, 1594.0)	(-997.0, 757.0)	
95% CI	(814.24, 890.79)	(596.11, 700.06)	(139.87, 269.00)
LS Mean (SE)	852.52 (19.47)	648.08 (26.43)	204.43 (32.84)
p-value			<0.0001
Week 36			
N	247	134	
Mean (SD)	863.18 (444.094)	635.96 (326.652)	
Median	818.00	612.00	
(Min, Max)	(51.0, 3181.0)	(13.0, 2080.0)	
Week 36 Change from Baseline			
N	247	134	
Mean (SD)	268.77 (391.292)	20.20 (328.820)	
Median	223.00	11.00	
(Min, Max)	(-754.0, 2193.0)	(-958.0, 1589.0)	
95% CI	(823.50, 912.72)	(566.30, 687.45)	(165.99, 316.49)
LS Mean (SE)	868.11 (22.69)	626.87 (30.81)	241.24 (38.27)
p-value			<0.0001
Week 48			
N	247	134	
Mean (SD)	882.10 (461.772)	626.63 (353.836)	
Median	850.00	597.00	
(Min, Max)	(44.0, 3188.0)	(84.0, 1784.0)	
Week 48 Change from Baseline			
N	247	134	
Mean (SD)	287.69 (395.752)	10.87 (352.066)	
Median	233.00	13.50	
(Min, Max)	(-667.0, 2032.0)	(-1184.0, 1409.0)	
95% CI	(840.95, 933.86)	(553.76, 679.93)	(192.20, 348.93)
LS Mean (SE)	887.41 (23.63)	616.85 (32.08)	270.56 (39.85)
p-value			<0.0001
Week 52			
N	249	134	
Mean (SD)	897.12 (485.296)	625.30 (359.018)	
Median	858.00	576.00	
(Min, Max)	(44.0, 3144.0)	(33.0, 1789.0)	
Week 52 Change from Baseline			
N	249	134	
Mean (SD)	302.11 (435.183)	9.54 (360.411)	
Median	224.00	21.50	
(Min, Max)	(-785.0, 2032.0)	(-1165.0, 1409.0)	
95% CI	(852.25, 951.66)	(548.54, 684.08)	(201.58, 369.71)
LS Mean (SE)	901.95 (25.28)	616.31 (34.47)	285.65 (42.76)
p-value			<0.0001

Note: [1]. The LS Mean treatment difference and p-value for the change in Ferritin is created via an ANCOVA model with treatment as the fixed effect and Day-0 baseline as the covariate. Between-treatment differences are calculated as the LS Mean (KRX-0502) – LS Mean (control).

Only subjects with both a baseline and post baseline observations for the parameter of interest were included.

Summary of Mean TSAT at Weeks 12, 24, 36, 48, and 52 and Change from Study-baseline by Treatment (ANCOVA Method), Full Analysis Population – shown in Table 16:

Table 16:

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Control in Safety Assessment Period (N=146)	Treatment Differences[1]
Day 0 Baseline			
N	244	131	
Mean (SD)	31.0 (10.99)	31.0 (11.75)	
Median	29.5	29.0	
(Min, Max)	(10, 83)	(10, 73)	
Week 12			
N	238	131	
Mean (SD)	40.2 (16.00)	31.4 (12.13)	
Median	37.0	29.0	
(Min, Max)	(12, 85)	(10, 79)	
Week 12 Change from Baseline			
N	238	131	
Mean (SD)	9.2 (17.95)	0.5 (15.91)	
Median	7.0	1.0	
(Min, Max)	(-61, 62)	(-54, 51)	
95% CI	(38.31, 42.03)	(28.92, 33.94)	(5.61, 11.87)
LS Mean (SE)	40.17 (0.95)	31.43 (1.28)	8.74 (1.59)
p-value			<0.0001
Week 24			
N	242	131	
Mean (SD)	39.9 (15.52)	31.6 (11.96)	
Median	38.0	29.0	
(Min, Max)	(13, 92)	(11, 79)	
Week 24 Change from Baseline			
N	242	131	
Mean (SD)	8.9 (17.49)	0.6 (15.40)	
Median	7.0	0.0	
(Min, Max)	(-43, 63)	(-52, 49)	
95% CI	(38.11, 41.70)	(29.18, 34.06)	(5.25, 11.31)
LS Mean (SE)	39.90 (0.91)	31.62 (1.24)	8.28 (1.54)
p-value			<0.0001
Week 36			
N	242	131	
Mean (SD)	39.8 (15.66)	30.4 (10.88)	
Median	37.0	28.0	
(Min, Max)	(14, 86)	(13, 67)	
Week 36 Change from Baseline			
N	242	131	
Mean (SD)	8.8 (17.47)	-0.6 (14.99)	
Median	7.0	-1.0	
(Min, Max)	(-57, 63)	(-45, 49)	
95% CI	(38.03, 41.57)	(27.95, 32.76)	(6.45, 12.43)
LS Mean (SE)	39.80 (0.90)	30.36 (1.22)	9.44 (1.52)
p-value			<0.0001
Week 48			
N	242	131	
Mean (SD)	40.6 (16.94)	29.4 (10.71)	
Median	38.0	28.0	
(Min, Max)	(13, 86)	(10, 74)	
Week 48 Change from Baseline			
N	242	131	
Mean (SD)	9.6 (19.25)	-1.5 (14.48)	
Median	7.0	-2.0	
(Min, Max)	(-45, 67)	(-48, 42)	
95% CI	(38.71, 42.49)	(26.85, 32.00)	(7.98, 14.37)
LS Mean (SE)	40.60 (0.96)	29.43 (1.31)	11.17 (1.62)
p-value			<0.0001
Week 52			
N	244	131	
Mean (SD)	39.4 (16.81)	29.7 (11.49)	
Median	35.0	28.0	

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Control in Safety Assessment Period (N=146)	Treatment Differences[1]
(Min, Max)	(7, 88)	(10, 72)	
Week 52 Change from Baseline			
N	244	131	
Mean (SD)	8.3 (17.97)	-1.3 (14.94)	
Median	6.0	0.0	
(Min, Max)	(-60, 62)	(-53, 43)	
95% CI	(37.48, 41.23)	(27.14, 32.25)	(6.49, 12.83)
LS Mean (SE)	39.35 (0.95)	29.69 (1.30)	9.66 (1.61)
p-value			<0.0001

Note: [1]. The LS Mean treatment difference and p-value for the change in Ferritin is created via an ANCOVA model with treatment as the fixed effect and Day-0 baseline as the covariate. Between-treatment differences are calculated as the LS Mean (KRX-0502) – LS Mean (control).

Only subjects with both a baseline and post baseline observations for the parameter of interest were included.

Summary of Mean Hemoglobin at Weeks 12, 24, 36, 48, and 52 and Change from Study-baseline by Treatment (ANCOVA method), Full Analysis Population – shown in Table 17:

Table 17:

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Control in Safety Assessment Period (N=146)	Treatment Differences[1]
Day 0 Baseline			
N	244	130	
Mean (SD)	11.61 (1.213)	11.72 (1.265)	
Median	11.45	11.70	
(Min, Max)	(8.7, 15.8)	(8.7, 15.7)	
Week 12			
N	231	128	
Mean (SD)	11.82 (1.375)	11.55 (1.268)	
Median	11.70	11.60	
(Min, Max)	(7.5, 17.4)	(6.7, 14.5)	
Week 12 Change from Baseline			
N	231	128	
Mean (SD)	0.19 (1.397)	-0.16 (1.522)	
Median	0.10	-0.05	
(Min, Max)	(-4.6, 4.0)	(-4.3, 3.5)	
95% CI	(11.67, 11.99)	(11.31, 11.75)	(0.03, 0.57)
LS Mean (SE)	11.83 (0.08)	11.53 (0.11)	0.30 (0.14)
p-value			0.0291
Week 24			
N	241	130	
Mean (SD)	11.55 (1.401)	11.47 (1.165)	
Median	11.30	11.40	
(Min, Max)	(6.6, 17.3)	(9.2, 15.4)	
Week 24 Change from Baseline			
N	241	130	
Mean (SD)	-0.08 (1.405)	-0.25 (1.394)	
Median	-0.10	-0.30	
(Min, Max)	(-6.3, 3.8)	(-2.9, 3.5)	
95% CI	(11.41, 11.72)	(11.23, 11.65)	(-0.14, 0.38)
LS Mean (SE)	11.56 (0.08)	11.44 (0.11)	0.12 (0.13)
p-value			0.3756
Week 36			
N	241	130	
Mean (SD)	11.54 (1.432)	11.31 (1.205)	
Median	11.20	11.20	

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Control in Safety Assessment Period (N=146)	Treatment Differences[1]
(Min, Max)	(8.6, 17.4)	(8.9, 14.9)	
Week 36 Change from Baseline			
N	241	130	
Mean (SD)	-0.08 (1.359)	-0.41 (1.577)	
Median	-0.10	-0.50	
(Min, Max)	(-5.1, 3.9)	(-3.8, 4.6)	
95% CI	(11.39, 11.71)	(11.06, 11.50)	(0.00, 0.54)
LS Mean (SE)	11.55 (0.08)	11.28 (0.11)	0.27 (0.14)
p-value			0.0482
Week 48			
N	241	130	
Mean (SD)	11.50 (1.502)	11.25 (1.296)	
Median	11.20	11.10	
(Min, Max)	(6.7, 18.2)	(7.9, 16.1)	
Week 48 Change from Baseline			
N	241	130	
Mean (SD)	-0.12 (1.395)	-0.47 (1.498)	
Median	-0.20	-0.30	
(Min, Max)	(-4.8, 4.9)	(-4.2, 3.5)	
95% CI	(11.35, 11.68)	(10.99, 11.44)	(0.03, 0.58)
LS Mean (SE)	11.52 (0.08)	11.21 (0.11)	0.30 (0.14)
p-value			0.0322
Week 52			
N	244	130	
Mean (SD)	11.42 (1.474)	11.11 (1.403)	
Median	11.20	11.00	
(Min, Max)	(8.3, 16.6)	(7.1, 15.3)	
Week 52 Change from Baseline			
N	244	130	
Mean (SD)	-0.20 (1.326)	-0.61 (1.581)	
Median	-0.20	-0.60	
(Min, Max)	(-3.9, 3.7)	(-4.9, 4.6)	
95% CI	(11.27, 11.60)	(10.85, 11.30)	(0.09, 0.64)
LS Mean (SE)	11.44 (0.08)	11.07 (0.11)	0.36 (0.14)
p-value			0.0105

Note: [1]. The LS Mean treatment difference and p-value for the change in Ferritin is created via an ANCOVA model with treatment as the fixed effect and Day-0 baseline as the covariate. Between-treatment differences are calculated as the LS Mean (KRX-0502) – LS Mean (control).

Only subjects with both a baseline and post baseline observations for the parameter of interest were included.

Summary of Mean Serum Bicarbonate Concentration at Weeks 12, 24, 36, 48 and 52 and Change from Study-baseline by Treatment (ANCOVA Method), Full Analysis Population – shown in Table 18:

Table 18:

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Control in Safety Assessment Period (N=146)	Treatment Differences[1]
Day 0 Baseline			
N	214	117	
Mean (SD)	23.92 (3.408)	23.65 (3.393)	
Median	24.00	23.00	
(Min, Max)	(13.0, 34.0)	(11.0, 32.0)	
Week 12			
N	190	101	
Mean (SD)	25.63 (3.358)	26.25 (3.481)	

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Control in Safety Assessment Period (N=146)	Treatment Differences[1]
Median	25.00	26.00	
(Min, Max)	(15.0, 36.0)	(16.0, 34.0)	
Week 12 Change from Baseline			
N	190	101	
Mean (SD)	1.57 (3.364)	2.41 (3.813)	
Median	1.05	2.00	
(Min, Max)	(-7.0, 13.0)	(-10.0, 14.0)	
95% CI	(25.17, 26.03)	(25.73, 26.91)	(-1.45, 0.01)
LS Mean (SE)	25.60 (0.22)	26.32 (0.30)	-0.72 (0.37)
p-value			0.0522
Week 24			
N	200	113	
Mean (SD)	25.39 (3.424)	25.66 (3.953)	
Median	25.45	26.00	
(Min, Max)	(16.0, 36.0)	(16.0, 34.0)	
Week 24 Change from Baseline			
N	200	113	
Mean (SD)	1.48 (3.499)	1.99 (3.854)	
Median	1.00	2.00	
(Min, Max)	(-13.0, 13.0)	(-6.0, 14.0)	
95% CI	(24.90, 25.79)	(25.15, 26.33)	(-1.13, 0.35)
LS Mean (SE)	25.35 (0.23)	25.74 (0.30)	-0.39 (0.38)
p-value			0.2974
Week 36			
N	212	117	
Mean (SD)	25.27 (3.152)	25.29 (3.700)	
Median	25.00	25.00	
(Min, Max)	(17.0, 33.0)	(17.0, 36.0)	
Week 36 Change from Baseline			
N	212	117	
Mean (SD)	1.36 (3.441)	1.64 (3.555)	
Median	1.00	1.00	
(Min, Max)	(-10.0, 16.0)	(-7.0, 14.0)	
95% CI	(24.82, 25.62)	(24.83, 25.91)	(-0.82, 0.53)
LS Mean (SE)	25.22 (0.20)	25.37 (0.27)	-0.15 (0.34)
p-value			0.6706
Week 48			
N	212	117	
Mean (SD)	24.81 (3.177)	25.24 (3.634)	
Median	25.00	25.20	
(Min, Max)	(15.0, 33.0)	(15.0, 34.0)	
Week 48 Change from Baseline			
N	212	117	
Mean (SD)	0.91 (3.614)	1.59 (4.081)	
Median	1.00	1.00	
(Min, Max)	(-12.0, 14.0)	(-9.0, 14.0)	
95% CI	(24.36, 25.20)	(24.74, 25.87)	(-1.23, 0.18)
LS Mean (SE)	24.78 (0.21)	25.30 (0.29)	-0.52 (0.36)
p-value			0.1458
Week 52			
N	214	117	
Mean (SD)	24.63 (4.049)	25.25 (3.871)	
Median	25.00	25.00	
(Min, Max)	(-9.0, 33.0)	(15.0, 35.0)	
Week 52 Change from Baseline			
N	214	117	
Mean (SD)	0.71 (4.369)	1.59 (4.668)	
Median	1.00	1.00	
(Min, Max)	(-37.0, 15.0)	(-9.0, 14.0)	
95% CI	(24.08, 25.11)	(24.60, 26.00)	(-1.57, 0.16)
LS Mean (SE)	24.60 (0.26)	25.30 (0.36)	-0.70 (0.44)
p-value			0.1117

Note: [1]. The LS Mean treatment difference and p-value for the change in Ferritin is created via an ANCOVA model with treatment as the fixed effect and Day-0 baseline as the covariate. Between-treatment differences are calculated as the LS Mean (KRX-0502) – LS Mean (control).

Only subjects with both a baseline and post baseline observations for the parameter of interest were included.

Summary of Cumulative IV iron intake to Week 52 by Treatment, Full Analysis Population, Method 1 to Handle Overlapping Doses – shown in Table 19:

Table 19:

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Control in Safety Assessment Period (N=146)	Treatment Differences[1]
Average Daily IV iron intake based on the Cumulative IV iron intake to week 52 (Visit 4 – 21)[2,3]			
N	278	138	
Mean (SD)	2.96 (4.260)	4.86 (4.374)	
Median	1.86	3.84	
(Min, Max)	(0.0, 44.3)	(0.0, 24.2)	
p-value[4]			<0.0001

Note: [1]. The LS Mean treatment difference and p-value for cumulative IV iron intake is created via an ANCOVA model with treatment as the fixed effect. Between-treatment differences are calculated as the LS Mean (KRX-0502) – LS Mean (control).

Note: [2]. Average Daily IV iron intake based on the Cumulative IV iron intake to week 52 is calculated as the total Cumulative IV iron intake divided be the total number of days on study drug.

Note: [3]. The Method 1 to Handle Overlapping Doses is the following: For the overlapping doses will be pro-rated based on days to only include a dose for the period of time on study drug during the Safety Assessment Period.

Note: [4]. In the case where basic assumptions are not met for ANCOVA, the Wilcoxon Rank Sum Test is used to calculate the p-value, and the CI and LS Mean removed.

Summary of Cumulative EPO (ESA) Administered to Week 52 by Treatment, Full Analysis Population, Method 1 to Handle Overlapping Doses – shown in Table 20:

Table 20:

Statistics	KRX-0502 in Safety Assessment Period (N=288)	Control in Safety Assessment Period (N=146)	Treatment Differences[1]
Average Daily EPO (ESA) intake based on the Cumulative EPO (ESA) intake to week 52 (Visit 4 – 21)[2,3]			
n	280	141	
Mean (SD)	1077.67 (1291.384)	1309.85 (1342.258)	
Median	724.24	993.46	
(Min, Max)	(0.0, 11015.0)	(0.0, 8171.9)	
p-value[4]			0.0322

Note: [1]. The LS Mean treatment difference and p-value for cumulative EPO (ESA) intake is created via an ANCOVA model with treatment as the fixed effect. Between-treatment differences are calculated as the LS Mean (KRX-0502) – LS Mean (control).

Note: [2]. Average Daily IV iron intake based on the Cumulative EPO (ESA) intake to week 52 is calculated as the total Cumulative EPO (ESA) intake divided be the total number of days on study drug.

Note: [3]. The Method 1 to Handle Overlapping Doses is the following: For the overlapping doses will be pro-rated based on days to only include a dose for the period of time on study drug during the Safety Assessment Period.

Note: [4]. In the case where basic assumptions are not met for ANCOVA, the Wilcoxon Rank Sum Test is used to calculate the p-value, and the CI and LS Mean removed.

Example 2

A Study of KRX-0502 (Ferric Citrate) in Managing Serum Phosphorus and Iron Deficiency in Anemic Subjects with Stage III to V Chronic Kidney Disease Not on Dialysis

A phase 2, proof of concept, multicenter, randomized, placebo-controlled, open-label clinical trial is performed.

The study lasts approximately five to seven months, with approximately eight to 12 weeks being allocated for subject screening, two weeks for washing subjects out of their current phosphate binders (if taking them), and 12 weeks allocated for treatment with study drug, which is either the ferric citrate disclosed herein, or placebo. For purposes of this Example, the ferric citrate disclosed herein is referred to as KRX-0502 (ferric citrate).

The objectives of the study are to determine the efficacy and safety of KRX-0502 (ferric citrate) in managing serum phosphorus and iron deficiency in anemic subjects with non-dialysis dependent Stage III to V chronic kidney disease (CKD).

Up to approximately 200 subjects are screened to randomize approximately 140 subjects. Eligible subjects are randomized in a 1:1 ratio to either KRX-0502 (ferric citrate) or placebo. There are approximately 70 subjects randomized per treatment arm. The dropout rate during the two-week washout and 12-week treatment periods is approximately 20% and therefore approximately 110 subjects complete 12 weeks of treatment with study drug (KRX-0502 (ferric citrate) or placebo). There are approximately 55 subjects completing 12 weeks of treatment with study drug (KRX-0502 (ferric citrate) or placebo).

The trial consists of three periods: screening, two-week washout, and 12-week treatment periods. It takes approximately eight to 12 weeks to screen approximately 200

subjects at approximately 10 to 15 sites. The two-week washout period is only for subjects currently taking a phosphate binder.

The trial enrolls two different types of anemic Stage III to V CKD subjects. They are as follows: 1) Subjects with a serum phosphorus ≥ 4.5 mg/dL and < 6.0 mg/dL who have failed a low phosphate diet and have not been initiated on any phosphate binder (de novo subjects) and have a documented history of anemia; or 2) Subjects who are currently taking phosphate binders to manage their serum phosphorus and have a documented history of anemia. De novo subjects do not enter a washout period and subjects currently taking phosphate binders enter a two-week washout period. Following two weeks of washout, these subjects have a serum phosphorus ≥ 4.5 mg/dL and < 6.0 mg/dL in order to enter the 12-week treatment period.

Enrollment is not stratified for de novo subjects vs. subjects currently taking phosphate binders.

Study Design/Methodology

This trial is a three-period clinical trial consisting of a screening period, a two-week washout period, and a 12-week treatment period. After a subject is determined to be eligible for enrollment, the subject is randomized to either KRX-0502 (ferric citrate) or placebo. Subjects are randomized in a 1:1 ratio to either KRX-0502 (ferric citrate) or placebo.

Subjects currently taking a phosphate binder are entered into a two-week washout period and, following the completion of the two-week washout period, are randomized to either KRX-0502 (ferric citrate) or placebo. Eligible subjects not taking a phosphate binder immediately start on study drug (KRX-0502 (ferric citrate) or placebo). There is no washout period in this subject population. All subjects have a serum phosphorus ≥ 4.5 mg/dL in order to enter the 12-week treatment period.

After starting treatment with study drug (KRX-0502 (ferric citrate) or placebo), subjects are titrated to therapeutic goal (serum phosphorus between 3.0 to 4.0 mg/dL). If a subject has a serum phosphorus ≥ 6.0 mg/dL for at least two visits in a row during the 12-week treatment period, the subject is considered a treatment failure, stops study drug and exits the study.

The use of IV iron and erythropoietin stimulating agents (ESAs) is not permitted during the two-week washout and 12-week treatment periods. If a subject's hemoglobin level (Hgb) is < 9.0 g/dL during the two-week washout, the subject is a screen failure. If a subject's Hgb is < 9.0 g/dL for at least two visits in a row during the 12-week treatment period, the subject is considered a treatment failure, stops study drug and exits the study.

Serum phosphorus, serum calcium, serum creatinine (used to estimate glomerular filtration rate), intact fibroblast growth factor 23 (FGF23), intact parathyroid hormone (iPTH) and several hematological parameters (ferritin, TSAT, unsaturated iron binding capacity (UIBC), TIBC, serum iron, hematocrit (HCT) and Hgb) are determined at screening, during the washout period, prior to the administration of study drug (KRX-0502 (ferric citrate) or placebo) at Visit 4 (Week 0), and weekly during the 12-week treatment period.

Urinary phosphorus is determined prior to the administration of study drug (KRX-0502 (ferric citrate) or placebo) at Visit 4 (Week 0), at Visit 7 (Week 4) and Visit 9 (Week 8) during the 12-week treatment period and at the end of the 12-week treatment period (Visit 11, Week 12).

The inclusion criteria for this trial are as follows:

1. Males and non-pregnant, non-lactating females;

2. Age > 18 years;

3. Stage III to V CKD subjects not on dialysis who have failed a low phosphate diet to control serum phosphorus and: (i) are currently taking a phosphate binder to manage their serum phosphorus and have a serum phosphorus at screening > 2.5 mg/dL and < 6.0 mg/dL, or (ii) are not taking a phosphate binder and have a serum phosphorus level at screening ≥ 4.5 mg/dL and < 6.0 mg/dL;

4. Documented history of anemia;

5. Serum ferritin < 200 ng/mL and TSAT 20%;

6. Hemoglobin > 9.5 g/dL and < 11.5 g/dL;

7. Glomerular filtration rate (GFR) < 60 mL/min;

8. If currently on a phosphate binder, willing to be discontinued from current phosphate binder(s), enter a washout period and be randomized to either KRX-0502 (ferric citrate) or placebo; and

9. Willing and able to give informed consent.

The exclusion criteria for this trial are as follows:

1. Parathyroidectomy within six months prior to Screening Visit (Visit 0);

2. Symptomatic gastrointestinal bleeding within three months prior to Screening Visit (Visit 0) and inflammatory bowel disease;

3. On dialysis;

4. IV iron administered within 60 days prior to randomization (Visit 4, Week 0);

5. Blood transfusion within 60 days prior to randomization (Visit 4, Week 0);

6. Kidney transplant or start of dialysis expected within three (3) months of randomization (Visit 4, Week 0);

7. Causes of anemia other than iron deficiency;

8. Serum parathyroid hormone >1000 pg/ml;

9. History of multiple drug allergies;

10. History of malignancy in the last five years (treated cervical or skin cancer may be permitted, upon approval);

11. Previous intolerance to oral ferric citrate;

12. Absolute requirement for oral iron therapy;

13. Absolute requirement for Vitamin C; however, multivitamins (i.e., Centrum, Nephrocaps, Renaphro, etc.) are allowed;

14. Absolute requirement for calcium-, magnesium-, or aluminum-containing drugs with meals;

15. Psychiatric disorder that interferes with the subject's ability to comply with the study protocol;

16. Planned surgery or hospitalization during the study (scheduled outpatient access surgery allowed);

17. Any other medical condition that renders the subject unable to or unlikely to complete the study or that would interfere with optimal participation in the study or produce significant risk to the subject;

18. Receipt of any investigational drug within 30 days of randomization (Visit 4, Week 0); and

19. Inability to cooperate with study personnel or history of noncompliance.

Study Drug Administration

KRX-0502 (ferric citrate) is supplied as 1-gram caplets of ferric citrate containing approximately 210 mg of ferric iron to those subjects randomized to ferric citrate.

Matching placebo is supplied to those subjects randomized to placebo.

All subjects are initiated on study drug with a fixed dose of KRX-0502 (ferric citrate) of 3 caplets per day (approximately 3 grams of ferric citrate as approximately 630 mg of ferric iron) or placebo (approximately 3 matching caplets per day). The target level for serum phosphorus is 3.0 to 4.0 mg/dL. Subjects are titrated as follows:

1. If serum phosphorus is at target (3.0 to 4.0 mg/dL), no adjustment in dose is required.

2. If serum phosphorus is < 3.0 mg/dL, the dose of KRX-0502 (ferric citrate) or placebo is decreased by 1 caplet per day and the subject's serum phosphorus is re-checked within seven days.

3. If the serum phosphorus is > 4.0 mg/dL, the dose of KRX-0502 (ferric citrate) or placebo is increased by 1 caplet per day and the subject's serum phosphorus is re-checked within seven days.

The maximum number of KRX-0502 (ferric citrate) or placebo caplets per day is 12, or 12 g/day of ferric citrate. If a subject has a serum phosphorus ≥ 6.0 mg/dL for at least two visits in a row during the 12-week treatment period, the subject is considered a treatment failure, stops study drug and exits the study.

If a subject's Hgb is < 9.0 g/dL during the two-week washout, the subject is a screen failure. If a subject's Hgb is < 9.0 g/dL for at least two visits in a row during the 12-week treatment period, the subject is considered a treatment failure, stops study drug and exits the study.

Subjects take KRX-0502 (ferric citrate) or placebo orally with meals or snacks or within one hour after their meals or snacks. Subjects are instructed not to take KRX-0502 (ferric citrate) or placebo if greater than one hour has passed since the ingestion of their meals or snacks.

Statistical Considerations: Efficacy

Change in serum phosphorus, ferritin and TSAT levels from baseline to end of treatment after 12 weeks are the primary endpoints.

This study demonstrates that KRX-0502 (ferric citrate) is statistically superior to placebo in managing serum phosphorus and iron deficiency in anemic Stage III to V CKD subjects, not on dialysis, requiring phosphate binders from baseline (Visit 4, Week 0) to endpoint (Visit 11, Week 12).

Change in calcium x phosphorus product, serum calcium, estimated glomerular filtration rate (eGFR), urinary phosphorus, bicarbonate levels, serum iron, UIBC, TIBC, iPTH, and intact fibroblast growth factor 23 (FGF23) from baseline (Visit 4, Week 0) to the end of treatment (Visit 11, Week 12) are also assessed as secondary endpoints.

Statistical Considerations: Sample Size

Up to approximately 200 subjects are screened to randomize approximately 140 subjects. Eligible subjects are randomized in a 1:1 ratio to either KRX-0502 (ferric citrate) or placebo. There are approximately 70 subjects randomized per treatment arm. The dropout rate during the two-week washout and 12-week treatment periods is approximately 20% and

therefore approximately 110 subjects complete 12 weeks of treatment with study drug (KRX-0502 (ferric citrate) or placebo). There are approximately 55 subjects completing 12 weeks of treatment with study drug (KRX-0502 (ferric citrate) or placebo).

The ending serum phosphorus at Visit 11 (Week 12) is approximately 4.3 mg/dL in the KRX-0502 (ferric citrate) group and 4.6 mg/dL in the placebo-treated group. The common standard deviation is approximately 0.5 mg/dL. Based on these parameters, the trial has at least 80% power to detect a difference between the two groups (alpha = 0.05, two sided).

The ending ferritin level at Visit 11 (Week 12) is approximately 300 ng/mL in the KRX-0502 (ferric citrate) group and 150 ng/mL in the placebo-treated group. The common standard deviation is approximately 75 ng/mL. Based on these parameters, the trial has at least 80% power to detect a difference between the two groups (alpha = 0.05, two sided).

The ending TSAT level at Visit 11 (Week 12) is approximately 25% in the KRX-0502 (ferric citrate) group and 17% in the placebo-treated group. The common standard deviation is approximately 5%. Based on these parameters, the trial has at least 80% power to detect a difference between the two groups (alpha = 0.05, two sided).

Finally, it should be noted that there are alternative ways of implementing the embodiments disclosed herein. Accordingly, the present embodiments are to be considered as illustrative and not restrictive. Furthermore, the claims are not to be limited to the details given herein, and are entitled their full scope and equivalents thereof.

CLAIMS

1. Ferric citrate for use in a method of reducing serum phosphorus by oral administration to a chronic kidney disease (CKD) patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides a mean reduction in serum phosphorus in said CKD patient of 2.00 – 2.50 mg/dl.

2. The method of claim 1, wherein the ferric citrate provides:

a mean reduction in serum phosphorus in said CKD patient selected from 1.90, 1.91, 1.92, 1.93, 1.94, 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09 and 2.10 mg/dl when administered for a period of 12 weeks; or

a mean reduction in serum phosphorus in said CKD patient selected from 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24 and 2.25 mg/dl when administered for a period of 24 weeks; or

a mean reduction in serum phosphorus in said CKD patient selected from 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19 and 2.20 mg/dl when administered for a period of 36 weeks;

a mean reduction in serum phosphorus in said CKD patient selected from 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 2.11, 2.12, 2.13, 2.14 and 2.15 mg/dl when administered for a period of 48 weeks; or

a mean reduction in serum phosphorus in said CKD patient selected from 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24, 2.25, 2.26, 2.27, 2.28, 2.29 and 2.30 mg/dl when administered for a period of 52 weeks.

3. Ferric Citrate for use in a method of increasing serum bicarbonate by oral administration to a chronic kidney disease (CKD) patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides an increase in serum bicarbonate in said CKD patient of 0.1 – 1.0 mEq/L.

4. The ferric citrate of claim 3, wherein the ferric citrate provides a mean increase in serum bicarbonate concentration in said CKD patient selected 0.70, 0.71, 0.72, 0.73, 0.74, 0.75, 0.76, 0.77, 0.78, 0.79 and 0.80 mEq/L when administered for a period of at least 52 weeks.

5. Ferric citrate for use in a method of increasing iron absorption by oral administration to a chronic kidney disease (CKD) patient in an amount ranging from 1 g to 18 g, wherein the ferric citrate provides for an increase in iron absorption in said CKD patient.

6. Ferric citrate for use in a method of maintaining iron stores by oral administration to a chronic kidney disease (CKD) patient in an amount ranging from 1 g to 18 g, wherein the ferric citrate provides for maintenance of iron stores in said CKD patient.

7. Ferric citrate for use in a method of improving at least one iron storage parameter by oral administration to chronic kidney disease (CKD) patient in an amount ranging from 1 g to 18 g, wherein the ferric citrate provides for an improvement in at least one iron storage parameter in said CKD patient.

8. The ferric citrate of claim 7, wherein the at least one iron storage parameter is selected from hematocrit, hemoglobin concentration, total iron-binding capacity, transferrin saturation, serum iron levels, liver iron levels, spleen iron levels, serum ferritin levels and combinations thereof.

9. The ferric citrate of claim 7 or 8, wherein the at least one iron storage parameter is hematocrit and wherein improving comprises increasing the hematocrit of said CKD patient.

10. The ferric citrate of claim 7 or 8, wherein the at least one iron storage parameter is hemoglobin concentration and wherein improving comprises increasing the hemoglobin concentration in said CKD patient.

11. The ferric citrate of claim 10, wherein the ferric citrate is administered at a dose of ferric iron ranging from 210 mg – 2,520 mg, and wherein the ferric citrate provides a mean increase in hemoglobin concentration in said CKD patient of 0.3 – 0.6 g/dl.

12. The ferric citrate of claim 7 or 8, wherein the at least one iron storage parameter is total iron-binding capacity and wherein improving comprises decreasing the total iron-binding capacity in said CKD patient.

13. The ferric citrate of claim 7 or 8, wherein the at least one iron storage parameter is transferrin saturation (TSAT) and wherein improving comprises increasing the transferrin saturation in said CKD patient.

14. The ferric citrate of claim 13, wherein the ferric citrate is administered at a dose of ferric iron ranging from 210 mg – 2,520 mg, and wherein the ferric citrate provides a mean increase in TSAT in said CKD patient of 5 – 10 %.

15 The ferric citrate of claim 7 or 8, wherein the at least one iron storage parameter is serum iron levels and wherein improving comprises increasing the serum iron levels in said CKD patient.

16. The ferric citrate of claim 7 or 8, wherein the at least one iron storage parameter is liver iron levels and wherein improving comprises increasing the liver iron levels in said CKD patient.

17. The ferric citrate of claim 7 or 8, wherein the at least one iron storage parameter is spleen iron levels and wherein improving comprises increasing the spleen iron levels in said CKD patient.

18. The ferric citrate of claim 7 or 8, wherein the at least one iron storage parameter is serum ferritin levels and wherein improving comprises increasing the serum ferritin levels in said CKD patient.

19. The ferric citrate of claim 18, wherein the ferric citrate is administered at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate provides a mean increase in serum ferritin in said CKD patient of 100 – 400 ng/ml.

20. Ferric citrate for use in a method of treating iron deficiency by oral administration to a chronic kidney disease (CKD) patient in an amount ranging from 1 g to 18 g, wherein the ferric citrate provides for treatment of iron deficiency in said CKD patient.

21. The ferric citrate of claim 20, wherein the ferric citrate reduces at least one symptom of iron deficiency selected from fatigue, dizziness, pallor, hair loss, irritability, weakness,

pica, brittle or grooved nails, Plummer-Vinson syndrome, impaired immune function, pagophagia, restless legs syndrome and combinations thereof.

22. The ferric citrate of claim 20, wherein the iron deficiency treated is anemia.

23. The ferric citrate of claim 22, wherein the ferric citrate provides a hemoglobin level in the CKD patient that is at or above a level selected from 11.0 g/dl, 11.5 g/dl, 12.0 g/dl, and 13.0 g/dl.

24. The ferric citrate of claim 22, wherein the ferric citrate provides a hemoglobin level in the CKD patient that is at or above a level selected from 6.8 mmol/L, 7.1 mmol/L, 7.4 mmol/L, and 8.1 mmol/L.

25. The ferric citrate of any of the preceding claims, wherein the chronic kidney disease patient is an end stage renal disease (ESRD) patient.

26. The ferric citrate of any of the preceding claims, wherein the chronic kidney disease patient is a non-dialysis chronic kidney disease (ND-CKD) patient.

27. The ferric citrate of any of the preceding claims, wherein the ferric citrate has a BET active surface area of from 27.99 m2/g to 32.34 m2/g.

28. The ferric citrate of any of the preceding claims, wherein the ferric citrate has a BET active surface area selected from 27.99 m2/g, 28.87 m2/g and 32.34 m2/g.

29. The ferric citrate of any of the preceding claims, wherein the ferric citrate is administered in a tablet dosage form.

30. The ferric citrate of claim 29, wherein the tablet dosage form comprises 1 gram of the ferric citrate.

31. Ferric citrate for use in a method of reducing intravenous (IV) iron use by oral administration to an end-stage renal disease (ESRD) patient at a dose of ferric iron ranging

from 210 mg – 2,520 mg, wherein the ferric citrate reduces the need for the ESRD patient to be administered IV iron by an amount ranging from 40 – 60 %.

32. The ferric citrate of claim 31, wherein the ferric citrate provides a mean reduction in average cumulative IV iron intake of said ESRD patient is selected from 50, 51, 52, 53, 54, 55, 56, 57, 58, 59 and 60 % when administered for a period of at least 52 weeks.

33. Ferric citrate for us in a method of reducing use of erythropoiesis-stimulating agents (ESAs) by oral administration to an end-stage renal disease (ESRD) patient at a dose of ferric iron ranging from 210 mg – 2,520 mg, wherein the ferric citrate reduces the need for the ESRD patient to be administered one or more ESAs by an amount ranging from 20 – 30 %.

34. The ferric citrate of claim 33, wherein the ferric citrate provides a decrease in median ESA intake of said patient is selected from 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30 % when the ferric citrate is administered for a period of at least 52 weeks.

35. The ferric citrate of any of claim 31-34, wherein the ferric citrate is administered in a 1 gram tablet dosage form, each dosage form comprising 210 mg of ferric iron.

36. The ferric citrate of claim 35, wherein the ESRD patient is administered up to 18 tablet dosage forms per day.

37. The ferric citrate of claim 35, wherein the ESRD patient is administered 6 tablet dosage forms per day.

38. The ferric citrate of any of claims 31-37, wherein the ferric citrate is administered within 1 hour of the ingestion of a meal or snack by the patient.

39. The ferric citrate of any of claims 31-38, wherein the ESRD patient was treated with thrice-weekly hemodialysis or with peritoneal dialysis for at least 3 months prior to administration of the ferric citrate.

40. An oral iron supplement, comprising ferric citrate in an amount effective to increase iron absorption, maintain iron stores, improve one or more iron storage parameters, treat iron deficiency or treat anemia in chronic kidney disease patients.

41. The oral iron supplement of claim 40, wherein the supplement comprises a tablet.

42. The oral iron supplement of claim 40 or 41, wherein the tablet comprises at least 70 wt% ferric citrate.

43. The oral iron supplement of any of claims 40-42, comprising at least about 500 mg ferric citrate.

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Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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15 October 2015

(54) **Title**: USE OF FERRIC CITRATE IN THE TREATMENT OF CHRONIC KIDNEY DISEASE PATIENTS

(57) **Abstract**: Methods of administering ferric citrate to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in chronic kidney disease patients, are disclosed.

WO 2013/192565 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/047134

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-4, 7-19(completely); 25-30, 40-43(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/047134

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/295 A61P3/00 A61P7/06 A61P13/12 A61K9/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	YOKOYAMA KEITARO ET AL: "Effect of oral JTT-751 (ferric citrate) on hyperphosphatemia in hemodialysis patients: results of a randomized, double-blind, placebo-controlled trial.", AMERICAN JOURNAL OF NEPHROLOGY 2012, vol. 36, no. 5, 2012, pages 478-487, XP008176600, ISSN: 1421-9670 the whole document	1-4, 7-19, 25-30, 40-43

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 June 2015	14/08/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hoff, Philippe

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/047134

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This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4, 7-19(completely); 25-30, 40-43(partially)

   Ferric citrate for use in a method of reducing serum phosphorus, of increasing serum bicarbonate or improving at least one iron storage parameter by oral administration to a chronic kidney disease (CKD) patient

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2. claims: 5, 6, 20-24, 31-39(completely); 25-30, 40-43(partially)

   Ferric citrate for use in a method of treating iron deficiency, of increasing iron absorption, of maintaining iron stores, of reducing intravenous iron use or reducing use of erythropoiesis-stimulating agents by oral administration to a chronic kidney disease patient.

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权利要求书3页 说明书73页

(54)发明名称

柠檬酸铁在治疗慢性肾脏疾病患者中的应用

(57)摘要

公开了在慢性肾脏疾病患者中给予柠檬酸铁以降低和/或控制血清磷水平、增加血清碳酸氢盐水平、改善一种或多种铁贮存参数(例如,增加血清铁蛋白水平、增加转铁蛋白饱和度(TSAT)、增加血红蛋白浓度)、增加铁吸收、维持铁贮存、治疗铁缺乏症、治疗贫血症、降低对静脉内铁剂的需求和/或降低对红细胞生成刺激剂(ESA)的需求的方法。

CN 104884055 A

1.用于通过以范围为210mg-2,520mg的三价铁剂量向慢性肾脏疾病(CKD)患者口服给药降低血清磷的方法中的柠檬酸铁,其中所述柠檬酸铁提供所述CKD患者的平均血清磷降低为2.00-2.50mg/dl。

2.权利要求1的方法,其中所述柠檬酸铁提供:

所述CKD患者的选自以下的平均血清磷降低:1.90、1.91、1.92、1.93、1.94、1.95、1.96、1.97、1.98、1.99、2.00、2.01、2.02、2.03、2.04、2.05、2.06、2.07、2.08、2.09 和2.10mg/dl,当给予12周的周期时;或

所述CKD患者的选自以下的平均血清磷降低:2.10、2.11、2.12、2.13、2.14、2.15、2.16、2.17、2.18、2.19、2.20、2.21、2.22、2.23、2.24和2.25mg/dl,当给予24周的周期时;或

所述CKD患者的选自以下的平均血清磷降低:2.10、2.11、2.12、2.13、2.14、2.15、2.16、2.17、2.18、2.19和2.20mg/dl,当给予36周的周期时;

所述CKD患者的选自以下的平均血清磷降低:1.95、1.96、1.97、1.98、1.99、2.00、2.01、2.02、2.03、2.04、2.05、2.06、2.07、2.08、2.09、2.10、2.11、2.12、2.13、2.14 和2.15mg/dl,当给予48周的周期时;或

所述CKD患者的选自以下的平均血清磷降低:1.95、1.96、1.97、1.98、1.99、2.00、2.01、2.02、2.03、2.04、2.05、2.06、2.07、2.08、2.09、2.10、2.11、2.12、2.13、2.14、2.15、2.16、2.17、2.18、2.19、2.20、2.21、2.22、2.23、2.24、2.25、2.26、2.27、2.28、2.29 和2.30mg/dl,当给予52周的周期时。

3.用于通过以范围为210mg-2,520mg的三价铁剂量向慢性肾脏疾病(CKD)患者口服给药增加血清碳酸氢盐的方法中的柠檬酸铁,其中所述柠檬酸铁提供所述CKD患者的血清碳酸氢盐的增加为0.1-1.0mEq/L。

4.权利要求3的柠檬酸铁,其中所述柠檬酸铁提供所述CKD患者的选自以下的平均血清碳酸氢盐浓度增加:0.70、0.71、0.72、0.73、0.74、0.75、0.76、0.77、0.78、0.79和0.80mEq/L,当给予至少52周的周期时。

5.用于通过以范围为1g至18g的量向慢性肾脏疾病(CKD)患者口服给药增加铁吸收的方法中的柠檬酸铁,其中所述柠檬酸铁提供所述CKD患者的铁吸收增加。

6.用于通过以范围为1g至18g的量向慢性肾脏疾病(CKD)患者口服给药维持铁贮存的方法中的柠檬酸铁,其中所述柠檬酸铁提供所述CKD患者的铁贮存维持。

7.用于通过以范围为1g至18g的量向慢性肾脏疾病(CKD)患者口服给药改善至少一种铁贮存参数的方法中的柠檬酸铁,其中所述柠檬酸铁提供所述CKD患者的至少一种铁贮存参数改善。

8.权利要求7的柠檬酸铁,其中至少一种铁贮存参数选自红细胞比容、血红蛋白浓度、总铁结合能力、转铁蛋白饱和度、血清铁水平、肝脏铁水平、脾脏铁水平、血清铁蛋白水平和它们的组合。

9.权利要求7或8的柠檬酸铁,其中至少一种铁贮存参数是红细胞比容和其中改善包括增加所述CKD患者的红细胞比容。

10.权利要求7或8的柠檬酸铁,其中至少一种铁贮存参数是血红蛋白浓度和其中改善包括增加所述CKD患者的血红蛋白浓度。

11.权利要求 10 的柠檬酸铁，其中所述柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量给予，和其中所述柠檬酸铁提供所述 CKD 患者的平均血红蛋白浓度增加为 0.3-0.6g/d1。

12.权利要求 7 或 8 的柠檬酸铁，其中至少一种铁贮存参数是总铁结合能力和其中改善包括降低所述 CKD 患者的总铁结合能力。

13.权利要求 7 或 8 的柠檬酸铁，其中至少一种铁贮存参数是转铁蛋白饱和度 (TSAT) 和其中改善包括增加所述 CKD 患者的转铁蛋白饱和度。

14.权利要求 13 的柠檬酸铁，其中所述柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量给予，和其中所述柠檬酸铁提供所述 CKD 患者的平均 TSAT 增加为 5-10％。

15.权利要求 7 或 8 的柠檬酸铁，其中至少一种铁贮存参数是血清铁水平和其中改善包括增加所述 CKD 患者的血清铁水平。

16.权利要求 7 或 8 的柠檬酸铁，其中至少一种铁贮存参数是肝脏铁水平和其中改善包括增加所述 CKD 患者的肝脏铁水平。

17.权利要求 7 或 8 的柠檬酸铁，其中至少一种铁贮存参数是脾脏铁水平和其中改善包括增加所述 CKD 患者的脾脏铁水平。

18.权利要求 7 或 8 的柠檬酸铁，其中至少一种铁贮存参数是血清铁蛋白水平和其中改善包括增加所述 CKD 患者的血清铁蛋白水平。

19.权利要求 18 的柠檬酸铁，其中所述柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量给予，其中所述柠檬酸铁提供所述 CKD 患者的平均血清铁蛋白增加为 100-400ng/ml。

20.用于通过以范围为 1g 至 18g 的量向慢性肾脏疾病 (CKD) 患者口服给药治疗铁缺乏症的方法中的柠檬酸铁，其中所述柠檬酸铁提供对所述 CKD 患者的铁缺乏症的治疗。

21.权利要求 20 的柠檬酸铁，其中所述柠檬酸铁减轻选自以下的铁缺乏症的至少一个症状 ：疲乏、眩晕、苍白、脱发、易怒、虚弱、异食癖、脆性或沟槽甲、普鲁默 - 文森综合症、免疫功能受损、食冰癖、不宁腿综合症和它们的组合。

22.权利要求 20 的柠檬酸铁，其中所治疗的铁缺乏症是贫血症。

23.权利要求 22 的柠檬酸铁，其中所述柠檬酸铁提供所述 CKD 患者的血红蛋白水平是在或超出选自以下的水平 ：11.0g/d1、11.5g/d1、12.0g/d1 和 13.0g/d1。

24.权利要求 22 的柠檬酸铁，其中所述柠檬酸铁提供所述 CKD 患者的血红蛋白水平是在或超出选自以下的水平 ：6.8mmol/L、7.1mmol/L、7.4mmol/L 和 8.1mmol/L。

25.前述权利要求中任一项的柠檬酸铁，其中所述慢性肾脏疾病患者是终末期肾病 (ESRD) 患者。

26.前述权利要求中任一项的柠檬酸铁，其中所述慢性肾脏疾病患者是非透析慢性肾脏疾病 (ND-CKD) 患者。

27.前述权利要求中任一项的柠檬酸铁，其中所述柠檬酸铁的 BET 活性表面积为 27.99m^2/g 至 32.34m^2/g。

28.前述权利要求中任一项的柠檬酸铁，其中所述柠檬酸铁的 BET 活性表面积选自 27.99m^2/g、28.87m^2/g 和 32.34m^2/g。

29.前述权利要求中任一项的柠檬酸铁，其中所述柠檬酸铁在片剂剂型中给予。

30.权利要求 29 的柠檬酸铁，其中所述片剂剂型包含 1 克的所述柠檬酸铁。

31.用于通过以范围为 210mg-2,520mg 的三价铁剂量向终末期肾病 (ESRD) 患者口服给

药降低静脉内（IV）铁剂使用的方法中的柠檬酸铁，其中所述柠檬酸铁降低所述 ESRD 患者对给予静脉内铁剂的需求达范围为 40-60％的量。

32. 权利要求 31 的柠檬酸铁，其中所述柠檬酸铁提供所述 ESRD 患者的平均累积静脉内铁剂摄入量的平均降低选自 50、51、52、53、54、55、56、57、58、59 和 60％，当给予至少 52 周的周期时。

33. 用于通过以范围为 210mg-2,520mg 的三价铁剂量向终末期肾病（ESRD）患者口服给药降低红细胞生成刺激剂（ESA）使用的方法中的柠檬酸铁，其中所述柠檬酸铁降低所述 ESRD 患者对给予一种或多种 ESA 的需求达范围为 20-30％的量。

34. 权利要求 33 的柠檬酸铁，其中所述柠檬酸铁提供所述患者的中值 ESA 摄入量减少选自 20、21、22、23、24、25、26、27、28、29 和 30％，当所述柠檬酸铁给予至少 52 周的周期时。

35. 权利要求 31-34 中任一项的柠檬酸铁，其中所述柠檬酸铁在 1 克片剂剂型中给予，每个剂型包含 210mg 的三价铁。

36. 权利要求 35 的柠檬酸铁，其中所述 ESRD 患者每天最多给予 18 个片剂剂型。

37. 权利要求 35 的柠檬酸铁，其中所述 ESRD 患者每天给予 6 个片剂剂型。

38. 权利要求 31-37 中任一项的柠檬酸铁，其中所述柠檬酸铁在所述患者吃完正餐或点心的 1 小时以内给予。

39. 权利要求 31-38 中任一项的柠檬酸铁，其中所述 ESRD 患者在给予所述柠檬酸铁之前用一周三次血液透析或者用腹膜透析治疗至少 3 个月。

40. 口服铁补充剂，包含柠檬酸铁，其含量在慢性肾脏疾病患者中有效增加铁吸收、维持铁贮存、改善一种或多种铁贮存参数、治疗铁缺乏症或治疗贫血症。

41. 权利要求 40 的口服铁补充剂，其中所述补充剂包括片剂。

42. 权利要求 40 或 41 的口服铁补充剂，其中所述片剂包含至少 70wt％柠檬酸铁。

43. 权利要求 40-42 中任一项的口服铁补充剂，包含至少约 500mg 柠檬酸铁。

柠檬酸铁在治疗慢性肾脏疾病患者中的应用

[0001] 领域

[0002] 本文公开的方法和组合物总的来讲涉及使用柠檬酸铁治疗慢性肾脏疾病 (CKD) 患者。

[0003] 背景

[0004] 慢性肾脏疾病 (CKD) 是肾脏排泄废物、浓缩尿液和保留电解质的能力的渐进性和进行性丧失。美国国家肾脏基金会 (The U.S.National Kidney Foundation) 根据肾脏损害的存在与否和肾脏功能的水平来定义慢性肾脏疾病，而与肾脏疾病的类型（临床诊断）无关。衡量肾脏功能的主要指标是肾小球滤过率 (glomerular filtration rate,GFR)，GFR 常常根据血清和尿液肌酸酐浓度估计为肌酸酐清除率。慢性肾脏疾病或衰竭定义为 GFR 小于 60ml/min 持续三个月或更长时间。美国国家肾脏基金会已建议基于 GFR，肾功能障碍的五个分期分类。

[0005] 肾功能障碍的分期（改编自美国国家肾脏基金会 -K/DOQI）

[0006]

分期	描述	肌酸酐清除率 (~GFR: ml/min/1.73 m^2)	代谢结果
1	GFR 正常或增加—处于早期肾损害风险增加或有早期肾损害的人	>90	-
2	早期肾功能不全	60-89	甲状旁腺激素的浓度开始升高(GFR~60-80)
3	中度肾衰竭 (慢性肾衰竭)	30-59	钙吸收减少(GFR<50) 脂蛋白活性下降 营养不良 左心室肥大发作 贫血发作
4	重度肾衰竭	15-29	甘油三酯浓度开始升高 高磷酸盐血症 代谢性酸中毒 有高钾血症的倾向
5	终末期肾病(尿毒症)	<15	发生氮质血症

[0007] 如上表所示，1 期是严重性最小，而 5 期或 ESRD 是严重性最大。在 CKD 的早分期（如分期 1-4），通常不需要透析。因此，经历 CKD 的较早分期的患者被描述为患有非透析依赖的慢性肾脏疾病。这样的患者也常称为非透析慢性肾脏疾病 (ND-CKD) 患者。当 GFR 小于 60cc/min 时，贫血症典型地最先出现在 CKD 3 期，这在透析之前很长时间是必需的，尽管贫血症可能出现在 CKD 的任何分期。在 5 期，患者可能需要透析治疗每周几次。一旦肾脏的变性过程开始，CKD 中的肾脏功能就不可逆地朝向终末期肾病 (ESRD,5 期）恶化。罹患 ESRD 的患者若不接受透析或肾脏移植将无法生存。

[0008] 根据美国国家肾脏基金会的统计，接近 2600 万美国成年人患有 CKD，另外还有数

百万人正处于风险增大的阶段。与年龄相匹配的、非 CKD 总人口相比，经历 CKD 较早分期的患者通常招致医疗费用每患者每年从 $14,000 美元增加到 $22,000 美元。然而，越来越多的证据表明，一些与 CKD 相关的费用增加和不良后果可通过预防措施、早检查和早治疗来预防或延迟。

[0009] 铁缺乏症和贫血症是 CKD（包括 ESRD）的常见并发症。贫血症是循环红细胞量减少的临床表现，通常通过血液中低血红蛋白浓度来检测出来。功能正常的肾脏产生促红细胞生成素，一种刺激红细胞前体增殖和分化的激素，最终导致红细胞生成（红细胞产生）。在 CKD 肾脏中，促红细胞生成素产生常常受损，导致促红细胞生成素缺乏并伴随红细胞生成的缺乏。贫血症与不良心血管后果、ESRD、死亡率和生活质量减低相关 (Macdougall,Curr Med Res Opin(2010)26:473-482)。贫血症在 CKD 中的普遍性随着肾脏功能降低而增加。非透析慢性肾脏疾病患者的大约 50％是患贫血症的，而到 CKD 患者开始透析的时候，高达 70％是患贫血症的 (Macdougall，同上，和 McClellan 等人，Curr Med Res Opin(2004)20:1501-1510)。

[0010] 铁缺乏症是 CKD 患者的贫血症的重要成因。估计的流行范围为 25-70％ (Hsu 等人，J Am Soc Nephrol(2002)13:2783-2786；Gotloib 等人，J Nephrol(2006)19:161-167；Mafra 等人，J Ren Nutr(2002)12:38-41；Kalantar-Zadeh 等人，Am J Kidney Dis(1995)26:292-299；和 Post 等人，Int Urol Nephrol(2006)38:719-723)。原因包括铁的摄入或吸收减少、炎症所致的铁螯合、失血和在对红细胞生成刺激剂 (ESA) 应答时用于红细胞产生的铁使用增加 (Fishbane 等人，Am J Kidney Dis(1997)29:319-333；Kooistra 等人，Nephrol Dial Transplant(1998)13:82-88；和 Akmal 等人，Clin Nephrol(1994)42:198-202)。根据 CKD 分期，20-70％的 CKD 患者表现出低铁指数 (Quinbi 等人，Nephrol Dial Transplant(2011)26:1599-1607)。在美国，估计有超过 100 万 CKD 3 期或 4 期患者患上铁缺乏症。低铁贮存的存在（“绝对性”缺铁）或满足红细胞生成需求可利用的铁不足够（“功能性”缺铁）与 CKD 患者的血红蛋白水平降低明显相关。铁缺乏症可由任意一种或多种因素引起，包括例如从食物摄入的铁不足够、铁利用增加、胃肠铁吸收差和由肾衰竭和细菌过度生长所致的广泛性吸收不良，及胃肠出血 (Macdougall，同上)。

[0011] 针对 CKD 患者中的贫血症和/或铁缺乏症的现行护理标准是给予红细胞生成刺激剂 (ESA) 和/或铁补充剂 (iron supplementation)。美国国家肾脏基金会肾脏病预后质量倡议 (The National Kidney Foundation Kidney Disease Outcomes Quality Initiative) 指南为患有 CKD 1 到 5 期并且没有接受透析的患者推荐口服或静脉内铁剂（参见“Using iron agents:KDOQI clinical practice guidelines and clinical practice recommendations for anemia inchronic kidney disease（使用铁剂：慢性肾脏病中贫血症的 KDOQI 临床实践指南与临床实践推荐），”Am J Kidney Dis(2006)47:S58-S70)。长期以来，已经知道铁的三价形式（也称为铁 (III) 或 Fe^{3+}）当口服给予时生物利用度较差。因此，在 CKD 患者中，铁补充剂的口服制剂典型地含有铁的二价形式（也称为铁 (II) 或 Fe^{2+}）。一些亚铁口服铁制品可供治疗所利用，包括葡萄糖酸亚铁、富马酸亚铁和硫酸亚铁。最常见的口服铁补充剂是硫酸亚铁，硫酸亚铁可给予最多一日三次，以便提供足够的剂量用于治疗铁缺乏的 CKD 患者。然而，在有些 CKD 患者中，口服铁剂因为不良副作用而耐受差，或者在维持足够的机体铁贮存时是无效的。副作用典型地包括

如腹泻、恶心、胀气和腹部不适等胃肠问题。另外，因为在它们典型地给予时的频次，所以口服亚铁形式对患者造成片剂负担并且具有明显消极的胃肠副作用，这导致用口服治疗方案时的非顺应性 (Mehdi 等人，同上)。

[0012] 一种替代的方案是向 CKD 患者给予静脉内铁剂。一些研究已表明，静脉内铁制剂对于治疗 CKD 患者的铁缺乏症和 / 或贫血症要比口服三价铁的铁补充剂或口服亚铁的铁补充剂的效果好 (Mehdi 等人，同上)。用于治疗 CKD 患者的有效的静脉内制剂包括羧基麦芽糖铁、菲立莫妥 (ferumoxytol)、葡萄糖酸铁、蔗糖铁和右旋糖酐铁。然而，静脉内铁剂与例如过敏反应和死亡等短期风险以及包括发生动脉粥样硬化、感染和死亡率增加在内的长期毒性相关 (Quinibi Arzneimittelforschung(2010)60:399-412)。此外，许多 CKD 诊所、特别是社区站点，对给予静脉内铁剂都是设备不足的，因为它们缺少透析中心的基础设施。这留下大量的 CKD 缺铁性患者无法进行静脉内铁剂治疗。

[0013] 因此，需要开发改善的治疗 CKD 患者的方法。

[0014] 概述

[0015] 本公开的某些方面提供临床上安全有效的磷酸盐结合剂，其可以在 CKD 患者包括非透析 CKD(ND-CKD) 患者和终末期 (end state) 肾病 (ESRD) 患者中，用于降低和 / 或控制血清磷水平、增加血清碳酸氢盐水平、改善一种或多种铁贮存 (iron storage) 参数 (例如，增加血清铁蛋白水平、增加转铁蛋白饱和度 (TSAT)、增加血红蛋白浓度)、增加铁吸收、维持铁贮存、治疗铁缺乏症、治疗贫血症、降低对静脉内铁剂 (IV iron) 的需求和 / 或降低对红细胞生成刺激剂 (erythropoiesis-stimulating agents,ESA) 的需求。在某些方面，所述磷酸盐结合剂对于向 CKD 患者长期给药，例如连续给药多达并且包括至少 56 周，在临床上是安全有效的。

[0016] 按照本公开的某些实施方案，用于作为磷酸盐结合剂申请行政上市许可的候选药剂是本文公开的柠檬酸铁 (ferric citrate)(也称为 KRX-0502(柠檬酸铁)，参见实施例 1)。临床前研究已经证明本文公开的柠檬酸铁结合膳食磷、减少膳食磷的肠吸收和降低血清磷酸盐水平的能力 (Mathew 等人，J Am Soc Nephrol(2006)17:357A ;Voormolen 等人，Nephrol Dial Transplant(2007)22:2909-2916 ; 和 Tonelli 等人，Circulation(2005)112:2627-2633)。本文公开的柠檬酸铁 (例如，KRX-0502(柠檬酸铁)) 在 ESRD 患者中的四个临床研究已经进行并且已经向美国食品及药品管理局报告为 KRX-0502(柠檬酸铁) 试验性新药 (the KRX-0502(ferric citrate)Investigational New Drug(IND)) 提交的组成部分。这些研究之一，3 期长期研究 (本文所述) 已经证实，本文公开的柠檬酸铁 (也称为 KRX-0502) 证明在四周疗效评估期 (four-week Efficacy Assessment Period) 内，对比安慰剂，血清磷有高度统计学显著性变化，并且当在 52 周安全性评估期 (52-week Safety Assessment Period) 内与活性剂对照剂相比时，在 ESRD 患者中能增加铁蛋白和转铁蛋白饱和度 (TSAT) 和降低静脉内铁剂和红细胞生成刺激剂的使用。

[0017] 按照本公开，已经发现本文公开的柠檬酸铁能够用作临床上安全有效的磷酸盐结合剂以在 CKD 患者包括非透析 CKD(ND-CKD) 患者和终末期 (end state) 肾病 (ESRD) 患者中控制和 / 或降低血清磷水平、增加血清碳酸氢盐水平、改善一种或多种铁贮存参数 (例如，增加血清铁蛋白水平、增加转铁蛋白饱和度 (TSAT)、增加血红蛋白浓度、增加铁吸收)、维持铁贮存、治疗铁缺乏症、治疗贫血症、降低对静脉内铁剂的需求和 / 或降低对红细胞生

成刺激剂 (ESA) 的需求。

[0018] 在一个方面，本公开提供降低和 / 或控制有其需要的患者的血清磷的方法。在有些实施方案中，所述方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予 CKD 患者，例如终末期肾病患者，其中所述柠檬酸铁提供平均血清磷降低为 2.00-2.50mg/dl。在有些实施方案中，所述柠檬酸铁在 1 克片剂剂型中给予，每个剂型包含 210mg 的三价铁。在有些实施方案中，所述患者每天最多给予 18 个片剂剂型。在有些实施方案中，所述患者每天给予 6 个片剂剂型。在有些实施方案中，所述柠檬酸铁在该患者吃完正餐或点心的 1 小时以内给予。在有些实施方案中，所述患者在给予所述柠檬酸铁之前用一周三次血液透析或者用腹膜透析治疗至少 3 个月。在有些实施方案中，所述柠檬酸铁的 BET 活性表面积 (active surface area) 大于约 16m^2/g。在有些实施方案中，所述 BET 活性表面积范围为约 16m^2/g 至约 20m^2/g。在有些实施方案中，所述 BET 活性表面积范围为约 27.99m^2/g 至约 32.34m^2/g。在有些实施方案中，所述 BET 活性表面积选自 27.99m^2/g、28.87m^2/g 和 32.34m^2/g。在有些实施方案中，所述柠檬酸铁的固有溶出速率为 1.88-4.0mg/cm^2/min。

[0019] 在另一个方面，本公开提供降低有其需要的患者的血清磷的方法。在有些实施方案中，所述方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予 CKD 患者，例如终末期肾病患者，其中所述柠檬酸铁提供 ：选自以下的平均血清磷降低 ：1.90、1.91、1.92、1.93、1.94、1.95、1.96、1.97、1.98、1.99、2.00、2.01、2.02、2.03、2.04、2.05、2.06、2.07、2.08、2.09 和 2.10mg/dl，当给予 12 周的周期时 ；选自以下的平均血清磷降低 ：2.10、2.11、2.12、2.13、2.14、2.15、2.16、2.17、2.18、2.19、2.20、2.21、2.22、2.23、2.24 和 2.25mg/dl，当给予 24 周的周期时 ；选自以下的平均血清磷降低 ：2.10、2.11、2.12、2.13、2.14、2.15、2.16、2.17、2.18、2.19 和 2.20mg/dl，当给予 36 周的周期时 ；选自以下的平均血清磷降低 ：1.95、1.96、1.97、1.98、1.99、2.00、2.01、2.02、2.03、2.04、2.05、2.06、2.07、2.08、2.09、2.10、2.11、2.12、2.13、2.14 和 2.15mg/dl，当给予 48 周的周期时 ；和选自以下的平均血清磷降低 ：1.95、1.96、1.97、1.98、1.99、2.00、2.01、2.02、2.03、2.04、2.05、2.06、2.07、2.08、2.09、2.10、2.11、2.12、2.13、2.14、2.15、2.16、2.17、2.18、2.19、2.20、2.21、2.22、2.23、2.24、2.25、2.26、2.27、2.28、2.29 和 2.30mg/dl，当给予 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 2.00mg/dl，当给予 12 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 2.20mg/dl，当给予 24 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 2.20mg/dl，当给予 36 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 2.10mg/dl，当给予 48 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 2.10mg/dl，当给予 52 周的周期时。

[0020] 在又一个方面，本公开提供增加有其需要的患者的血清碳酸氢盐的方法。在有些实施方案中，所述方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予 CKD 患者，例如终末期肾病患者，其中所述柠檬酸铁提供选自以下的血清碳酸氢盐增加 ：0.70、0.71、0.72、0.73、0.74、0.75、0.76、0.77、0.78、0.79 和 0.80mEq/L，当给予至少 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加为 0.71mEq/L。在有些实施方案中，所述柠檬酸铁在 1 克片剂剂型中给予，每个剂型包含 210mg 的三价铁。在有些实施方案中，所述患者每天最多给予 18 个片剂剂型。在有些实施方案中，所述

患者每天给予 6 个片剂剂型。在有些实施方案中，所述柠檬酸铁在该患者吃完正餐或点心的 1 小时以内给予。在有些实施方案中，所述患者在给予所述柠檬酸铁之前用一周三次血液透析或者用腹膜透析治疗至少 3 个月。在有些实施方案中，所述柠檬酸铁的 BET 活性表面积大于约 16m^2/g。在有些实施方案中，所述 BET 活性表面积范围为约 16m^2/g 至约 20m^2/g。在有些实施方案中，所述 BET 活性表面积范围为约 27.99m^2/g 至约 32.34m^2/g。在有些实施方案中，所述 BET 活性表面积选自 27.99m^2/g、28.87m^2/g 和 32.34m^2/g。在有些实施方案中，所述柠檬酸铁的固有溶出速率为 1.88-4.0mg/cm^2/min。

[0021] 在又一个方面，本公开提供维持有其需要的患者的铁贮存的方法。在有些实施方案中，所述方法包括将柠檬酸铁以每天约 1g 至约 18g 的剂量范围口服给予 CKD 患者，例如非透析慢性肾脏疾病患者或终末期肾病患者。在有些实施方案中，所述柠檬酸铁在 1 克片剂剂型中给予。在有些实施方案中，所述患者每天最多给予 18 个片剂剂型。在有些实施方案中，所述柠檬酸铁的 BET 活性表面积大于约 16m^2/g。在有些实施方案中，所述 BET 活性表面积范围为约 16m^2/g 至约 20m^2/g。在有些实施方案中，所述 BET 活性表面积范围为约 27.99m^2/g 至约 32.34m^2/g。在有些实施方案中，所述 BET 活性表面积选自 27.99m^2/g、28.87m^2/g 和 32.34m^2/g。在有些实施方案中，所述柠檬酸铁的固有溶出速率为 1.88-4.0mg/cm^2/min。

[0022] 在又一个方面，本公开提供改善有其需要的患者的一种或多种铁贮存参数的方法。在有些实施方案中，所述方法包括将柠檬酸铁以每天约 1g 至约 18g 的剂量范围口服给予 CKD 患者，例如非透析慢性肾脏疾病患者或终末期肾病患者。在有些实施方案中，至少一种铁贮存参数可选自血清铁蛋白水平、转铁蛋白饱和度 (TSAT)、血红蛋白浓度、红细胞比容 (hematocrit)、总铁结合能力、铁吸收水平、血清铁水平、肝脏铁水平、脾脏铁水平和它们的组合。在有些实施方案中，所述柠檬酸铁在 1 克片剂剂型中给予。在有些实施方案中，所述患者每天最多给予 18 个片剂剂型。在有些实施方案中，所述柠檬酸铁的 BET 活性表面积大于约 16m^2/g。在有些实施方案中，所述 BET 活性表面积范围为约 16m^2/g 至约 20m^2/g。在有些实施方案中，所述 BET 活性表面积范围为约 27.99m^2/g 至约 32.34m^2/g。在有些实施方案中，所述 BET 活性表面积选自 27.99m^2/g、28.87m^2/g 和 32.34m^2/g。在有些实施方案中，所述柠檬酸铁的固有溶出速率为 1.88-4.0mg/cm^2/min。

[0023] 在另一个实施方案中，至少一种铁贮存参数是红细胞比容，且改善包括增加患者的红细胞比容。在其它的实施方案中，至少一种铁贮存参数是血红蛋白浓度，且改善包括增加患者的血红蛋白浓度。在又一些实施方案中，至少一种铁贮存参数是总铁结合能力，且改善包括降低患者的总铁结合能力。在又一些实施方案中，至少一种铁贮存参数是转铁蛋白饱和度，且改善包括增加患者的转铁蛋白饱和度。在又一些实施方案中，至少一种铁贮存参数是血清铁水平，且改善包括增加患者的血清铁水平。在又一些实施方案中，至少一种铁贮存参数是肝脏铁水平，且改善包括增加患者的肝脏铁水平。在又一些实施方案中，至少一种铁贮存参数是脾脏铁水平，且改善包括增加患者的脾脏铁水平。在又一些实施方案中，至少一种铁贮存参数是血清铁蛋白水平，且改善包括增加患者的血清铁蛋白水平。

[0024] 在又一个实施方案中，至少一种铁贮存参数是血清铁蛋白水平，本公开提供增加有其需要的患者的血清铁蛋白的方法。在有些实施方案中，所述方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予 CKD 患者，例如终末期肾病患者，其中所述柠檬

酸铁提供该患者的选自以下的平均血清铁蛋白增加：150-310、151-309、152-308、153-307、154-306、155-306、155-305、155-304、155-303 和 155-302ng/ml，当给予至少 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 150-305ng/ml。在有些实施方案中，所述柠檬酸铁在 1 克片剂剂型中给予，每个剂型包含 210mg 的三价铁。在有些实施方案中，所述患者每天最多给予 18 个片剂剂型。在有些实施方案中，所述患者每天给予 6 个片剂剂型。在有些实施方案中，所述柠檬酸铁在该患者吃完正餐或点心的 1 小时以内给予。在有些实施方案中，所述患者在给予所述柠檬酸铁之前用一周三次血液透析或者用腹膜透析治疗至少 3 个月。在有些实施方案中，所述柠檬酸铁的 BET 活性表面积大于约 $16m^2/g$。在有些实施方案中，所述 BET 活性表面积范围为约 $16m^2/g$ 至约 $20m^2/g$。在有些实施方案中，所述 BET 活性表面积范围为约 $27.99m^2/g$ 至约 $32.34m^2/g$。在有些实施方案中，所述 BET 活性表面积选自 $27.99m^2/g$、$28.87m^2/g$ 和 $32.34m^2/g$。在有些实施方案中，所述柠檬酸铁的固有溶出速率为 1.88-4.0mg/cm^2/min。

[0025] 在又一个实施方案中，至少一种铁贮存参数是转铁蛋白饱和度 (TSAT)，本公开提供增加有其需要的患者的转铁蛋白饱和度 (TSAT) 的方法。在有些实施方案中，所述方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予 CKD 患者，例如终末期肾病患者，其中所述柠檬酸铁提供平均 TSAT 增加为 5-10％，当给予至少 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供该患者的平均转铁蛋白饱和度 (TSAT) 增加为 6-9％。在有些实施方案中，所述柠檬酸铁提供该患者的平均转铁蛋白饱和度 (TSAT) 增加为 8％。在有些实施方案中，所述柠檬酸铁在 1 克片剂剂型中给予，每个剂型包含 210mg 的三价铁。在有些实施方案中，所述患者每天最多给予 18 个片剂剂型。在有些实施方案中，所述患者每天给予 6 个片剂剂型。在有些实施方案中，所述柠檬酸铁在该患者吃完正餐或点心的 1 小时以内给予。在有些实施方案中，所述柠檬酸铁的 BET 活性表面积大于约 $16m^2/g$。在有些实施方案中，所述 BET 活性表面积范围为约 $16m^2/g$ 至约 $20m^2/g$。在有些实施方案中，所述 BET 活性表面积范围为约 $27.99m^2/g$ 至约 $32.34m^2/g$。在有些实施方案中，所述 BET 活性表面积选自 $27.99m^2/g$、$28.87m^2/g$ 和 $32.34m^2/g$。在有些实施方案中，所述柠檬酸铁的固有溶出速率为 1.88-4.0mg/cm^2/min。

[0026] 在又一个实施方案中，至少一种铁贮存参数是血红蛋白浓度，本公开提供增加有其需要的患者的血红蛋白浓度的方法。在有些实施方案中，所述方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予 CKD 患者，例如终末期肾病患者，其中所述柠檬酸铁提供该患者的平均血红蛋白浓度增加为 0.3-0.6g/dl，当给予至少 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供该患者的平均血红蛋白浓度增加为 0.3-0.5g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加为 0.4g/dl。在有些实施方案中，所述柠檬酸铁在 1 克片剂剂型中给予，每个剂型包含 210mg 的三价铁。在有些实施方案中，所述患者每天最多给予 18 个片剂剂型。在有些实施方案中，所述患者每天给予 6 个片剂剂型。在有些实施方案中，所述柠檬酸铁在该患者吃完正餐或点心的 1 小时以内给予。在有些实施方案中，所述柠檬酸铁的 BET 活性表面积大于约 $16m^2/g$。在有些实施方案中，所述 BET 活性表面积范围为约 $16m^2/g$ 至约 $20m^2/g$。在有些实施方案中，所述 BET 活性表面积范围为约 $27.99m^2/g$ 至约 $32.34m^2/g$。在有些实施方案中，所述 BET 活性表面积选自 $27.99m^2/g$、$28.87m^2/g$ 和 $32.34m^2/g$。在有些实施方案中，所述柠檬酸铁的固有溶出速率为 1.88-4.0mg/

cm^2/min。

[0027] 在又一个方面，本公开提供增加有其需要的患者的铁吸收的方法。在有些实施方案中，所述方法包括将柠檬酸铁以每天约 1g 至约 18g 的剂量范围口服给予 CKD 患者，例如非透析慢性肾脏疾病患者或终末期肾病患者。在有些实施方案中，所述柠檬酸铁在 1 克片剂剂型中给予。在有些实施方案中，所述患者每天最多给予 18 个片剂剂型。在有些实施方案中，所述柠檬酸铁的 BET 活性表面积大于约 $16m^2/g$。在有些实施方案中，所述 BET 活性表面积范围为约 $16m^2/g$ 至约 $20m^2/g$。在有些实施方案中，所述 BET 活性表面积范围为约 $27.99m^2/g$ 至约 $32.34m^2/g$。在有些实施方案中，所述 BET 活性表面积选自 $27.99m^2/g$、$28.87m^2/g$ 和 $32.34m^2/g$。在有些实施方案中，所述柠檬酸铁的固有溶出速率为 1.88-4.0mg/cm^2/min。

[0028] 在又一个方面，本公开提供治疗有其需要的患者的铁缺乏症的方法。在有些实施方案中，所述方法包括将柠檬酸铁以每天约 1g 至约 18g 的剂量范围口服给予 CKD 患者，例如非透析慢性肾脏疾病患者或终末期肾病患者。在有些实施方案中，所述铁缺乏症是贫血症。在有些实施方案中，所述治疗提供该患者的血红蛋白水平在选自 12.0g/dl 和 7.4mmol/L 的水平或超出选自 12.0g/dl 和 7.4mmol/L 的水平。在其它的实施方案中，所述治疗提供该患者的血红蛋白水平在选自 13.0g/dl 和 8.1mmol/L 的水平或超出选自 13.0g/dl 和 8.1mmol/L 的水平。在又一些实施方案中，所述治疗提供该患者的血红蛋白水平在选自 6.8mmol/L、7.1mmol/L、7.4mmol/L 和 8.1mmol/L 的水平或超出选自 6.8mmol/L、7.1mmol/L、7.4mmol/L 和 8.1mmol/L 的水平。在又一些实施方案中，所述治疗提供该患者的血红蛋白水平在选自 11.0g/dl、11.5g/dl、12.0g/dl 和 13.0g/dl 的水平或超出选自 11.0g/dl、11.5g/dl、12.0g/dl 和 13.0g/dl 的水平。在有些实施方案中，所述治疗减轻选自以下的铁缺乏症的至少一个症状：疲乏、眩晕、苍白、脱发、易怒、虚弱、异食癖、脆性或沟槽甲、普鲁默 - 文森综合症 (Plummer-Vinson syndrome)、免疫功能受损、食冰癖、不宁腿综合症和它们的组合。在有些实施方案中，所述柠檬酸铁在 1 克片剂剂型中给予。在有些实施方案中，所述患者每天最多给予 18 个片剂剂型。在有些实施方案中，所述柠檬酸铁的 BET 活性表面积大于约 $16m^2/g$。在有些实施方案中，所述 BET 活性表面积范围为约 $16m^2/g$ 至约 $20m^2/g$。在有些实施方案中，所述 BET 活性表面积范围为约 $27.99m^2/g$ 至约 $32.34m^2/g$。在有些实施方案中，所述 BET 活性表面积选自 $27.99m^2/g$、$28.87m^2/g$ 和 $32.34m^2/g$。在有些实施方案中，所述柠檬酸铁的固有溶出速率为 1.88-4.0mg/cm^2/min。

[0029] 在又一个方面，本公开提供降低 CKD 患者（例如终末期肾病患者）的静脉内 (IV) 铁剂使用的方法。在有些实施方案中，所述方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予所述患者，其中所述柠檬酸铁降低终末期肾病患者对给予静脉内铁剂的需求达选自以下的量：50、51、52、53、54、55、56、57、58、59 和 60％，当给予至少 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供选自以下的平均累积静脉内铁剂摄入量的平均降低：51.0、51.1、51.2、51.3、51.4、51.5、51.6、51.7、51.9 和 52.0％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为 51.6％。在有些实施方案中，所述柠檬酸铁在 1 克片剂剂型中给予，每个剂型包含 210mg 的三价铁。在有些实施方案中，所述患者每天最多给予 18 个片剂剂型。在有些实施方案中，所述患者每天给予 6 个片剂剂型。在有些实施方案中，所述柠檬酸铁在该患者吃完正餐或点心的 1 小时以内给予。在

有些实施方案中，所述患者在给予所述柠檬酸铁之前用一周三次血液透析或者用腹膜透析治疗至少 3 个月。在有些实施方案中，所述柠檬酸铁的 BET 活性表面积大于约 16m^2/g。在有些实施方案中，所述 BET 活性表面积范围为约 16m^2/g 至约 20m^2/g。在有些实施方案中，所述 BET 活性表面积范围为约 27.99m^2/g 至约 32.34m^2/g。在有些实施方案中，所述 BET 活性表面积选自 27.99m^2/g、28.87m^2/g 和 32.34m^2/g。在有些实施方案中，所述柠檬酸铁的固有溶出速率为 1.88-4.0mg/cm^2/min。

[0030] 在又一个方面，本公开提供降低 CKD 患者（例如终末期肾病患者）的红细胞生成刺激剂 (ESA) 使用的方法。在有些实施方案中，所述方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予所述患者，其中所述柠檬酸铁降低患者对给予一种或多种 ESA 的需求达选自以下的量 :20、21、22、23、24、25、26、27、28、29 和 30％，当给予至少 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供选自以下的中值 ESA 摄入量减少 ：27.0、27.1、27.2、27.3、27.4、27.5、27.6、27.7、27.9 和 28.0％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为 27.1％。在有些实施方案中，所述柠檬酸铁在 1 克片剂剂型中给予，每个剂型包含 210mg 的三价铁。在有些实施方案中，所述患者每天最多给予 18 个片剂剂型。在有些实施方案中，所述患者每天给予 6 个片剂剂型。在有些实施方案中，所述柠檬酸铁在该患者吃完正餐或点心的 1 小时以内给予。在有些实施方案中，所述患者在给予所述柠檬酸铁之前用一周三次血液透析或者用腹膜透析治疗至少 3 个月。在有些实施方案中，所述柠檬酸铁的 BET 活性表面积大于约 16m^2/g。在有些实施方案中，所述 BET 活性表面积范围为约 16m^2/g 至约 20m^2/g。在有些实施方案中，所述 BET 活性表面积范围为约 27.99m^2/g 至约 32.34m^2/g。在有些实施方案中，所述 BET 活性表面积选自 27.99m^2/g、28.87m^2/g 和 32.34m^2/g。在有些实施方案中，所述柠檬酸铁的固有溶出速率为 1.88-4.0mg/cm^2/min。

[0031] 详述

[0032] 在有些方面，本公开提供在慢性肾脏疾病 (CKD) 患者中使用柠檬酸铁以降低和 / 或控制血清磷水平、增加血清碳酸氢盐水平、改善一种或多种铁贮存参数 (例如，增加血清铁蛋白水平、增加转铁蛋白饱和度 (TSAT)、增加血红蛋白浓度)、增加铁吸收、维持铁贮存、治疗铁缺乏症、治疗贫血症、降低对静脉内铁剂的需求和 / 或降低对红细胞生成刺激剂 (ESA) 的需求的方法。在每一种情况下，该方法包括将柠檬酸铁给予 CKD 患者，包括非透析 CKD(ND-CKD) 患者以及终末期肾病 (ESRD) 患者。在有些方面，所述柠檬酸铁的给药历经一段长的时间周期，包括例如多达 52 周并且包括 52 周。在有些实施方案中，所述柠檬酸铁的给药历经多达 56 周并且包括 56 周的周期。

[0033] 在这些公开的方法的每一种中，柠檬酸铁可以在一段时间周期即至少 52 周内，和在有些实施方案中，多达 56 周或更长并且包括 56 周或更长时间内给予所述 CKD 患者。另外，在这些方法的每一种中，所述柠檬酸铁可以在含有 210mg 三价铁的 1g 片剂或小胶囊剂 (caplet) 剂型中口服给予所述 CKD 患者。多达 18 个片剂或小胶囊剂可以在一整天里给予。

[0034] 本公开也提供药物组合物，其也可以是铁补充剂，可以将其给予 CKD 患者。所述组合物 / 铁补充剂包含柠檬酸铁以及如下所述的其它药学上可接受的成分。所述组合物 / 铁补充剂配制成向 CKD 患者提供铁剂，并且由所述组合物 / 铁补充剂提供的铁量足以在 CKD 患者中增加铁吸收、改善一种或多种铁贮存参数、治疗铁缺乏症和 / 或治疗贫血症。所述组

合物 / 铁补充剂可以在如下所述的任何数量的剂型中提供。具体地说，所述组合物 / 铁补充剂可以作为口服片剂剂型提供。

[0035] 下面详细说明了柠檬酸铁、剂型、组合物、合成方法和使用方法的某些实施方案。所公开的实施方案不意欲构成对所述权利要求的限制。相反，所述权利要求意欲覆盖所有的替代、修改和等同方案。

[0036] 柠檬酸铁的治疗用途

[0037] 如下文更详细的说明，本文公开的是能够用于在 CKD 患者包括非透析 CKD (ND-CKD) 患者和终末期 (end state) 肾病 (ESRD) 患者中降低和 / 或控制血清磷水平、增加血清碳酸氢盐水平、改善一种或多种铁贮存参数 (例如，增加血清铁蛋白水平、增加转铁蛋白饱和度 (TSAT)、增加血红蛋白浓度)、增加铁吸收、维持铁贮存、治疗铁缺乏症、治疗贫血症、降低对静脉内铁剂的需求和 / 或降低对红细胞生成刺激剂 (ESA) 的需求的方法和剂型。

[0038] 因此，在各种不同的方面，本文公开的柠檬酸铁可以给予 CKD 患者以降低和 / 或控制血清磷。在各种不同的方面，本文公开的柠檬酸铁可以给予 CKD 患者以增加血清碳酸氢盐。在各种不同的方面，本文公开的柠檬酸铁可以给予 CKD 患者以改善一种或多种铁贮存参数，包括以增加血清铁蛋白，以增加转铁蛋白饱和度 (TSAT) 和以增加血红蛋白浓度。在各种不同的方面，本文公开的柠檬酸铁可以给予 CKD 患者以增加铁吸收。在各种不同的方面，本文公开的柠檬酸铁可以给予 CKD 患者以维持铁贮存。在各种不同的方面，本文公开的柠檬酸铁可以给予 CKD 患者以治疗铁缺乏症。在各种不同的方面，本文公开的柠檬酸铁可以给予 CKD 患者以治疗贫血症。在各种不同的方面，本文公开的柠檬酸铁可以给予 CKD 患者以降低对静脉内铁剂和 / 或红细胞生成刺激剂 (ESA) 的需求。

[0039] 治疗 CKD 患者的方法也被公开。在各种不同的方面，本公开提供降低和 / 或控制血清磷的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，其中所述柠檬酸铁提供血清磷的降低。在各种不同的方面，本公开提供增加血清碳酸氢盐的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，其中所述柠檬酸铁提供血清碳酸氢盐的增加。在各种不同的方面，本公开提供改善一种或多种铁贮存参数的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，其中所述柠檬酸铁提供一种或多种铁贮存参数的改善。在各种不同的方面，本公开提供增加血清铁蛋白的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，其中所述柠檬酸铁提供血清铁蛋白的增加。在各种不同的方面，本公开提供增加转铁蛋白饱和度 (TSAT) 的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，其中所述柠檬酸铁提供 TSAT 的增加。在各种不同的方面，本公开提供增加血红蛋白浓度的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，其中所述柠檬酸铁提供血红蛋白浓度的增加。在各种不同的方面，本公开提供增加铁吸收的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，其中所述柠檬酸铁提供铁吸收的增加。在各种不同的方面，本公开提供维持铁贮存的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，其中所述柠檬酸铁提供铁贮存的维持。在各种不同的方面，本公开提供治疗铁缺乏症的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，其中所述柠檬酸铁提供对铁缺乏症的治疗。在各种不同的方面，本公开提供治疗贫血症的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，其中所述柠檬酸铁提供对贫血症的治疗。在各种不同的方面，本公开提供在 CKD 患者中降低静脉内 (IV) 铁剂使用的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，其中所述柠檬酸铁降低 CKD 患者对给予静脉内铁剂的需求。在各种不同的方面，本公开提供在

CKD 患者中降低红细胞生成刺激剂 (ESA) 使用的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，其中所述柠檬酸铁当给予时降低 CKD 患者对给予一种或多种 ESA 的需求。在所述方法的每一种中，所述柠檬酸铁可以给予多达 52 周并且包括 52 周（包括多达 56 周并且包括 56 周）的时间周期。

[0040] 慢性肾脏疾病患者

[0041] 在各种不同的方面，将本文公开的柠檬酸铁给予任何慢性肾脏疾病 (CKD) 患者以治疗与 CKD（例如本文描述的 CKD) 相关的任何病症和紊乱。具有肾小球滤过率 (GFR)<60ml/min/1.73m^{2}持续 3 个月的所有个体都被分类为患有 CKD，不考虑肾脏损害的存在与否。那些需要透析或肾脏移植的 CKD 个体通常被称为终末期肾病 (ESRD) 患者。因此，当患者达到 CKD 的非透析依赖的较早分期的结论时，他或她在传统上被分类为 ESRD 患者。在此之前，那些患者被称为非透析依赖的 CKD 患者。然而，具有 CKD 晚期分期（例如 5 期）的患者（他们还没有开始透析或他们一直没有被推荐移植）也通常被称为非透析依赖的 CKD 患者。

[0042] 非透析 CKD(ND-CKD) 患者是已诊断为那些患有早分期的慢性肾脏疾病但还没有在医学上指导接受透析的患者。如上所述，美国国家肾脏基金会定义了慢性肾脏疾病的 5 个分期。典型地，在透析从医学角度讲是必需的之前，患者从 1 期进展到 4 期。

[0043] 如本文所用的，ND-CKD 意欲涵盖已诊断为患有慢性肾脏疾病但在所述柠檬酸铁的给药期间不接受透析的所有患者。这样的患者可包括例如从来没有经受过透析的患者，和在有些实施方案中，经受过透析但在所述柠檬酸铁的给药期间不接受透析的患者。

[0044] 在各种不同的方面，ESRD 患者典型地是已诊断为患有慢性肾脏疾病晚分期的患者。在有些例子中，短语“终末期肾病”用于指 CKD 的第五个分期。因此，如本文所用的，ESRD 患者是患有 CKD 的高级分期（例如 5 期）并且已经开始血液透析或腹膜透析和 / 或由卫生保健提供者已推荐进行肾脏移植的患者。

[0045] 在有些实施方案中，CKD 患者表现出下列特征中的一种或多种 ：血清磷水平介于 2.5mg/dL 和 8.0mg/dL 之间 ；当停用磷酸盐结合剂时，血清磷水平大于或等于 6.0mg/dL ；每天服用 3 到 18 粒以下成分的丸剂 ：醋酸钙、碳酸钙、碳酸镧、司维拉姆 (sevelamer)（碳酸盐或盐酸盐或等同的司维拉姆粉末）、起到磷酸盐结合剂作用的任何其它药剂或任何上述药剂的组合 ；血清铁蛋白水平为小于 1000mg/L ；转铁蛋白饱和水平 (TSAT) 在筛查时为小于 50％ ；预期寿命超过 1 年 ；或任何上述特征的组合。

[0046] 另外，CKD 患者可服用除柠檬酸铁之外的磷结合剂，尽管这并不是必需的。CKD 患者可以是哺乳动物，在有些实施方案中是人类。在有些实施方案中，CKD 患者是任何年龄和 / 或体重的女性或男性。在有些实施方案中，CKD 患者是年龄至少 18 岁并且一直在接受一周三次血液透析和 / 或腹膜透析至少 3 个月的男性或未怀孕、未哺乳的女性。

[0047] 血清磷

[0048] 磷酸盐对于入量的细胞过程是极其重要的。它是骨骼的重要组成成分之一和构成 DNA 和 RNA 的核酸的整体组成成分。另外，三磷酸腺苷 (ATP) 的磷酸键携带所有细胞功能所必需的能量。磷酸盐在骨、血清和尿液中作为缓冲剂起作用，并且在酶和蛋白质上添加磷酸基团和 / 或从酶和蛋白质上去除磷酸基团是调节其活性的常见机制。鉴于磷酸盐影响的广度，其稳态可理解地是一个受到高度调节的过程。

[0049] CKD 患者典型地证明了血清磷酸盐水平升高。在非 CKD 患者中，正常血清磷酸盐水

平应该是在 0.81mmol/L 和 1.45mmol/L 之间。在 CKD 患者中，然而，血清磷酸盐水平典型地随着肾脏功能丧失而明显增加，机体损失其通过尿液排泄磷酸盐的能力。这意味着 CKD 患者典型地经历高磷酸盐血症，高磷酸盐血症是一种电解质失衡，其中，在血液中有磷酸盐水平异常升高。高磷酸盐血症在大多数 CKD 患者中都会发生并且典型地与继发性甲状旁腺功能亢进和骨营养不良的进展相关。另外，在透析患者当中，高磷酸盐血症目前一直与心血管死亡率增加相关。为了减慢继发性甲状旁腺功能亢进的进展和降低血管钙化和心血管死亡率的风险，血清磷的适当控制在 CKD 患者的临床处理当中是至关重要的。在 CKD 患者中，控制血清磷酸盐水平所采取的典型措施包括膳食磷限制、透析和口服磷酸盐结合剂。遗憾的是，膳食限制在晚期分期的 CKD（例如 ESRD）中的效果很有限。因此，为了在 CKD 患者中限制膳食磷的吸收，口服磷酸盐结合剂是必需的。

[0050] 根据本文公开的方法进行治疗的 CKD 患者可经历血清磷酸盐水平的改善。在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者经历血清磷酸盐水平的降低。在有些实施方案中，本公开提供降低 CKD 患者的血清磷的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，例如终末期肾病患者或非透析慢性肾脏疾病患者，其中所述柠檬酸铁提供该患者的血清磷降低。在有些实施方案中，本公开提供治疗 CKD 患者的高磷酸盐血症的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，例如终末期肾病患者或非透析慢性肾脏疾病患者，其中所述柠檬酸铁提供该患者的血清磷降低。在有些实施方案中，本公开提供降低血清磷的方法，该方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予终末期肾病患者，其中所述柠檬酸铁提供该患者的血清磷降低。在有些实施方案中，所述柠檬酸铁给予持续 12 周的周期。在有些实施方案中持续 24 周的周期，在有些实施方案中持续 36 周的周期，在有些实施方案中持续 48 周的周期，在有些实施方案中持续 52 周的周期，和在有些实施方案中持续多达 56 周并且包括 56 周的周期。在有些实施方案中持续 53 周的周期。在有些实施方案中持续 54 周的周期，在有些实施方案中持续 55 周的周期。在有些实施方案中持续 56 周的周期。

[0051] 在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 1.00-3.00mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 1.10-2.90mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 1.20-2.80mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 1.30-2.70mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 1.40-2.60mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 1.50-2.50mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 1.60-2.40mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 1.70-2.30mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为1.80-2.20mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为1.90-2.10mg/dl。以上范围为了效率的目的以这种格式被公开，并且以上任何范围可以与任何方法、制剂或其组合相结合。

[0052] 在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 1.00-1.25mg/dl、1.00-1.50mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 1.00-1.75mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 1.00-2.00mg/dl。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :2.00-2.25mg/dl。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :2.00-2.50mg/dl。在有些实施方案

中，所述柠檬酸铁提供选自以下的平均血清磷降低 :2.00-2.75mg/dl。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :2.00-3.00mg/dl。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :1.00-2.25mg/dl。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :1.00-2.50mg/dl。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :1.00-2.75mg/dl。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :1.00-3.00mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 2.00-2.50mg/dl。以上范围为了效率的目的以这种格式被公开，并且以上任何范围可以与任何方法、制剂或其组合相结合。

[0053] 在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 1.00。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 1.10。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :大于大于 1.20。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 1.30。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 1.40。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 1.50。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 1.60。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 1.70。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 1.80。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 1.90。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 2.00。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 2.10。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 2.20。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 2.30。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 2.40。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 2.50。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 2.60。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 2.70。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于 2.80。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为大于2.90mg/dl。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方法、制剂、如下文公开的下边界或其组合相结合。

[0054] 在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于3.00mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于 2.90mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于2.80mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于2.70mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于 2.60mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于 2.50mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于 2.40mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于 2.30mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于2.20mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于2.10mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于 2.00mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于 1.90mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于1.80mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于 1.70mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于1.60mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清

磷降低为小于 1.50mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于 1.40mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于 1.30mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于 1.20mg/dl。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为小于 1.10mg/dl。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方法、制剂、以上公开的上边界或其组合相结合。

[0055] 在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为约 1.90、1.91、1.92、1.93、1.94、1.95、1.96、1.97、1.98、1.99、2.00、2.01、2.02、2.03、2.04、2.05、2.06、2.07、2.08、2.09 和 2.10mg/dl 中的一种，当给予 12 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为约 2.00mg/dl，当给予 12 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为约 2.10、2.11、2.12、2.13、2.14、2.15、2.16、2.17、2.18、2.19、2.20、2.21、2.22、2.23、2.24 和 2.25mg/dl 中的一种，当给予 24 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为约 2.20mg/dl，当给予 24 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为约 2.10、2.11、2.12、2.13、2.14、2.15、2.16、2.17、2.18、2.19 和 2.20mg/dl 中的一种，当给予 36 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为约 2.20mg/dl，当给予 36 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 1.95mg/dl、1.96、1.97、1.98、1.99、2.00、2.01、2.02、2.03、2.04、2.05、2.06、2.07、2.08、2.09、2.10、2.11、2.12、2.13、2.14 和 2.15mg/dl 中的一种，当给予 48 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为约 2.10mg/dl，当给予 48 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为约 1.95mg/dl，1.96、1.97、1.98、1.99、2.00、2.01、2.02、2.03、2.04、2.05、2.06、2.07、2.08、2.09、2.10、2.11、2.12、2.13、2.14、2.15、2.16、2.17、2.18、2.19、2.20、2.21、2.22、2.23、2.24、2.25、2.26、2.27、2.28、2.29 和 2.30mg/dl 中的一种，当给予 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为约 2.10mg/dl，当给予 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为约 .20、0.21、0.22、0.23、0.24、0.25、0.26、0.27、0.28、0.29、0.30、0.31、0.32、0.33、0.34 和 0.35mg/dl 中的一种，当给予 56 周的周期时，根据 52 周的基线来衡量。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 0.30mg/dl，当给予 56 周的周期时，根据 52 周的基线来衡量。

[0056] 在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :20-35％。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :20-35％、22-33％和 25-30％。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 27-28.5％。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 27-28.4％。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :大于 20、大于 21、大于 22、大于 23、大于 24、大于 25、大于 26、大于 27、大于 28、大于 29、大于 30、大于 31、大于 32、大于 33 和大于 34％。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :小于 35、小于 34、小于 33、小于 32、小于 33、小于 32、小于 31、小于 30、小于 29、小于 28、小于 27、小于 26、小于 25、小于 24、小于 23、小于 22 和小于 21％。

[0057] 在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :1.90、1.91、1.92、1.93、1.94、1.95、1.96、1.97、1.98、1.99、2.00、2.01、2.02、2.03、2.04、2.05、2.06、

2.07、2.08、2.09 和 2.10mg/dl，当给予 12 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 2.00mg/dl，当给予 12 周的周期时。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :2.10、2.11、2.12、2.13、2.14、2.15、2.16、2.17、2.18、2.19、2.20、2.21、2.22、2.23、2.24 和 2.25mg/dl，当给予 24 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 2.20mg/dl，当给予 24 周的周期时。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :2.10、2.11、2.12、2.13、2.14、2.15、2.16、2.17、2.18、2.19 和 2.20mg/dl，当给予 36 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 2.20mg/dl，当给予 36 周的周期时。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :1.95、1.96、1.97、1.98、1.99、2.00、2.01、2.02、2.03、2.04、2.05、2.06、2.07、2.08、2.09、2.10、2.11、2.12、2.13、2.14 和 2.15mg/dl，当给予 48 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 2.10mg/dl，当给予 48 周的周期时。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :1.95、1.96、1.97、1.98、1.99、2.00、2.01、2.02、2.03、2.04、2.05、2.06、2.07、2.08、2.09、2.10、2.11、2.12、2.13、2.14、2.15、2.16、2.17、2.18、2.19、2.20、2.21、2.22、2.23、2.24、2.25、2.26、2.27、2.28、2.29 和 2.30mg/dl，当给予 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 2.10mg/dl，当给予 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清磷降低 :0.20、0.21、0.22、0.23、0.24、0.25、0.26、0.27、0.28、0.29、0.30、0.31、0.32、0.33、0.34 和 0.35mg/dl，当给予 56 周的周期时，根据 52 周的基线来衡量。在有些实施方案中，所述柠檬酸铁提供平均血清磷降低为 0.30mg/dl，当给予 56 周的周期时，根据 52 周的基线来衡量。

[0058] 在有些实施方案中，所述柠檬酸铁提供如表 A 所示的平均血清磷降低 :

[0059] 表 A:

[0060]

平均血清磷(mg/dL)	安慰剂(n=91)	柠檬酸铁(n=92)
基线(52 周)	5.3	5.2
治疗结束[1] (56 周)	7.2	4.9
在 56 周时相对于基线的变化	1.9	-0.3
相对于安慰剂的最小二乘方(LS)平均差 p-值[2]		-2.3 p<0.0001

[0061] [1.] 对于缺失数据使用结转的最后观察。

[0062] [2]LS 平均治疗差异和 p- 值通过用治疗作为固定效应和基线作为协变量的 ANCOVA 模型来创建。

[0063] 在有些实施方案中，所述柠檬酸铁提供如表 B 所示的平均血清磷降低 :

[0064] 表 B:

[0065]

N=277	基线	周				
		12	24	36	48	52
柠檬酸铁平均血清磷(mg/dL)[1]	7.4	5.4	5.2	5.2	5.3	5.3
相对于基线的变化		-2.0	-2.2	-2.2	-2.1	-2.1
%相对于基线的变化		-27%	-30%	-30%	-28%	-28%
p-值		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

[0066] [1.] 对于缺失数据使用结转的最后观察。

[0067] 在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者（例如 ESRD 患者）经历其血清磷水平的维持，使得其血清磷水平在所述柠檬酸铁的给药期间基本上保持不变。

[0068] 血清碳酸氢盐

[0069] 代谢性酸中毒是当机体产生过多的酸时和 / 或当肾脏方法将足够的酸从机体排除时发生在 CKD 患者中的一种病症。如果不加以遏制，代谢性酸中毒会导致酸血症，血液 pH 降到 7.35 以下，这是由于机体产氢增加和 / 或机体方法在肾脏内形成碳酸氢盐 (HCO_3^-)。在 CKD 患者中，代谢性酸中毒的结果可以是严重的，包括昏迷和死亡。因此，重要的是使 CKD 患者在其血流中维持正常水平的碳酸氢盐。对于非 CKD 患者，血清碳酸氢盐的典型量度范围分别为 22mEq/L-28mEq/L 或 22mmol/L 至 28mmol/L。在 CKD 患者中，然而，血清碳酸氢盐浓度可以随着肾脏失去其产生碳酸氢盐的能力而大大地降低。

[0070] 根据本文公开的方法进行治疗的 CKD 患者可经历血清碳酸氢盐浓度的增加。在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者经历血清碳酸氢盐浓度的增加。在有些实施方案中，本公开提供增加 CKD 患者（例如 ESRD 患者或 ND-CKD 患者）血清碳酸氢盐浓度的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，其中所述柠檬酸铁提供该患者的血清碳酸氢盐浓度的增加。在有些实施方案中，本公开提供增加血清碳酸氢盐浓度的方法，该方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予 CKD 患者，其中所述柠檬酸铁提供该患者的血清碳酸氢盐浓度的增加。在有些实施方案中，所述患者每天最多给予 18 个片剂剂型。在有些实施方案中，所述柠檬酸铁给予持续 12 周的周期，在有些实施方案中持续 36 周的周期，在有些实施方案中持续 52 周的周期，和在有些实施方案中持续多达并且包括 56 周的周期。

[0071] 在有些实施方案中，所述柠檬酸铁提供该患者的平均血清碳酸氢盐浓度增加为 0.1-1.0mEq/L。在有些实施方案中，所述柠檬酸铁提供该患者的选自以下的平均血清碳酸氢盐浓度增加 :0.70、0.71、0.72、0.73、0.74、0.75、0.76、0.77、0.78、0.79 和 0.80mEq/L。在有些实施方案中，所述柠檬酸铁提供该患者的平均血清碳酸氢盐浓度增加为 0.71mEq/L。

[0072] 在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加大于 0.70mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加大于 0.71mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加大于 0.72mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加大于 0.73mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加大于 0.74mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加大于 0.75mEq/L。在有些实施方案中，所述柠檬

酸铁提供平均血清碳酸氢盐浓度增加大于0.76mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加大于0.77mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加大于0.78mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加大于0.79mEq/L。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方法、制剂、如下文公开的下边界或其组合相结合。

[0073] 在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加小于0.80mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加小于0.79mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加小于0.78mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加小于0.77mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加小于0.76mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加小于0.75mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加小于0.74mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加小于0.73mEq/L。在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加小于0.72mEq/L。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方法、制剂、以上公开的上边界或其组合相结合。

[0074] 在有些实施方案中，所述柠檬酸铁提供平均血清碳酸氢盐浓度增加为0.71mEq/L，当给予52周的周期时。

[0075] 在有些实施方案中，根据本文公开的方法进行治疗的CKD患者（例如ESRD患者）经历其血清碳酸氢盐浓度的维持，使得其血清碳酸氢盐水平在所述柠檬酸铁的给药期间基本上保持不变。

[0076] 铁贮存参数

[0077] 患有CKD的患者可证明系统性铁状态的标志物低下或不足。这意味着CKD患者在其体内可能没有贮存足够的铁来维持恰当的铁水平。在工业化国家生活的多数营养良好的非CKD人在其体内贮存的铁大约为4克到5克。这种铁约2.5g含在血红蛋白中，血红蛋白携带着氧通过血液。余下的多半约1.5克到2.5克铁含在所有细胞中存在的铁结合复合物中，但是在骨髓和例如肝脏和脾脏等器官中更高度浓缩。肝脏的铁贮存量在非CKD身体中是铁的主要生理储备。在机体的总铁含量中，约400mg用在使用铁进行细胞过程例如氧贮存（肌红蛋白）或进行产能量的氧化还原反应（细胞色素蛋白）的蛋白质中。除了贮存的铁之外，少量的铁，典型地约3-4mg通过与称为转铁蛋白的蛋白质结合的血浆进行循环。因为其毒性，游离的可溶性二价铁（铁(II)或Fe^{2+}）在体内通常保持在低浓度下。

[0078] 铁缺乏症首先使机体内的贮存铁耗尽。因为多数被机体利用的铁是血红蛋白所必需的，所以缺铁性贫血症是铁缺乏症的主要临床表现。将氧运输到组织中对于人生命是多么重要，而严重的贫血伤害或杀死患有CKD的病人，包括ND-CKD患者和ESRD患者，因为剥夺了其含氧器官。铁缺乏的CKD患者将在细胞用完进行细胞内过程所需的铁之前，患上因氧充分耗尽引起的器官损伤，和在有些例子中可能死于因氧充分耗尽引起的器官损伤。

[0079] 有一些系统性铁状态标志物可以进行测量以确定CKD患者是否有足够的铁贮存来维持足够的健康。这些标志物可以是循环铁贮存、铁-结合复合物中贮存的铁或它们二者，也通常称为铁贮存参数。铁贮存参数可包括，例如，红细胞比容、血红蛋白浓度(Hb)、总铁结合能力(TIBC)、转铁蛋白饱和度(TSAT)、血清铁水平、肝脏铁水平、脾脏铁水平和血清

铁蛋白水平。其中，红细胞比容、血红蛋白浓度 (Hb)、总铁结合能力 (TIBC)、转铁蛋白饱和度 (TSAT) 和血清铁水平通常被称为循环铁贮存。肝脏铁水平、脾脏铁水平和血清铁蛋白水平通常被称为贮存铁或在铁 - 结合复合物中贮存的铁。

[0080] 在有些实施方案中，本公开提供改善有其需要的患者的一种或多种铁贮存参数的方法。在有些实施方案中，所述方法包括将柠檬酸铁以每天约 1g 至约 18g 的剂量范围口服给予 CKD 患者，例如非透析慢性肾脏疾病患者或终末期肾病患者。在有些实施方案中，至少一种铁贮存参数可选自血清铁蛋白水平、转铁蛋白饱和度 (TSAT)、血红蛋白浓度、红细胞比容、总铁结合能力、铁吸收水平、血清铁水平、肝脏铁水平、脾脏铁水平和它们的组合。在有些实施方案中，所述柠檬酸铁在 1 克片剂剂型中给予。在有些实施方案中，所述患者每天最多给予 18 个片剂剂型。在有些实施方案中，所述柠檬酸铁给予持续 12 周的周期，在有些实施方案中持续 36 周的周期，在有些实施方案中持续 52 周的周期，和在有些实施方案中持续多达并且包括 56 周的周期。

[0081] 在另一个实施方案中，至少一种铁贮存参数是红细胞比容，且改善包括增加患者的红细胞比容。在其它的实施方案中，至少一种铁贮存参数是血红蛋白浓度，且改善包括增加患者的血红蛋白浓度。在又一些实施方案中，至少一种铁贮存参数是总铁结合能力，且改善包括降低患者的总铁结合能力。在又一些实施方案中，至少一种铁贮存参数是转铁蛋白饱和度，且改善包括增加患者的转铁蛋白饱和度。在又一些实施方案中，至少一种铁贮存参数是血清铁水平，且改善包括增加患者的血清铁水平。在又一些实施方案中，至少一种铁贮存参数是肝脏铁水平，且改善包括增加患者的肝脏铁水平。在又一些实施方案中，至少一种铁贮存参数是脾脏铁水平，且改善包括增加患者的脾脏铁水平。在又一个实施方案中，至少一种铁贮存参数是血清铁蛋白水平，且改善包括增加患者的血清铁蛋白水平。

[0082] 血清铁蛋白

[0083] 肝脏贮存的铁蛋白是机体内贮存铁的主要来源。铁蛋白是一种细胞内蛋白，该蛋白贮存铁并以受控方式释放它。从医学角度讲，血液样品和 / 或肝脏组织样品中存在的铁蛋白量反映出肝脏内贮存的铁量 (尽管铁蛋白是普遍存在的并可以在机体内除肝脏之外的许多其它组织中发现)。铁蛋白以无毒形式将铁贮存在肝脏内并将其运输到有需要的部位。在非 CKD 患者中，正常铁蛋白血液血清水平，有时称为参比区间 (reference interval)，对于男性通常在 30-300ng/ml 之间，对于女性通常在 15-200ng/ml 之间。在 CKD 患者中，然而，血清铁蛋白水平典型地随着被铁蛋白结合及在肝脏内贮存的可利用的铁量减少而明显降低，这种情况发生在机体失去了其吸收和贮存铁的能力时。

[0084] 在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者经历血清铁蛋白水平增加。在有些实施方案中，本公开提供增加有其需要的患者的血清铁蛋白的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，例如 ESRD 患者或 ND-CKD 患者，其中所述柠檬酸铁提供血清铁蛋白增加。在有些实施方案中，本公开提供增加血清铁蛋白的方法，该方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予 CKD 患者，其中所述柠檬酸铁提供该患者的血清铁蛋白增加。在有些实施方案中，所述柠檬酸铁给予持续 12 周的周期，在有些实施方案中持续 24 周的周期，在有些实施方案中持续 36 周的周期，在有些实施方案中持续 48 周的周期，和在有些实施方案中持续 52 周的周期。

[0085] 在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 100-400ng/ml。在

有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 110-390ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 120-380ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 130-370ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为约 140-360ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 150-350ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 160-340ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 170-330ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 180-320ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 190-310ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 200-300ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 210-290ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 220-280ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 230-270ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 240-260ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 100-400ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 100-375ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 100-350ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 100-325ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 100-300ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 100-275ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 150-310ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 151-309ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 152-308ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 153-307ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 154-306ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 155-306ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 155-305ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 155-304ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 155-303ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 155-302ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 150-305ng/ml。以上范围为了效率的目的以这种格式被公开，并且以上任何范围可以与任何方法、制剂或其组合相结合。

[0086] 在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 302ng/ml，当给予 52 周的周期时。

[0087] 在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 100ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 110ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 120ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 130ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 140ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 150ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 160ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 170ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 180ng/ml。在有些实施方案中，所述柠檬

酸铁提供平均血清铁蛋白增加大于 190ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 200ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 210ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 220ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 230ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 240ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 250ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 260ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 270ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 280ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 290ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 300ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 310ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 320ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 330ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 340ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 350ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 360ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于370ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 380ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 390ng/ml。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方法、制剂、如下文公开的下边界或其组合相结合。

[0088] 在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清铁蛋白增加：小于 400ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 390ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 380ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 370ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 360ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 350ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 340ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 330ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 320ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 310ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 300ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 290ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 280ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 270ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 260ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 250ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 240ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 230ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 220ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 210ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 200ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 190ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 180ng/ml。在有些实施方案中，所

述柠檬酸铁提供平均血清铁蛋白增加小于 170ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 160ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 150ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 140ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 130ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 120ng/ml。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 110ng/ml。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方法、制剂、如上公开的上边界或其组合相结合。

[0089] 在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清铁蛋白增加：约 280、281、282、283、284、285、286、287、288、289、290、291、292、293、294、295、296、297、298、299、300、301、302、303、304、305、306、307、308、309 和 310mg/dl，当给予 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 302mg/dl，当在 52 周的周期内给予时。

[0090] 在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为约 1-100％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为约 10-90％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为约 20-80％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为约 30-70％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为约 40-60％。

[0091] 在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清铁蛋白增加：40、41、42、43、44、45、46、47、48、49、50、51、52、53、54、55、56、57、58、59 和 60％。在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清铁蛋白增加：48.0、48.1、48.2、48.3、48.4、48.5、48.6、48.7、48.9、49.0、49.1、49.2、49.3、49.4、49.5、49.6、49.7、49.8、49.9、50.0、50.1、50.2、50.3、50.4、50.5、50.6、50.7、50.8、50.9 和 50.8％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 50.8％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 50.8％，当给予 52 周的周期时。

[0092] 在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 1％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 10％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 20％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 30％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 40％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 50％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 60％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 70％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 80％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加大于 90％。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方法、制剂、如下文公开的下边界或其组合相结合。

[0093] 在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 100％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 90％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 80％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 70％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小

于 60％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 50％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 40％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 30％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 20％。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加小于 10％。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方方、制剂、以上公开的上边界或其组合相结合。

[0094] 在有些实施方案中，所述柠檬酸铁提供选自以下的平均血清铁蛋白增加：49.0、49.1、49.2、49.3、49.4、49.5、49.6、39.7、49.8、49.9 和 50.0％，当给予 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均血清铁蛋白增加为 49.2％，当给予 52 周的周期时。

[0095] 在有些实施方案中，所述柠檬酸铁提供如表 C 所示的平均血清铁蛋白增加：

[0096] 表 C:

[0097]

平均铁蛋白(ng/mL)[1]	活性剂对照 (n=134)	柠檬酸铁 (n=249)
基线(第 0 天)	616	595
第 12 周	657	751
第 24 周	658	847
第 36 周	636	863
第 48 周	627	882
第 52 周	625	897
在第 52 周相对于基线的变化 %相对于基线的变化	9 1.5%	302 50.8%
在第 52 周相对于活性剂对照组的 LS 平均差异[2] p-值[2]		286 p<0.0001

[0098] [1] 对于缺失数据使用结转的最后观察。

[0099] [2] LS 平均治疗差异和 p- 值通过用治疗作为固定效应和基线作为协变量的 ANCOVA 模型来创建。

[0100] 在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者（例如 ESRD 患者）经历其血清铁蛋白水平的维持，使得其血清铁蛋白水平在所述柠檬酸铁的给药期间基本上保持不变。

[0101] 转铁蛋白饱和度 (TSAT)

[0102] 除了贮存的铁之外，少量的铁，典型地约 3-4mg 通过与称为转铁蛋白的蛋白质结合的血浆循环。因此，血清铁水平可以由血液中与转铁蛋白结合的铁循环量来表示。转铁蛋白是一种由肝脏产生的糖蛋白，可结合一个或两个三价铁（铁 (III) 或 Fe^{3+}）离子。它是血液中最普遍和最动态的铁载体，因此是机体运输贮存铁供全身使用的能力的必需组分。转铁蛋白饱和度（或 TSAT）测得为百分比并计算为血清铁和总铁结合能力的比率，乘以 100。该值告诉临床医生多少血清铁实际上与可用于结合铁的转铁蛋白总量相结合。举例来说，TSAT 值为 35％是指在血液样品中，转铁蛋白的可利用的铁结合位点的 35％被铁占据。在非 CKD 患者中，典型的 TSAT 值对于男性为大约 15-50％而对于女性为大约 12-45％。在 CKD 患

者中，然而，TSAT 值典型地随着被转铁蛋白结合的可利用的铁量减少而明显降低，这种情况发生在机体失去了其吸收和贮存铁的能力时。

[0103] 在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者经历 TSAT 值增加。在有些实施方案中，本公开提供增加有其需要的患者的转铁蛋白饱和度 (TSAT) 的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，例如 ESRD 患者或 ND-CKD 患者，其中所述柠檬酸铁提供该患者的 TSAT 增加。在有些实施方案中，本公开提供增加转铁蛋白饱和度 (TSAT) 的方法，该方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予终末期肾病患者，其中所述柠檬酸铁提供该患者的 TSAT 增加。在有些实施方案中，所述柠檬酸铁给予持续 12 周的周期，在有些实施方案中持续 24 周的周期，在有些实施方案中持续 36 周的周期，在有些实施方案中持续 48 周的周期，和在有些实施方案中持续 52 周的周期。

[0104] 在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加为 1-20％。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加为 1-15％。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加为 1-12％。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加为 5-12％。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加为 5-10％。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加为 6-9％。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加为 8％。

[0105] 在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加大于 1％。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加大于 2％。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加大于 3％。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加大于 4％。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加大于 5％。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加大于 6％。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加大于 7％。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加大于 8％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加大于 9％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加大于 10％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加大于 11％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加大于 12％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加大于 13％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加大于 14％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加大于 15％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加大于 16％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加大于 17％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加大于 18％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加大于 19％。以上边界为了效率的目的以这种格式被公开，并且以上任何范围可以与任何方法、制剂、如下文公开的下边界或其组合相结合。

[0106] 在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加小于 20％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 19％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 18％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 17％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 16％。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 15％。在有些实施方案中，所述

柠檬酸铁提供平均 TSAT 增加小于 14%。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 13%。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 12%。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 11%。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 10%。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 9%。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 8%。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 7%。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 6%。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 5%。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 4%。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 3%。在有些实施方案中，所述柠檬酸铁提供平均 TSAT 增加小于 2%。以上边界为了效率的目的以这种格式被公开，并且以上任何范围可以与任何方法、制剂、以上公开的上边界或其组合相结合。

[0107] 在有些实施方案中，所述柠檬酸铁提供选自以下的平均转铁蛋白饱和度 (TSAT) 增加 :5%、6%、7%、8%、9%、10%、11%、12%、13%、14%、15%、16%、17%和 18%，当给予 52 周的周期时。在有些实施方案中，所述柠檬酸铁提供平均转铁蛋白饱和度 (TSAT) 增加为 8%，当给予 52 周的周期时。

[0108] 在有些实施方案中，所述柠檬酸铁提供如表 D 所示的平均转铁蛋白饱和度 (TSAT) 增加 :

[0109] 表 D:

[0110]

平均 TSAT (%)[1]	活性剂对照 (n=131)	柠檬酸铁 (n=244)
基线(第 0 天)	31	31
第 12 周	31	40
第 24 周	32	40
第 36 周	30	40
第 48 周	29	41
第 52 周	30	39
在第 52 周相对于基线的变化 %相对于基线的变化	-1 -3.2%	8 25.8%
在第 52 周相对于活性剂对照组的 LS 平均差异 [2] p-值 [2]		10 p<0.0001

[0111] [1] 对于缺失数据使用结转的最后观察。

[0112] [2] LS 平均治疗差异和 p- 值通过用治疗作为固定效应和基线作为协变量的 ANCOVA 模型来创建。

[0113] 在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者 (例如 ESRD 患者) 经历其 TSAT 值的维持，使得其转铁蛋白饱和度 (TSAT) 值在所述柠檬酸铁的给药期间基本上保持不变。

[0114] 红细胞比容

[0115] 红细胞比容 (hematocrit)，也称为红细胞压积 (packed cell volume) 或红细胞容

积分数(erythrocyte volume fraction),是红细胞在血液中所占容积的百分比。对于非CKD患者,红细胞比容对于男性典型地为血液容积的约45%而对于妇女典型地为血液容积的约40%。在CKD患者中,然而,红细胞比容通常由于铁吸收差和/或铁贮存能力差而显著耗尽。

[0116] 本文公开的柠檬酸铁可以给予CKD患者以增加红细胞比容。准确的给药时间将必需视患者的不同而异,取决于例如CKD患者所经历的CKD严重程度、患者正在经历或没有经历的铁吸收水平和治疗保健专业人士的判断。在有些实施方案中,本公开提供增加有其需要的患者的红细胞比容的方法,该方法包括将柠檬酸铁口服给予CKD患者,例如ESRD患者或ND-CKD患者,其中所述柠檬酸铁提供该患者的红细胞比容增加。在有些实施方案中,本公开提供增加CKD患者的红细胞比容的方法,该方法包括将柠檬酸铁以范围为210mg-2,520mg的三价铁剂量口服给予所述患者,其中所述柠檬酸铁该患者的红细胞比容增加。在有些实施方案中,所述柠檬酸铁给予52周的周期。在有些实施方案中,所述增加为1%至30%。在有些实施方案中,所述增加为1%至20%。在有些实施方案中,所述增加为1%至15%,在有些实施方案中,所述增加为1%至12%,在有些实施方案中,所述增加为1%至10%,在有些实施方案中,所述增加为1%至9%,在有些实施方案中,所述增加为1%至8%,在有些实施方案中,所述增加为1%至7%,在有些实施方案中,所述增加为1%至6%,在有些实施方案中,所述增加为1%至5%,在有些实施方案中,所述增加为1%至4%,在有些实施方案中,所述增加为1%至3%,和在有些实施方案中,所述增加为1%至2%。

[0117] 在有些实施方案中,根据本文公开的方法进行治疗的CKD患者(例如ESRD患者)经历其红细胞比容水平的维持,使得其血液中红细胞的总容积在所述柠檬酸铁的给药期间基本上保持不变。

[0118] 血红蛋白浓度

[0119] 血红蛋白浓度,也称为平均小体(corpuscular)血红蛋白浓度或MCHC,是血红蛋白在给定的红细胞压积中所占浓度的一种度量。典型地,将血红蛋白的总量除以红细胞比容计算得出血红蛋白浓度。血红蛋白浓度也可以测得为质量或重量分数并用百分数(%)表示。从数值上讲,然而,血红蛋白浓度的质量或摩尔度量及质量或重量分数(%)是完全相同的,假定红细胞密度为1g/ml,血浆中的血红蛋白损失可忽略不计。对于非CKD患者,典型的血红蛋白浓度的质量或摩尔度量范围分别为32g/dl-36g/dl或4.9mmol/L到5.5mmol/L。在CKD患者中,然而,血红蛋白浓度可以随着机体失去了其吸收和贮存铁的能力而大大地降低。

[0120] 在有些实施方案中,根据本文公开的方法进行治疗的CKD患者经历血红蛋白浓度增加。在有些实施方案中,本公开提供增加有其需要的患者的血红蛋白浓度的方法,该方法包括将柠檬酸铁口服给予CKD患者,例如ESRD患者或ND-CKD患者,其中所述柠檬酸铁提供该患者的血红蛋白浓度增加。在有些实施方案中,本公开提供增加血红蛋白浓度的方法,该方法包括将柠檬酸铁以范围为210mg-2,520mg的三价铁剂量口服给予CKD患者,其中所述柠檬酸铁提供该患者的血红蛋白浓度增加。在有些实施方案中,所述柠檬酸铁给予持续12周的周期,在有些实施方案中持续24周的周期,在有些实施方案中持续36周的周期,在有些实施方案中持续48周的周期,和在有些实施方案中持续52周的周期。

[0121] 在有些实施方案中,所述柠檬酸铁提供平均血红蛋白浓度增加为0.1-5.0g/dl。在

有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加为0.1-4.0g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加为0.1-3.0g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加为0.1-2.0g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加为0.1-1.0g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加为0.2-0.9g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加为0.3-0.8g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加为0.3-0.7g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加为0.3-0.6g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加为0.3-0.5g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加为0.4g/dl。

[0122] 在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加大于0.1g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加大于0.2g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加大于0.3g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加大于0.4g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加大于0.5g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加大于0.6g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加大于0.7g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加大于0.8g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加大于0.9g/dl。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方法、制剂、如下文公开的下边界或其组合相结合。

[0123] 在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加小于1.0g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加小于0.9g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加小于0.8g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加小于0.7g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加小于0.6g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加小于0.5g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加小于0.4g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加小于0.3g/dl。在有些实施方案中，所述柠檬酸铁提供平均血红蛋白浓度增加小于0.2g/dl。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方法、制剂、以上公开的上边界或其组合相结合。

[0124] 在有些实施方案中，所述柠檬酸铁提供如表E所示的平均血红蛋白浓度增加：

[0125] 表E:

[0126]

平均血红蛋白(g/dL)[1]	活性剂对照 (n=130)	柠檬酸铁 (n=244)
基线(第0天)	11.7	11.6
第52周	11.1	11.4
在第52周相对于基线的变化	-0.6	-0.2
在第52周相对于活性剂对照组的LS平均差异[2] p-值[2]		0.4 p<0.0105

[0127] [1.]对于缺失数据使用结转的最后观察。

[0128] [2.]LS 平均治疗差异和 p- 值通过用治疗作为固定效应和基线作为协变量的 ANCOVA 模型来创建。

[0129] 在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者（例如 ESRD 患者）经历其血红蛋白浓度的维持，使得其血红蛋白水平在所述柠檬酸铁的给药期间基本上保持不变。

[0130] 总铁结合能力 (TIBC)

[0131] 总铁结合能力 (TIBC) 是血液中铁与转铁蛋白结合的能力的度量。典型地，抽取血液样品并测量该样品可携带的最大铁量，得出 TIBC。因此，TIBC 间接地测量转铁蛋白，转铁蛋白是血液中转运铁的一种蛋白质。对于非 CKD 患者，典型的 TIBC 的质量或摩尔度量是分别在 250-370μg/dL 或 45-66μmol/L 的范围内。在 CKD 患者中，然而，TIBC 典型地增加超出这些水平，因为机体必须产生更多的转铁蛋白才能将铁递送到红细胞前体细胞以产生血红蛋白。

[0132] 在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者经历 TIBC 降低。在有些实施方案中，本公开提供降低有其需要的患者的 TIBC 的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，例如 ESRD 患者或 ND-CKD 患者，其中所述柠檬酸铁提供该患者的 TIBC 降低。在有些实施方案中，本公开提供降低 CKD 患者的 TIBC 的方法，该方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予所述患者，其中所述柠檬酸铁提供该患者的 TIBC 降低。在有些实施方案中，所述柠檬酸铁给予 52 周的周期。在有些实施方案中，所述降低为 0.1％至 30％，在有些实施方案中，所述降低为 0.1％至 28％，在有些实施方案中，所述降低为 0.1％至 26％，在有些实施方案中，所述降低为 0.1％至 25％，在有些实施方案中，所述降低为 0.1％至 24％，在有些实施方案中，所述降低为 0.1％至 23％，在有些实施方案中，所述降低为 0.1％至 22％，在有些实施方案中，所述降低为 0.1％至 21％，在有些实施方案中，所述降低为 0.1％至 20％，在有些实施方案中，所述降低为 0.1％至 15％，在有些实施方案中，所述降低为 0.1％至 10％，和在有些实施方案中，所述降低为 0.1％至 5％。

[0133] 在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者（例如 ESRD 患者）经历其 TIBC 的维持，使得其 TIBC 水平在所述柠檬酸铁的给药期间基本上保持不变。

[0134] 铁吸收

[0135] CKD 患者可受累铁吸收低下或不至，这可导致其它的健康担心，例如铁耗尽和贫血症。对于人类，大多数从食物或补充剂中吸收的铁在小肠内、特别是在十二指肠内被十二指肠内衬 (lining) 中存在的特化肠上皮细胞吸收。这些细胞可以将转运分子特异化，允许它们将铁从肠内腔移动到机体其它部位。为了被吸收，膳食铁必须作为蛋白质的组成部分（例如血红素）存在，或者它必须是呈二价铁（铁 (II) 或 Fe^{2+}）形式。肠上皮细胞表达三价铁还原酶 Dcytb，Dcytb 将三价铁（铁 (III) 或 Fe^{3+}）还原成二价铁。然后，二价金属转运蛋白将铁转运跨越肠上皮细胞的细胞膜后进入细胞内。

[0136] 在非 CKD 人中，机体通过改变与这些步骤中的一个或多个有关的蛋白质的表达水平来调节铁水平。例如，在对缺铁性贫血应答时，细胞可能会产生更多的 Dcytb 酶和更多的金属转运蛋白以便增加从肠内腔吸收的铁量，在 CKD 患者中，机体调节这些步骤中的一个或多个的能力受损，进而导致铁吸收降低或不足。

[0137] 根据本文公开的方法进行治疗的CKD患者可经历铁吸收增加。在有些实施方案中，被吸收的铁由给予CKD患者的柠檬酸铁提供；它是三价铁离子，从肠内腔吸收进入机体内。因为柠檬酸铁经口服给予，所以增加的铁吸收发生在整个肠。尽管不希望受任何理论的束缚，但是相信增加的铁吸收可归因于向CKD患者给予的柠檬酸铁中柠檬酸盐的存在。一些研究表明，铁结合柠檬酸盐（柠檬酸的共轭碱）一起给药起到显著地增加（例如，数倍于）从膳食来源吸收的铁量（参见例如，Ballot等人，Br.J.Nutr.(1987)57,331-343；Gillooly等人，Br.J.Nutr.(1983)49,331-342；Zhang等人，Eur.J.Nutr.(2007)46,95-102；和Salovaara等人，J.Agric.Food Chem.(2002)50,6233-6238)。

[0138] 本文公开的柠檬酸铁可以给予CKD患者以增加铁吸收。准确的给药时间将必需视患者的不同而异，取决于例如CKD患者所经历的CKD分期、患者正在经历或没有经历的铁吸收水平和治疗保健专业人士的判断。在有些实施方案中，本公开提供增加终末期肾病患者的铁吸收的方法，该方法包括将柠檬酸铁口服给予所述患者，其中所述柠檬酸铁提供该患者吸收的铁量增加。在有些实施方案中，本公开提供增加终末期肾病患者的铁吸收的方法，该方法包括将柠檬酸铁以范围为210mg-2,520mg的三价铁剂量口服给予所述患者，其中所述柠檬酸铁提供该患者吸收的铁量增加。在有些实施方案中，所述柠檬酸铁给予52周的周期。

[0139] 铁缺乏症和贫血症

[0140] 如上所述，在工业化国家生活的多数营养良好的非CKD人在其体内以某种方式（例如，作为循环铁或贮存铁或它们二者）贮存的铁大约为4克到5克。该量的减少代表铁缺乏，铁缺乏在CKD患者中很常见。在CKD患者中，铁缺乏的症状可出现在该病症进展到缺铁性贫血之前。铁缺乏的症状其中可包括例如疲乏、眩晕、苍白、脱发、易怒、虚弱、异食癖、脆性或沟槽甲、普鲁默-文森综合症（覆盖舌、咽和食管的黏膜的疼痛性萎缩）、免疫功能受损、食冰癖和不宁腿综合症。

[0141] 根据本文公开的方法进行治疗的CKD患者可经历铁缺乏症改善。在有些实施方案中，根据本文公开的方法进行治疗的CKD患者经历铁缺乏症减轻。这种减轻可随着本文公开的柠檬酸铁的给药增加了CKD患者身体内铁总量而出现。在有些实施方案中，根据本文公开的方法进行治疗的CKD患者经历铁缺乏症的一种或多种症状减少，其中所述症状选自疲乏、眩晕、苍白、脱发、易怒、虚弱、异食癖、脆性或沟槽甲、普鲁默-文森综合症（覆盖舌、咽和食管的黏膜的疼痛性萎缩）、免疫功能受损、食冰癖、不宁腿综合症和上述症状的组合。在有些实施方案中，根据本文公开的方法进行治疗的CKD患者经历铁缺乏症的一种或多种症状的消除，其中所述症状选自疲乏、眩晕、苍白、脱发、易怒、虚弱、异食癖、脆性或沟槽甲、普鲁默-文森综合症（覆盖舌、咽和食管的黏膜的疼痛性萎缩）、免疫功能受损、食冰癖、不宁腿综合症和上述症状的组合。

[0142] 在有些实施方案中，所述铁缺乏症是贫血症。在有些实施方案中，所述铁缺乏症是缺铁性贫血症。缺铁性贫血症以循环红细胞水平低下为特征，在CKD患者中，可由铁的膳食摄入、吸收和/或贮存不足够引起。红细胞含有血红蛋白中结合的铁并且典型地在机体内铁量缺乏时不形成。

[0143] 缺铁性贫血症的典型特征为苍白（皮肤和黏膜中的氧合血红蛋白降低所致的苍白颜色）、疲乏、头晕和虚弱。然而，缺铁性贫血症的体征可以视CKD患者的不同而异。因为

CKD 患者中的铁缺乏症倾向于慢慢地发生，适应于疾病时可以发生，它可能有一段时间未被认识。在有些例子中，CKD 患者可发生呼吸困难（麻烦的呼吸）、异食癖（不寻常迷恋的食物渴望）、常常导致 OCD 型强迫症和痴迷的焦虑症、易怒或悲伤、咽喉痛、便秘、嗜睡、耳鸣、口腔溃疡、心悸、脱发、昏倒或感到晕眩、抑郁症、用力时呼吸急促、抽搐的肌肉、浅黄色皮肤、麻刺感（麻木）或烧灼感、错过月经周期、经量多的月经周期、缓慢社会发展、舌炎（舌的炎症或感染）、口角唇炎（嘴角的炎性病变）、凹甲（匙状甲）或虚弱甲或脆性甲、食欲不振、瘙痒症（广泛性瘙痒）、普鲁默 - 文森综合症（覆盖舌、咽和食管的黏膜的疼痛性萎缩）和不宁腿综合症，等等。

[0144] 贫血症典型地基于测量来自患者的血液样品中的完全血细胞计数做出诊断。典型地，用自动计数器来报告样品中的红细胞总数、血红蛋白水平和通过流式细胞术的红细胞大小。然而，显微镜载玻片上的染色血涂片可以使用显微镜来检查以便统计样品中的红细胞总数并且对贫血症做出诊断。在许多国家，测量四种参数（红细胞计数、血红蛋白浓度、平均小体体积和红细胞分布宽度）以确定贫血症的存在。世界卫生组织设定了血红蛋白水平的某些阈值 (Hb)，使得当 CKD 患者的血红蛋白水平降到那些值以下时，就可以对贫血症做出诊断。那些值是 ：对于年龄 0.5-5.0 岁的儿童，Hb ＝ 11.0g/dL 或 6.8mmol/L ；对于年龄 5-12 岁的儿童，Hb ＝ 11.5g/dL 或 7.1mmol/L ；对于年龄 12-15 岁的青少年，Hb ＝ 12.0g/dL 或 7.4mmol/L ；对于年龄 15 岁及以上的未怀孕妇女，Hb ＝ 12.0g/dL 或 7.4mmol/L ；对于怀孕妇女，Hb ＝ 11.0g/dL 或 6.8mmol/L ；和对于年龄超过 15 岁的男性，Hb ＝ 13.0g/dL 或 8.1mmol/L。

[0145] 根据本文公开的方法进行治疗的 CKD 患者可经历贫血症改善。根据本文公开的方法进行治疗的 CKD 患者可经历缺铁性贫血症改善。在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者经历贫血症或缺铁性贫血症的一种或多种症状减少。在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者经历贫血症或缺铁性贫血症的一种或多种症状的消除。在有些实施方案中，所述贫血症或缺铁性贫血症的一种或多种症状选自苍白、疲乏、头晕、虚弱、呼吸困难、异食癖、焦虑、易怒或悲伤、咽喉痛、便秘、嗜睡、耳鸣、口腔溃疡、心悸、脱发、昏倒或感到晕眩、抑郁症、用力时呼吸急促、抽搐的肌肉、浅黄色皮肤、麻刺感（麻木）或烧灼感、错过月经周期、经量多的月经周期、缓慢社会发展、舌炎、口角唇炎、凹甲、食欲不振、瘙痒症、普鲁默 - 文森综合症、不宁腿综合症和上述症状的组合。

[0146] 在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者可经历贫血症和 / 或缺铁性贫血症改善，因为血红蛋白水平升高和 / 或维持在超出阈值水平。在有些实施方案中，治疗 CKD 患者的贫血症的方法被公开，该凡法包括将柠檬酸铁口服给予所述 CKD 患者，其中所述柠檬酸铁提供所述 CKD 患者的血红蛋白水平在或超出范围为 11.0g/dL-13.0g/dL 的水平，包括选自以下的水平 ：11.0g/dL、11.5g/dL、12.0g/dL 和 13.0g/dL。在有些实施方案中，治疗 CKD 患者的贫血症的方法被公开，该方法包括将柠檬酸铁口服给予所述 CKD 患者，其中所述柠檬酸铁提供所述 CKD 患者的血红蛋白水平是在或超出选自以下的水平 ：6.8mmol/L、7.1mmol/L、7.4mmol/L 和 8.1mmol/L。在有些实施方案中，治疗男性 CKD 患者的贫血症的方法被公开，该方法包括将柠檬酸铁口服给予所述男性 CKD 患者，其中所述柠檬酸铁提供该男性 CKD 患者的血红蛋白水平是在或超出选自以下的水平 ：13.0g/dL 和 8.1mmol/L。在有些实施方案中，治疗女性 CKD 患者的贫血症的方法被公开，该方法包括

将柠檬酸铁口服给予所述女性 CKD 患者，其中所述柠檬酸铁提供该女性 CKD 患者的血红蛋白水平是在或超出选自以下的水平 ：12.0g/dL 和 7.4mmol/L。

[0147] 在有些实施方案中，用于治疗 CKD 患者的贫血症的方法中的柠檬酸铁被公开，其中所述柠檬酸铁提供所述 CKD 患者的血红蛋白水平是在或超出范围为以下的水平 ：11.0g/dL-13.0g/dL，包括选自以下的水平 ：11.0g/dL、11.5g/dL、12.0g/dL 和 13.0g/dL。在有些实施方案中，用于治疗 CKD 患者的贫血症的方法中的柠檬酸铁被公开，其中所述柠檬酸铁提供所述 CKD 患者的血红蛋白水平是在或超出选自以下的水平 ：6.8mmol/L、7.1mmol/L、7.4mmol/L 和 8.1mmol/L。在有些实施方案中，用于治疗男性 CKD 患者的贫血症的方法中的柠檬酸铁被公开，其中所述柠檬酸铁提供该男性 CKD 患者的血红蛋白水平是在或超出选自以下的水平 ：13.0g/dL 和 8.1mmol/L。在有些实施方案中，用于治疗女性 CKD 患者的贫血症的方法中的柠檬酸铁被公开，其中所述柠檬酸铁提供该女性 CKD 患者的血红蛋白水平是在或超出选自以下的水平 ：12.0g/dL 和 7.4mmol/L。

[0148] 静脉内铁剂

[0149] 患有 CKD 的患者可能是处于铁缺乏症的风险中或者可能罹患铁缺乏症。铁缺乏症，也称为铁质缺乏或低铁血症，是营养缺乏的一种常见类型，并且可以在 CKD 患者中随着身体失去其从肠内腔吸收铁和 / 或贮存铁以备长期使用的能力而发生。当体内铁丢失或减少没有通过例如从饮食中摄入足够的铁量来代偿时，铁缺乏症可随时间的流逝而发生。当铁缺乏症的状态留着不纠正时，它可导致缺铁性贫血症。因此，不治疗的长期铁缺乏的直接后果可以是缺铁性贫血，并且在有些例子是贫血。

[0150] 在 CKD 患者中，典型地有三种可以治疗缺铁性贫血症的方式。第一种方法是吃铁含量高的食物。如果这还不足够，则临床医生可开出口服铁补充剂的处方。然而，许多口服铁补充剂在 CKD 患者中可引起诸多不良副作用，这导致患者非顺应性。在 CKD 患者不能服用口服铁补充剂的那些例子中，他或她可能必须使用静脉内补铁法。

[0151] 静脉内 (IV) 补铁法是一种用针注射到肌肉或注射到静脉内而递送铁的一种方法。接受静脉内铁剂的 CKD 患者通常就是这样做的，因为他们不能服用口服铁剂。具体地说，ESRD 患者是正在接受透析并在透析期间常常失血。这些患者通常也服用红细胞生成刺激剂 (ESA - 参见下文) 并且也因为这一点可能需要额外的铁。静脉内铁剂通过与装有铁溶液的 IV 袋相连的针递送到 CKD 患者的静脉内。这种手术在医生办公室或诊所实施并且可能需要长达数小时，取决于治疗时医生所开出的处方。CKD 患者通常在几次访视的过程中接受铁注射直到他的或她的铁水平是正确的为止。在有些例子中，CKD 患者可能需要永久性静脉内补铁法。

[0152] 静脉内铁补充剂的副作用其中包括 ：胃肠疼痛，包括恶心和痉挛 ；呼吸问题 ；皮肤问题，包括皮疹 ；胸痛 ；低血压 ；和过敏反应。

[0153] 根据本文公开的方法进行治疗的 CKD 患者可经历对静脉内铁补充剂的需求减少。在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者经历累积的静脉内铁补充剂减少。在有些实施方案中，本公开提供降低有其需要的患者的静脉内 (IV) 铁剂使用的方法，该方法包括将柠檬酸铁口服给予 CKD 患者，特别是 ESRD 患者，其中所述柠檬酸铁提供该患者的静脉内铁剂使用降低。在有些实施方案中，本公开提供降低终末期肾病患者的静脉内 (IV) 铁剂使用的方法，该方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口

服给予所述患者，其中所述柠檬酸铁提供该患者的静脉内铁剂使用降低。在有些实施方案中，所述柠檬酸铁给予 52 周的周期。

[0154] 在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为 1-100％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为 10-90％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为 20-80％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为 30-70％。以上范围为了效率的目的以这种格式被公开，并且以上任何范围可以与任何方法、制剂或其组合相结合。

[0155] 在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为 40-60％。在有些实施方案中，所述柠檬酸铁提供选自以下的平均累积静脉内铁剂摄入量的平均降低 :50、51、52、53、54、55、56、57、58、59 和 60％。在有些实施方案中，所述柠檬酸铁提供选自以下的平均累积静脉内铁剂摄入量的平均降低 :51.0、51.1、51.2、51.3、51.4、51.5、51.6、51.7、51.9 和 52.0％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为 51.6％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为 51.6％，当给予 52 周的周期时。

[0156] 在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 10％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 20％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 30％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 40％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 50％。

[0157] 在有些实施方案中，所述柠檬酸铁提供选自以下的平均累积静脉内铁剂摄入量的平均降低 :小于 100％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 90％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 80％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 70％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 60％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 50％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 40％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 30％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 20％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 10％。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方法、制剂、如上公开的上边界或其组合相结合。

[0158] 在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 60％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 70％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 90％。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方法、制剂、如下文公开的下边界或其组合相结合。

[0159] 在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者（例如 ESRD 患者）经历所需的静脉内铁补充剂量的维持，使得 CKD 患者接受的静脉内铁补充剂总量在所述柠檬酸铁的给药期间基本上保持不变。

[0160] 红细胞生成刺激剂

[0161] 除控制以上所述的 CKD 患者的缺铁性贫血症的方式之外，CKD 患者，特别是 ESRD 患者也可服用一种或多种红细胞生成刺激剂 (ESA) 以努力控制贫血症。ESA 的工作是帮助机体产血红细胞。然后，这些红细胞从骨髓释放到血流中，在血流中它们帮助维持血液铁水平。红细胞生成刺激剂，常缩写为 ESA，是在结构和 / 或功能上与细胞因子红细胞生成素类似的药剂，在机体内刺激红细胞产生（红细胞生成 (erythropoeisis)）。典型的 ESA 在结构上和生物学上类似于天然存在的蛋白质促红细胞生成素。商业上可获得的 ESA 的实例包括红细胞生成素 (Epo)、依泊汀 (Epoetin) α (Procrit/Epogen)、依泊汀 β (NeoRecormon)、达贝泊汀 (Darbepoetin) α (Aranesp) 和甲氧基聚乙二醇 - 依泊汀 β (Mircera)。目前被批准用于美国市场的两种 ESA 是依泊汀 α (Procrit, Epogen) 和达贝泊汀 α (Aranesp)。

[0162] ESA 常常给予 ESRD 患者。这些患者通常具有较低的血红蛋白水平，因为他们不能产生足够的红细胞生成素。ESA 使用最常发生的副作用其中包括 ：高血压 ；浮肿 ；发热 ；眩晕 ；恶心 ；和注射部位疼痛。除这些副作用之外，还有 ESA 使用所致的一些安全性问题。ESA 增加静脉血栓栓塞（静脉内的血凝块）的风险。ESA 也可以引起血红蛋白上升得太高，这把患者置于心脏病发作、中风、心力衰竭和死亡的风险中。

[0163] 根据本文公开的方法进行治疗的 CKD 患者可经历维持血红蛋白水平所需的 ESA 量减少。在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者经历 ESA 使用减少。在有些实施方案中，本公开提供降低 CKD 患者、特别是 ESRD 患者的 ESA 使用的方法，该方法包括将柠檬酸铁口服给予所述患者，其中所述柠檬酸铁提供该患者的 ESA 使用降低。在有些实施方案中，本公开提供降低终末期肾病患者的 ESA 使用的方法，该方法包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予所述患者，其中所述柠檬酸铁提供该患者的 ESA 使用降低。在有些实施方案中，所述柠檬酸铁给予 52 周的周期。

[0164] 在有些实施方案中，所述柠檬酸铁提供中值 ESA 摄入量减少 1-50％。在有些实施方案中，所述柠檬酸铁提供中值 ESA 摄入量减少 10-40％。在有些实施方案中，所述柠檬酸铁提供中值 ESA 摄入量减少 20-30％。在有些实施方案中，所述柠檬酸铁提供选自以下的中值 ESA 摄入量减少 ：20、21、22、23、24、25、26、27、28、29 和 30％。在有些实施方案中，所述柠檬酸铁提供选自以下的中值 ESA 摄入量减少 ：27.0、27.1、27.2、27.3、27.4、27.5、27.6、27.7、27.9 和 28.0％。在有些实施方案中，所述柠檬酸铁提供中值 ESA 摄入量减少 27.1％。在有些实施方案中，所述柠檬酸铁提供中值 ESA 摄入量减少 27.1％，当给予 52 周的周期时。

[0165] 在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 20％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 21。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 22％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 23％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 24％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 25％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的

平均降低为大于 26％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 27％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 28％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为大于 29％。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方法、制剂、如下文公开的下边界或其组合相结合。

[0166] 在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 30％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 29％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 28％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 27％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 26％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 25％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 24％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 23％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 22％。在有些实施方案中，所述柠檬酸铁提供平均累积静脉内铁剂摄入量的平均降低为小于 21％。以上边界为了效率的目的以这种格式被公开，并且以上任何边界可以与任何方法、制剂、如上公开的上边界或其组合相结合。

[0167] 在有些实施方案中，根据本文公开的方法进行治疗的 CKD 患者、特别是 ESRD 患者经历维持血红蛋白水平所需的 ESA 量的维持，使得该患者使用的 ESA 总量在所述柠檬酸铁的给药期间基本上保持不变。

[0168] 口服铁补充剂

[0169] 在有些实施方案中，本公开提供包含其含量有效增加 CKD 患者的铁吸收的柠檬酸铁的口服铁补充剂。在有些实施方案中，本公开提供包含其含量有效维持 CKD 患者的铁贮存的柠檬酸铁的口服铁补充剂。在有些实施方案中，本公开提供包含其含量有效改善 CKD 患者的一种或多种铁贮存参数的柠檬酸铁的口服铁补充剂。在有些实施方案中，所述一种或多种铁贮存参数选自红细胞比容、血红蛋白浓度 (Hb)、总铁结合能力 (TIBC)、转铁蛋白饱和度 (TSAT)、血清铁水平、肝脏铁水平、脾脏铁水平和血清铁蛋白水平。在有些实施方案中，本公开提供包含其含量有效治疗 CKD 患者的铁缺乏症的柠檬酸铁的口服铁补充剂。在有些实施方案中，本公开提供包含其含量有效治疗 CKD 患者的贫血症的柠檬酸铁的口服铁补充剂。

[0170] 在有些实施方案中，本公开提供包含三价铁的剂量为 210mg 的柠檬酸铁的口服铁补充剂。在有些实施方案中，所述包含柠檬酸铁的口服铁补充剂可以以范围为 210mg-2,520mg 的三价铁剂量给予。

[0171] 在有些实施方案中，本公开提供用于制造增加 CKD 患者的铁吸收的口服铁补充剂的柠檬酸铁。在有些实施方案中，本公开提供用于制造维持 CKD 患者的铁贮存的口服铁补充剂的柠檬酸铁。在有些实施方案中，本公开提供用于制造改善 CKD 患者的一种或多种铁贮存参数的口服铁补充剂的柠檬酸铁。在有些实施方案中，所述一种或多种铁贮存参数选自红细胞比容、血红蛋白浓度 (Hb)、总铁结合能力 (TIBC)、转铁蛋白饱和度 (TSAT)、血清铁水平、肝脏铁水平、脾脏铁水平和血清铁蛋白水平。在有些实施方案中，本公开提供用于制

造治疗 CKD 患者的铁缺乏症的口服铁补充剂的柠檬酸铁。在有些实施方案中，本公开提供用于制造治疗 CKD 患者的贫血症的口服铁补充剂的柠檬酸铁。

[0172] 在有些实施方案中，本公开提供用于制造包含三价铁的剂量为 210mg 的口服铁补充剂的柠檬酸铁。

[0173] 柠檬酸铁

[0174] 在各种不同的方面，本公开涉及在 CKD 患者中应用柠檬酸铁降低和 / 或控制血清磷水平、增加血清碳酸氢盐水平、改善一种或多种铁贮存参数（例如，增加血清铁蛋白水平、增加转铁蛋白饱和度 (TSAT)、增加血红蛋白浓度）、增加铁吸收、维持铁贮存、治疗铁缺乏症、治疗贫血症、降低对静脉内铁剂的需求和 / 或降低对红细胞生成刺激剂 (ESA) 的需求。在各种不同的方面，本公开涉及在 CKD 患者中应用包含柠檬酸铁和药学上可接受的粘合剂的药物组合物降低和 / 或控制血清磷水平、增加血清碳酸氢盐水平、改善一种或多种铁贮存参数（例如，增加血清铁蛋白水平、增加转铁蛋白饱和度 (TSAT)、增加血红蛋白浓度）、增加铁吸收、维持铁贮存、治疗铁缺乏症、治疗贫血症、降低对静脉内铁剂的需求和 / 或降低对红细胞生成刺激剂 (ESA) 的需求。

[0175] 因此，本文公开的是柠檬酸铁的制品及包含所述柠檬酸铁的药物组合物。在各种不同的实施方案中，所述柠檬酸铁制品和所述包含所述柠檬酸铁制品的药物组合物满足某些溶出、压片和崩解标准。在各种不同的方面，所述药物组合物可包括作为活性成分的柠檬酸铁和粘合剂。所述药物组合物还可包括润滑剂和 / 或崩解剂（在有些实施方案中，其可以与粘合剂相同）。

[0176] 本文中以用途公开的柠檬酸铁制品的某些实施方案在美国专利号 7,767,851、8,093,423、8,299,298 和 8,338,642 和 PCT 公布号 WO 2004/074444、WO 2007/022435、WO 2007/089571、WO 2007/089577 和 WO 2011/011541 中也被公开。然而，柠檬酸铁制品的某些实施方案对于本公开是独特的。与市售的或化学级形式的柠檬酸铁相比，本文公开的柠檬酸铁制品表现出 BET 活性表面积提高。BET 理论解释了固体表面上的气体分子的物理吸附。该理论用作测量材料的比表面积的基础。该理论使得可以采用非常准确的方式计算出材料的表面积并因此能够把似乎是同一种材料的独立制备物之间的差异区分开来。例如，活性碳是经过加工的碳的一种形式，使其极端多孔并因此具有非常大的表面积。采用得自 BET 理论的计算法，活性碳已通过实验方法确定其表面积大约为 $3000m^2g^{-1}$。这种表面积明显高于其它碳制品的活性表面积，即使它们由同一种材料制成。

[0177] 在有些实施方案中，本文公开的柠檬酸铁制品的 BET 活性表面积超过 $16m^2/g$。在有些实施方案中，本文公开的高纯度柠檬酸铁制品的 BET 活性表面积超过 $20m^2/g$。在有些实施方案中，本文公开的高纯度柠檬酸铁制品的 BET 活性表面积超过 $25m^2/g$。在有些实施方案中，本文公开的高纯度柠檬酸铁制品的 BET 活性表面积超过 $30m^2/g$。在有些实施方案中，本文公开的高纯度柠檬酸铁制品的 BET 活性表面积超过 $35m^2/g$。在有些实施方案中，本文公开的高纯度柠檬酸铁制品的 BET 活性表面积超过 $40m^2/g$。在有些实施方案中，本文公开的高纯度柠檬酸铁制品的 BET 活性表面积超过 $45m^2/g$。在有些实施方案中，本文公开的高纯度柠檬酸铁制品的 BET 活性表面积超过 $50m^2/g$。在有些实施方案中，本文公开的柠檬酸铁制品的 BET 活性表面积范围为 $16.17m^2/g$ 至 $19.85m^2/g$。在有些实施方案中，本文公开的柠檬酸铁制品的 BET 活性表面积选自 $16.17m^2/g$ 和 $19.85m^2/g$。在有些实施方案中，本文

公开的柠檬酸铁制品的 BET 活性表面积超过 27m²/g。在有些实施方案中，本文公开的柠檬酸铁制品的 BET 活性表面积范围为 27.99m²/g 至 32.34m²/g。在有些实施方案中，本文公开的柠檬酸铁制品的 BET 活性表面积范围为 28.5m²/g 至 31.5m²/g。在有些实施方案中，本文公开的柠檬酸铁制品的 BET 活性表面积选自 27.99m²/g、28.87m²/g 和 32.34m²/g。在有些实施方案中，本文公开的柠檬酸铁制品的 BET 活性表面积选自 28.5m²/g、29.1m²/g、30.6m²/g 和 31.5m²/g。这与本公开的申请日期相同的已知的和市售的其它柠檬酸铁制品例如化学级制品形成了鲜明的对比。柠檬酸铁的商品级制品的 BET 活性表面积明显低于本公开的柠檬酸铁制品。因此，本文公开的柠檬酸铁制品具有明显较大的表面积可供吸附或化学反应之用，使得本文公开的柠檬酸铁制品比商业制品的反应性明显更好。

[0178] 采用在 PCT 公布号 WO2004/074444 中公开的方法生产的五种柠檬酸铁制品确定的 BET 活性表面积已经被确定。与柠檬酸铁的商品等级制品的 BET 活性表面积相比，那些 BET 活性表面积见下表 1：

[0179] 表 1. 各种形式的柠檬酸铁的 BET 活性表面积

[0180]

样品	平均溶出速率 (mg/cm²/min)	BET 活性表面积
RFS-12-1 (西格玛公司/市售)	0.76	0.61
RFS-12-2 (西格玛公司/市售)		
STM-134-1 (对比材料 1)	2.47	16.17
STM-134-2 (对比材料 2)		
STM-182-1 (实验室规模 500g 批次 1)	2.61	19.85
STM-182-2 (实验室规模 500g 批次 2)		

[0181] 采用在 PCT 公布号 WO2011/011541 中公开的方法生产的五种柠檬酸铁制品确定的 BET 活性表面积已经被确定。与柠檬酸铁的商品等级制品的 BET 活性表面积相比，那些 BET 活性表面积见下表 2：

[0182] 表 2.BET 活性表面积

[0183]

样品	BET 活性表面积(m²/g)
RFS-12-1 (西格玛公司/市售)	0.61

[0184]

RFS-12-2 (西格玛公司/市售)	
样品#10-1 (造粒前(API+ProSolv))[1]	27.99
样品#10-2 (造粒前(API+ProSolv))[2]	32.34
样品#11-1 (造粒前(API+ProSolv))[3]	28.87
样品#11-2 (造粒前(API+ProSolv))[4]	
样品#11-3 (造粒前(API+ProSolv))[5]	

[0185] [1]来自 PCT 公布号 WO 2011/011541 的实施例 10。

[0186] [2]来自 PCT 公布号 WO 2011/011541 的实施例 10。

[0187] [3]来自 PCT 公布号 WO 2011/011541 的实施例 11。

[0188] [4]来自 PCT 公布号 WO 2011/011541 的实施例 11。

[0189] [5]来自 PCT 公布号 WO 2011/011541 的实施例 11。

[0190] 采用本文公开的方法生产的另外四种柠檬酸铁制品的 BET 活性表面积也已经被确定。与柠檬酸铁的商品等级制品的 BET 活性表面积相比，那些 BET 活性表面积见下表 3：

[0191] 表 3. BET 活性表面积

[0192]

样品	BET 活性表面积(m^2/g)
RFS-12-1 (西格玛公司/市售)	0.61
RFS-12-2 (西格玛公司/市售)	
批号 35102	30.6
批号 35103	29.1
批号 35105	31.5
批号 35106	28.5

[0193] 因此，在表 1、2 和 3 中公开的柠檬酸铁制品的实施方案的 BET 活性表面积明显高于商品级柠檬酸铁的 BET 活性表面积。

[0194] 表 4 说明本文公开的柠檬酸铁的三价铁的分析含量 (assay content)。三价铁的分析含量代表如表 4 所示的每一种柠檬酸铁制品中的三价铁的量。在有些实施方案中，三价铁的分析含量大于或远远超出约 20% w/w。在有些实施方案中，三价铁的分析含量为 21.2% w/w。在有些实施方案中，三价铁的分析含量为 22.1% w/w。在有些实施方案中，三价铁的分析含量为 22.4% w/w。在有些实施方案中，三价铁的分析含量为介于 21% w/w 和 23% w/w 之间。

[0195] 表 4：三价铁含量

[0196]

批次	材料平衡	+水	修订后的材料平衡 (材料平衡+水)	杂质含量	%铁(III)
A	94.60	1.9	96.50	3.5	21.2
B	94.40	2.1	96.50	3.5	21.2
C	93.40	2.0	95.40	4.6	22.4
D	92.90	2.2	95.10	4.9	22.1

[0197] 本文公开的柠檬酸铁是铁 (III) 与柠檬酸的络合物。在有些方面，铁 (III) 与柠檬酸的摩尔比为 1:0.70 至 1:0.78。在有些方面，铁 (III) 与柠檬酸的摩尔比为 1:0.69 至 1:0.87。在有些方面，铁 (III) 与柠檬酸的摩尔比为 1:0.75 至 1:1.10。在有些方面，铁 (III) 与柠檬酸的摩尔比为 1:0.78 至 1:0.95。在有些方面，铁 (III) 与柠檬酸的摩尔比为 1:0.80 至 1:0.92。在有些方面，铁 (III) 与柠檬酸的摩尔比为 1:0.81 至 1:0.91。在有些方面，铁 (III) 与柠檬酸的摩尔比为 1:0.75 至 1:1.15。在有些方面，铁 (III) 与柠檬酸的摩尔比为 1:0.80 至 1:1.10。

[0198] 在有些方面，铁 (III) 与水的摩尔比为 1:0.32 至 1:0.42。在有些方面，铁 (III) 与水的摩尔比为 1:0.32 至 1:0.46。在有些方面，铁 (III) 与水的摩尔比为 1:1.8 至 1:3.2。在有些方面，铁 (III) 与水的摩尔比为 1:1.8 至 1:3.2。在有些方面，铁 (III) 与水的摩尔比为 1:2.4 至 1:3.1。在有些方面，铁 (III) 与水的摩尔比为 1:2.7 至 1:3.1。

[0199] 与市售的或化学级形式的柠檬酸铁相比，本文公开的柠檬酸铁制品更易溶解。在溶出测试中，本公开的柠檬酸铁的溶解百分比在 5 分钟内为 91％或更高，在 15 分钟内为 96％或更高，在 30 分钟内为 96％或更高和在 60 分钟内为 95％或更高，采用附录 II 在 USP<711> 容器中的柠檬酸铁制品上进行的溶出测试中。表 5 说明根据本公开所述的柠檬酸铁的四个示例性批次的溶出测试数据。溶出测试所用的具体标准建立基线为 100，所以，到达一定程度，某个批次的溶出会大于 100％，它是一个相对于该标准的溶出速率。

[0200] 表 5. 溶出测试数据

[0201]

批次	5 分钟	15 分钟	30 分钟	60 分钟
A	101％	102％	101％	101％
B	101％	102％	102％	102％
C	97％	97％	97％	97％
D	91％	96％	96％	95％

[0202] 因此，在有些实施方案中，采用附录 II 在 USP<711> 容器中进行的溶出测试中，在 15 分钟内溶解的柠檬酸铁百分比为 80％或更高。在有些实施方案中，采用附录 II 在 USP<711> 容器中进行的溶出测试中，在 15 分钟内溶解的柠檬酸铁百分比为 85％或更高。在有些实施方案中，采用附录 II 在 USP<711> 容器中进行的溶出测试中，在 15 分钟内溶解的柠檬酸铁百分比为 90％或更高。在有些实施方案中，采用附录 II 在 USP<711> 容器中进行的溶出测试中，在 15 分钟内溶解的柠檬酸铁百分比为 91％或更高。在有些实施方案中，采用附录 II 在 USP<711> 容器中进行的溶出测试中，在 15 分钟内溶解的柠檬酸铁百分比为 95％或更高。在有些实施方案中，采用附录 II 在 USP<711> 容器中进行的溶出测试中，在 15 分钟内溶解的柠檬酸铁百分比为 96％或更高。在有些实施方案中，采用附录 II 在 USP<711> 容器中进行的溶出测试中，在 15 分钟内溶解的柠檬酸铁百分比为 97％或更高。在有些实施方案中，采用附录 II 在 USP<711> 容器中进行的溶出测试中，在 15 分钟内溶解的柠檬酸铁百分比为 100％或更高。

[0203] 与市售的或化学级形式的柠檬酸铁相比，本文公开的柠檬酸铁制品更易溶解。相信本文公开的柠檬酸铁制品的溶解度增加是本文公开的柠檬酸铁制品的这种独特的明显增大的活性表面积的结果。固有溶出速率定义为纯物质在恒定表面积的条件下的溶出速率。药物物质的固有溶出速率和生物利用度受到其固态性质的影响，所述固态性质包括 :结晶性、无定形性、多态性、水合作用、溶剂化作用、颗粒大小和颗粒表面积。测得的固有溶出速率依赖于这些固态性质并且典型地通过在维持恒定的温度、搅拌速率和 pH 的同时，使材料的恒定表面积暴露在适当的溶解介质中来确定。

[0204] 在有些实施方案中，本文公开的柠檬酸铁制品的固有溶出速率为大于 2.28mg/cm^2/min。在有些实施方案中，本文公开的柠檬酸铁制品的固有溶出速率超过 2.28mg/cm^2/min。在有些实施方案中，本文公开的柠檬酸铁制品的固有溶出速率为 2.99mg/cm^2/min。在有些实施方案中，本文公开的柠檬酸铁制品的固有溶出速率范围为 2.28mg/cm^2/min

至 2.99mg/cm^2/min。在有些实施方案中，本文公开的柠檬酸铁制品的固有溶出速率选自 2.28mg/cm^2/min 和 2.99mg/cm^2/min。这与柠檬酸铁的其它制品例如已知的和市售的化学级制品形成了鲜明的对比。柠檬酸铁的商品级制品的固有溶出速率明显低于本公开的柠檬酸铁制品。因此，本文公开的柠檬酸铁制品具有明显较高的固有溶出速率，使得本文公开的柠檬酸铁制品比商业制品明显更易溶解。

[0205] 确定了根据本公开所述方法生产的柠檬酸铁制品的固有溶出速率。与柠檬酸铁的商品等级制品的溶出速率相比，平均固有溶出速率见下表 6：

[0206] 表 6. 固有溶出速率

[0207]

样品	平均固有溶出速率 (mg/cm^2/min)
RFS-12（西格玛公司 / 市售）	0.83
高纯度柠檬酸铁	2.64

[0208] 因此，表 6 中公开的本发明的柠檬酸铁制品的固有溶出速率明显高于商品级柠檬酸铁的固有溶出速率。

[0209] 制造方法

[0210] 本公开提供的柠檬酸铁制品的示例性制造方法在美国专利号 7,767,851、8,093,423、8,299,298 和 8,338,642 和 PCT 公布号 WO 2004/074444、WO 2007/022435、WO 2007/089571、WO 2007/089577 和 WO 2011/011541 中被公开。

[0211] 给药方式

[0212] 本文公开的柠檬酸铁可以有利地用于人类医学。如本文所公开的，本文公开的柠檬酸铁可用于在 CKD 患者中降低和 / 或控制血清磷水平、增加血清碳酸氢盐水平、改善一种或多种铁贮存参数（例如，增加血清铁蛋白水平、增加转铁蛋白饱和度 (TSAT)、增加血红蛋白浓度）、增加铁吸收、维持铁贮存、治疗铁缺乏症、治疗贫血症、降低对静脉内铁剂的需求和 / 或降低对红细胞生成刺激剂 (ESA) 的需求。本文公开的柠檬酸铁也可以有利地用作铁补充剂。在各种不同的方面，本文公开的柠檬酸铁可以经口服给予。在有些实施方案中，所述柠檬酸铁在口服剂型中给予。在有些实施方案中，所述柠檬酸铁在口服片剂剂型中给予。在有些实施方案中，所述片剂是呈小胶囊剂 (caplet) 的形式。

[0213] 当用于治疗上述疾病和 / 或病症时，或当用作铁补充剂时，本文公开的柠檬酸铁可以单独给予或使用，或者结合其它药剂一起给予或使用。本文公开的柠檬酸铁也可以单独给予或使用或者结合其它药用活性剂一起给予或使用，所述其它药用活性剂包括具有以下作用的其它药剂：已知在 CKD 患者中降低和 / 或控制血清磷水平、增加血清碳酸氢盐水平、改善一种或多种铁贮存参数（例如，增加血清铁蛋白水平、增加转铁蛋白饱和度 (TSAT)、增加血红蛋白浓度）、增加铁吸收、维持铁贮存、治疗铁缺乏症、治疗贫血症、降低对静脉内铁剂的需求和 / 或降低对红细胞生成刺激剂 (ESA) 的需求。

[0214] 治疗方法在上文已公开并且包括将柠檬酸铁以范围为 210mg-2,520mg 的三价铁剂量口服给予所述患者。因此，本文公开的柠檬酸铁可以经口服给予。在各种不同的方面，本文公开的柠檬酸铁可以在包含 1 克柠檬酸铁且三价铁的剂量为约 210mg 的口服片剂剂型

中给予。

[0215] 本文公开的柠檬酸铁用于增强从肠内腔吸收铁及在吸收后增强/维持铁的贮存。相信铁的吸收和贮存增强可能由于向CKD患者给予的柠檬酸铁中存在的柠檬酸盐所致。尽管不希望受任何理论的束缚,但是一些研究已经表明铁结合柠檬酸盐(柠檬酸的共轭碱)一起给药起到显著地增加(例如,数倍于)从膳食来源吸收的铁量(参见例如,Ballot 等 人 ,Br.J.Nutr.(1987)57,331-343 ;Gillooly 等 人 ,Br.J.Nutr.(1983)49,331-342 ; Zhang 等 人 ,Eur.J.Nutr.(2007)46,95-102 ; 和 Salovaara 等 人 ,J.Agric.Food Chem.(2002)50,6233-6238)。

[0216] 可以给予本文公开的柠檬酸铁,在有些实施方案中每天一次,在有些实施方案中每天两次,在有些实施方案中每天三次,和在有些实施方案中每天超过两次。在各种不同的方面,所述柠檬酸铁可以以日剂量的形式给予,该日剂量可以在一天内分成几次给予。举例来说,柠檬酸铁的单个日剂量可以是6克,并且这6克可以在这一天内分成好一个等份,使得2克在早上服用,2克在下午服用,最后2克在晚上服用,一天共计6克。

[0217] 本文公开的柠檬酸铁能够用于在CKD患者中降低和/或控制血清磷水平、增加血清碳酸氢盐水平、改善一种或多种铁贮存参数(例如,增加血清铁蛋白水平、增加转铁蛋白饱和度(TSAT)、增加血红蛋白浓度)、增加铁吸收、维持铁贮存、治疗铁缺乏症、治疗贫血症、降低对静脉内铁剂的需求和/或降低对红细胞生成刺激剂(ESA)的需求,同时也降低了与口服铁补充剂(例如含有亚铁的补充剂)和/或静脉内铁剂补充剂的已知形式相关的不良药物作用。

[0218] 药物组合物和铁补充剂

[0219] 本文公开的是含有柠檬酸铁的药物组合物,其包含本文公开的柠檬酸铁制品和粘合剂。在有些实施方案中,所述药物组合物可以作为铁补充剂提供给CKD患者。在有些实施方案中,所述药物组合物可以作为磷酸盐结合剂提供给CKD患者和/或以在CKD患者中降低和/或控制血清磷水平、增加血清碳酸氢盐水平、改善一种或多种铁贮存参数(例如,增加血清铁蛋白水平、增加转铁蛋白饱和度(TSAT)、增加血红蛋白浓度)、增加铁吸收、维持铁贮存、治疗铁缺乏症、治疗贫血症、降低对静脉内铁剂的需求和/或降低对红细胞生成刺激剂(ESA)的需求。在各种不同的实施方案中,所述药物组合物满足了某些溶出、压片和/或崩解标准。在各种不同的方面,所述药物组合物可包括作为活性成分的柠檬酸铁和粘合剂。所述药物组合物还可包括润滑剂和/或崩解剂(在有些实施方案中,其可以与粘合剂相同)。在有些实施方案中,所述药物组合物是口服片剂剂型。

[0220] 本公开提供的药物组合物和口服片剂剂型的某些实施方案在PCT公布号WO 2011/011541中被公开。然而,其它的实施方案对于本公开是独特的。

[0221] 口服片剂剂型和口服铁补充剂

[0222] 在一个方面,所述药物组合物是包括柠檬酸铁和粘合剂的片剂。如本文所用的,“片剂”是例如用压片机通过压片压力生产的产品。在其它的实施方案中,所述片剂可包括柠檬酸铁、粘合剂、润滑剂和崩解剂。在有些实施方案中,单个片剂包含1克的柠檬酸铁,其中三价铁剂量为210mg。在有些实施方案中,所述片剂能够在CKD患者中用于降低和/或控制血清磷水平、增加血清碳酸氢盐水平、改善一种或多种铁贮存参数(例如,增加血清铁蛋白水平、增加转铁蛋白饱和度(TSAT)、增加血红蛋白浓度)、增加铁吸收、维持铁贮存、治疗

铁缺乏症、治疗贫血症、降低对静脉内铁剂的需求和/或降低对红细胞生成刺激剂(ESA)的需求。在有些实施方案中,所述片剂能够作为口服铁补充剂给予CKD患者。

[0223] 在有些实施方案中,所述片剂和/或口服铁补充剂可以表征为片剂和/或口服铁补充剂中存在的柠檬酸铁的高载药量,其值为该制剂的大于大约65%(重量)、该制剂的大于大约70%(重量)、该制剂的大于大约75%(重量)、该制剂的大于大约80%(重量)、该制剂的大于大约85%(重量)、该制剂的大于大约90%(重量)和高达该制剂的大约92%。中间值,例如大约80%(重量)柠檬酸铁、大约85%(重量)柠檬酸铁和大约90%(重量)柠檬酸铁,也可以用于柠檬酸铁片剂和/或口服铁补充剂。以这些高负载的重量百分比生产的片剂和/或口服铁补充剂的特征受到诸多变量的控制,例如粘合剂、粘合剂量、崩解剂、崩解剂量、所使用的制药方法(例如,造粒法、直接压片法)、压片参数,等等。因此,如果制备片剂和/或口服铁补充剂并且它具有轻量的分层或脱盖,那么通过改变上述变量中的一种或多种,分层或脱盖可被纠正。

[0224] 在各种不同的实施方案中,所述片剂和/或口服铁补充剂含有一种或多种组分,其中选自一种或多种粘合剂、一种或多种润滑剂和一种或多种崩解剂。

[0225] 粘合剂可以是本领域已知的任何粘合剂。粘合剂的实例可包括但不限于羟丙基纤维素(HPC)、羟丙基甲基纤维素(HPMC)、海藻酸钠、海藻酸、瓜尔胶(guar gum)、阿拉伯胶(acacia gum)、黄原胶、卡波普(carbolpol)、纤维素胶(羧甲基纤维素)、乙基纤维素、麦芽糊精、PVP/VA、聚维酮、微晶纤维素、淀粉、部分或完全预胶化淀粉和甲基纤维素中的一种或多种。所述麦芽糊精、PVP/VA和甲基纤维素当用在柠檬酸铁片剂和/或口服铁补充剂中时起到速释粘合剂的功能。

[0226] 还应该理解,多种粘合剂的组合可以用于控制和改变粘合剂的效果。例如,粘合剂体系可以由羟丙基纤维素和聚乙烯吡咯烷酮(聚维酮)加或不加微晶纤维素制成。羟丙基纤维素和聚维酮中的一种或两种可以用预胶化淀粉替代。

[0227] 在各种不同的方面,所述片剂和/或口服铁补充剂可包括润滑剂。对于柠檬酸铁片剂和/或口服铁补充剂,作为润滑剂的一个实例,可以使用硬脂酸镁、硬脂酸钙、硬脂酰富马酸钠及其组合。其它合适的润滑剂包括聚乙二醇(分子量超过3350)、十二烷基硫酸钠、滑石粉、矿物油、亮氨酸和泊洛沙姆(poloxamer)中的一种或多种。

[0228] 在各种不同的方面,所述片剂和/或口服铁补充剂可包括崩解剂。所述崩解剂可包括在片剂和/或口服铁补充剂中。所述崩解剂可与粘合剂相同或不同。作为一个例子但不限于,微晶纤维素具有粘合剂和崩解剂两种特性,因此微晶纤维素在片剂和/或口服铁补充剂中能够用作唯一的粘合剂/崩解剂。其它合适崩解剂的实例包括交联羧甲基纤维素钠、交聚维酮、羟基乙酸淀粉钠和淀粉。

[0229] 所述粘合剂可以以范围为大约4.5%(重量)至大约30%(重量)的量存在于片剂和/或口服铁补充剂。所述崩解剂可以以范围为大约1.5%(重量)至大约15%(重量)的量存在于片剂和/或口服铁补充剂。在各种不同的实施方案中,一些非淀粉类崩解剂通常以较低的重量百分比使用,例如低至0.25%,因此片剂和/或口服铁补充剂中存在的崩解剂在有些情况下可以低至0.25%。

[0230] 所述润滑剂可以以范围为大约0.5%(重量)至大约3%(重量)的量存在于片剂和/或口服铁补充剂中。还应该理解,一些组分,例如微晶纤维素,可以起到具有崩解剂

和粘合剂两种特性的功能。

[0231] 各个片剂和/或口服铁补充剂的重量可取决于所生产的最终剂量;例如,125mg、250mg、500mg、667mg、750mg和1,000mg的柠檬酸铁。在有些实施方案中,所述片剂包含1克的柠檬酸铁并因此三价铁的剂量为210mg。

[0232] 在各种不同的实施方案中,片剂和/或口服铁补充剂采用欧巴代悬浮或等同方法在有孔包衣锅(perforated pan coater)中包衣至增重大约2%至5%。硬脂酸钙和欧巴代紫色(Opadry purple)可以分别用不同的润滑剂或包衣体系替代或与其一起使用。

[0233] 在其它的变体中,所述片剂和/或口服铁补充剂的含水量可降低。在一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于20%。在另一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于19%。在另一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于18%。在另一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于17%。在另一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于16%。在另一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于15%。在另一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于14%。在另一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于13。在另一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于12%。在另一个实施方案中,所述含水量通过LOD%测量,为小于11%。在另一个实施方案中,所述含水量,通过LOD%测量,为小于10%。在另一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于9%。在另一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于8%。在另一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于7%。在另一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于6%。在另一个实施方案中,所述片剂的含水量,通过LOD%测量,为小于5%。

[0234] LOD(干燥失重)是一种热重分析的水分测定方法。在热重分析过程中,材料的水分包括在加热期间挥发的物质,并因此造成材料失重。除水之外,这可能还包括醇类或分解产物。当采用热重分析测量方法(使用红外、卤光、微波或炉进行干燥)时,在水和其它易挥发组分之间没有区别。

[0235] 在有些实施方案中,所述片剂和/或口服铁补充剂包含选自以下量的柠檬酸铁:大约1000mg、大约667mg、大约500mg、大约250mg和大约125mg。在有些实施方案中,所述片剂和/或口服铁补充剂包含1克(1000mg)的柠檬酸铁。在有些实施方案中,所述片剂和/或口服铁补充剂包含1克的柠檬酸铁,其中含有大约210mg的三价铁。

[0236] 在有些实施方案中,所述片剂和/或口服铁补充剂包含1.3克的柠檬酸铁。在有些实施方案中,所述片剂和/或口服铁补充剂包含1.5克的柠檬酸铁。在有些实施方案中,所述片剂和/或口服铁补充剂包含1.6克的柠檬酸铁。在有些实施方案中,所述片剂和/或口服铁补充剂包含选自以下量的柠檬酸铁:100mg、125mg、150mg、175mg、200mg、225mg、250mg、275mg、300mg、325mg、350mg、375mg、400mg、425mg、450mg、475mg、500mg、525mg、550mg、575mg、600mg、625mg、650mg、675mg、700mg、725mg、750mg、775mg、800mg、825mg、850mg、875mg、900mg、925mg、950mg、975mg、1000mg、1025mg、1050mg、1075mg、1100mg、1125mg、1150mg、1175mg、1200mg、1225mg、1250mg、1275mg、1300mg、1325mg、1350mg、1375mg、1400mg、1425mg、1450mg、1475mg、1500mg、1525mg、1550mg、1575mg、1600mg、1625mg、1650mg、1675mg、1700mg、1725mg、1750mg、1775mg、1800mg、1825mg、1850mg、1875mg、1900mg、1925mg、

1950mg、1975mg 和 2000mg。

[0237] 在有些实施方案中，所述片剂和 / 或口服铁补充剂包含介于大约 65wt％和 92wt％之间的柠檬酸铁；介于大约 4.5wt％和 30wt％之间的粘合剂；和介于 0.5wt％和 3wt％之间的润滑剂。在有些实施方案中，所述润滑剂选自硬脂酸镁、硬脂酸钙和硬脂酰富马酸钠中的一种或多种。

[0238] 在有些实施方案中，所述片剂和 / 或口服铁补充剂包含 65％（重量）至 92％（重量）的柠檬酸铁和 4.5％（重量）至 30％（重量）的粘合剂，其中所述片剂的平均表面积与质量之比等于或大于 $1m^2$/ 克，和其中所述片剂的 LOD％水为小于 20％水 w/w。在有些实施方案中，所述片剂和 / 或口服铁补充剂的平均表面积与质量之比可以等于或大于 $5m^2$/ 克。在有些实施方案中，所述片剂和 / 或口服铁补充剂的平均表面积与质量之比等于或大于 $10m^2$/ 克。在有些实施方案中，所述片剂和 / 或口服铁补充剂包含至少 70％重量的柠檬酸铁。在有些实施方案中，所述片剂和 / 或口服铁补充剂包含至少 80％重量的柠檬酸铁。在有些实施方案中，所述片剂和 / 或口服铁补充剂包含至少 90％重量的柠檬酸铁。在有些实施方案中，所述粘合剂包括羟丙基纤维素 (HPC)、羟丙基甲基纤维素 (HPMC)、海藻酸钠、海藻酸、瓜尔胶、阿拉伯胶、黄原胶、卡波普 (carbolpol)、纤维素胶（羧甲基纤维素）、乙基纤维素、麦芽糊精、PVP/VA、聚维酮、微晶纤维素、淀粉（部分或完全预胶化淀粉）和甲基纤维素中的一种或多种。在有些实施方案中，所述片剂和 / 或口服铁补充剂的 LOD％水为小于 15％水 w/w。在有些实施方案中，所述片剂和 / 或口服铁补充剂的 LOD％水为小于 10％水 w/w。在有些实施方案中，所述片剂和 / 或口服铁补充剂还包含选自以下的崩解剂：微晶纤维素、交联羧甲基纤维素钠、交聚维酮、羟基乙酸淀粉钠和淀粉中的一种或多种。在有些实施方案中，所述片剂和 / 或口服铁补充剂还包含选自以下的润滑剂：硬脂酸镁、硬脂酸钙和硬脂酰富马酸钠中的一种或多种。在有些实施方案中，所述片剂和 / 或口服铁补充剂包含介于 0.5％和 3％之间的润滑剂。在有些实施方案中，所述粘合剂包含预胶化淀粉。在有些实施方案中，所述润滑剂包含硬脂酸钙和硬脂酰富马酸钠。在有些实施方案中，所述片剂和 / 或口服铁补充剂中的至少 80％柠檬酸铁在小于或等于 60 分钟的时间内溶解，根据试验方法 USP<711> 来衡量。在有些实施方案中，所述片剂和 / 或口服铁补充剂包含大约 1000mg 的柠檬酸铁。在有些实施方案中，所述片剂和 / 或口服铁补充剂包含大约 667mg 的柠檬酸铁。在有些实施方案中，所述片剂和 / 或口服铁补充剂包含大约 500mg 的柠檬酸铁。

[0239] 表 7 提供根据本公开的一个实施方案所述的柠檬酸铁片剂和 / 或口服铁补充剂的配方：

[0240] 表 7. 柠檬酸铁片剂和 / 或口服铁补充剂的配方

[0241]

原料描述	理论值 kg/批	% w/w
柠檬酸铁	14.89	87.6
预胶化淀粉	1.70	10.0
硬脂酸钙	0.406	2.4
纯净水	15.30*	N/A*
素片合计	17.00	100.0
欧巴代紫色 03K100000	0.51	15.0
纯净水	2.89*	85.0*
包衣片合计	17.5	100.0

[0242] *- 纯净水在制造过程中在干燥阶段期间被除去

[0243] 表 8 提供根据本公开的一个实施方案所述的柠檬酸铁片剂和 / 或口服铁补充剂的配方 :

[0244] 表 8:

[0245]

原料描述	目标值 kg/批次	理论值 100 kg/批号	% w/w 个体	% w/w 包衣片
柠檬酸铁	14.9	80.0 – 90.0	80.0 – 90.0	76.2 – 88.2
预胶化淀粉	1.7	8.0 – 15.0	8.0 – 15.0	7.6 – 14.7
硬脂酸钙(1)	0.4	1.0 – 3.0	1.0 – 3.0	0.9 – 2.9
OR - 硬脂酰富马酸钠(1)	0.4	2.0 – 3.0	2.0 – 3.0	1.9 – 2.9
纯净水	15.3*	72.0 – 135.0*	*	*
素片合计	17.0	100.0	100.0	N/A*
欧巴代紫色	0.9	5.3	15.0	2.0 – 5.0
纯净水	5.1*	30.0*	85.0*	N/A*
包衣片合计	17.5 到 17.9	35.3	100.0	100.0

[0246] (1)- 使用硬脂酸钙或硬脂酰富马酸钠作为润滑剂

[0247] *- 纯净水被除去。

[0248] 表 9 提供根据本公开的一个实施方案所述的柠檬酸铁片剂和 / 或口服铁补充剂的配方 :

[0249] 表 9:

[0250]

原料描述	目标值 kg/ 批	% w/w 个体
柠檬酸铁	14.89	87.6
预胶化淀粉	1.7	10.0
硬脂酸钙 (1)	0.406	2.4

[0251]

纯净水	15.30	N/A
素片合计	17.00	100.0
欧巴代紫色	0.51	15.0
纯净水	2.89	85.0
包衣片合计	17.5	100.0

[0252] 表 10 提供根据本公开的一个实施方案所述的柠檬酸铁片剂和 / 或口服铁补充剂的配方 :

[0253] 表 10:

[0254]

原料 / 成分	配方组成% w/w
柠檬酸铁	70.0 到 99.0
淀粉	0.0 到 30.0
微晶纤维素	0.0 到 30.0
聚乙烯吡咯烷酮	0.0 到 30.0
硬脂酸钙	0.0 到 3.0
硬脂酰富马酸钠	0.0 到 3.0
纯净水	N/A*
素片合计	100.0
薄膜包衣材料	0.0 到 5.0
纯净水	N/A*
包衣片合计	100.0

[0255] *- 纯净水被除去。

[0256] 表 11 提供根据本公开的一个实施方案所述的柠檬酸铁片剂和 / 或口服铁补充剂的配方 :

[0257] 表 11:

[0258]

原料	重量 mg±10%

柠檬酸铁	1500
淀粉	150
微晶纤维素	0
聚乙烯吡咯烷酮	0
硬脂酸钙	16
硬脂酰富马酸钠	0
纯净水	N/A*
素片合计 -mg	1666
薄膜包衣材料	50
纯净水	N/A*
包衣片合计 -mg	1766

[0259] *-纯净水被除去。

[0260] 剂量

[0261] 本文公开的片剂和/或口服铁补充剂可以制成适应柠檬酸铁的多种剂量。个体片剂和/或口服铁补充剂的重量可取决于所生产的最终剂量;例如,125mg、250mg、500mg、667mg、750mg 和 1,000mg 的柠檬酸铁/片。在各种不同的方面,所述柠檬酸铁在包含 1 克含有大约 210mg 三价铁的柠檬酸铁的片剂剂型中提供。片剂和/或口服铁补充剂的给药数量可以做调整以符合待给予的柠檬酸铁的所需量。例如,CKD 患者被指导服用在一个剂量中每天 4 克柠檬酸铁,该 CKD 患者可服用 4 个片剂和/或口服铁补充剂,每一个包含 1 克的柠檬酸铁;或者可服用 8 个片剂和/或口服铁补充剂,每一个包含 500mg 的柠檬酸铁。

[0262] 在有些实施方案中,向 CKD 患者给予的柠檬酸铁的日剂量可以为 1 克-18 克,按三价铁的剂量范围为 210mg-3,780mg。在有些实施方案中,给予包含 1 克柠檬酸铁的一个或多个片剂,每一个片剂的三价铁剂量为 210mg,以在 CKD 患者中降低和/或控制血清磷水平、增加血清碳酸氢盐水平、改善一种或多种铁贮存参数(例如,增加血清铁蛋白水平、增加转铁蛋白饱和度(TSAT)、增加血红蛋白浓度)、增加铁吸收、维持铁贮存、治疗铁缺乏症、治疗贫血症、降低对静脉内铁剂的需求和/或降低对红细胞生成刺激剂(ESA)的需求。

[0263] 在有些实施方案中,所述柠檬酸铁以每天 1 个片剂的日剂量给予,所述片剂包含 1 克含有 210mg 三价铁的柠檬酸铁,总日剂量为 1 克柠檬酸铁和 210mg 三价铁。在有些实施方案中,所述柠檬酸铁以每天 2 个片剂的日剂量给予,每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁,总日剂量为 2 克柠檬酸铁和 420mg 三价铁。在有些实施方案中,所述柠檬酸铁以每天 3 个片剂的日剂量给予,每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁,总日剂量为 3 克柠檬酸铁和 630mg 三价铁。在有些实施方案中,所述柠檬酸铁以每天 4 个片剂的

日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 4 克柠檬酸铁和 840mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 5 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 5 克柠檬酸铁和 1,050mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 6 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 6 克柠檬酸铁和 1,260mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 7 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 7 克柠檬酸铁和 1,470mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 8 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 8 克柠檬酸铁和 1,680mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 9 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 9 克柠檬酸铁和 1,890mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 10 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 10 克柠檬酸铁和 2,100mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 11 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 11 克柠檬酸铁和 2,310mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 12 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 12 克柠檬酸铁和 2,520mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 13 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 13 克柠檬酸铁和 2,730mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 14 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 14 克柠檬酸铁和 2,940mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 15 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 15 克柠檬酸铁和 3,150mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 16 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 16 克柠檬酸铁和 3,360mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 17 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 17 克柠檬酸铁和 3,570mg 三价铁。在有些实施方案中，所述柠檬酸铁以每天 18 个片剂的日剂量给予，每一个片剂包含 1 克含有 210mg 三价铁的柠檬酸铁，总日剂量为 18 克柠檬酸铁和 3,780mg 三价铁。

实施例

[0264] 以下实施例详细说明了本文公开的柠檬酸铁的应用。对技术人员本领域来说显而易见的是，对材料和方法二者的许多修改可以在不偏离本公开的范围的情况下予以实施。

[0265] 实施例 1

[0266] A 在正在接受透析的终末期肾病 (ESRD) 患者中作为磷酸盐结合剂的柠檬酸铁的三个周期、58 周试验

[0267] 本试验的主要目的如下：

[0268] 1. 为了确定多达十二 (12) 个小胶囊剂 / 天的 KRX-0502（柠檬酸铁）在接受血液透析或腹膜透析的终末期肾病患者中历经 52 周的长期安全性。

[0269] 2. 为了确定 KRX-0502（柠檬酸铁）在四周、随机化、开放标签、安慰剂对照疗效评估期中的疗效。

[0270] 研究理由

[0271] 临床前试验已经证明柠檬酸铁降低正在接受一周三次血液透析的 ESRD 患者的血清磷水平的能力。这些试验使用了大约 12g/ 天的柠檬酸铁持续四周的最大量。

[0272] 本临床试验确定了当在安全性评估期（持续 52 周）中与活性剂对照相比和在随机化、开放标签、安慰剂对照四周疗效评估期中与安慰剂相比时，柠檬酸铁在 56 周治疗期内在控制和处理血清磷水平中的长期安全性。

[0273] 研究设计

[0274] 本试验为三个周期、多中心、安全性和疗效临床试验。第一个周期是两周洗脱（洗脱期），第二个周期是 52 周随机化、开放标签、活性剂对照安全性评估（安全性评估期），第三个周期是四周、随机化、开放标签、安慰剂对照疗效评估（疗效评估期），在安全性评估期的期间，仅在用柠檬酸铁治疗的随机化患者中进行。

[0275] 1 期（洗脱期）。患者洗脱他们目前的磷酸盐结合剂多达大约两周。只有在洗脱期的期间达到血清磷≥ 6.0mg/dL 的患者才移到安全性评估期。在洗脱期间没有达到血清磷≥ 6.0mg/dL 的患者为筛选失败。

[0276] 2 期（安全性评估期）。在洗脱后，患者按 2:1 随机分到柠檬酸铁组或醋酸钙、司维拉姆碳酸盐或醋酸钙和司维拉姆碳酸盐的任何组合的活性剂对照组，由 PI 和 / 或患者决定。柠檬酸铁和活性剂对照药物均由赞助方提供。患者按照他们的随机化分配在 52 周内进行安全性评估。如果患者是≥ 80％依从服用 12 个小胶囊剂 / 天的柠檬酸铁或 12 粒丸剂 / 天的醋酸钙和 / 或司维拉姆碳酸盐至少连续 2 次访视但血清磷 >8.0mg/dL，那么该患者被认为是治疗失败并停止研究药物但继续完成所有试验访视。柠檬酸铁或活性剂对照药物停止，该患者返回到他们最初的肾病专科医生照顾，但继续跟踪所有试验访视和结果。

[0277] 3 期（疗效评估期）。在安全性评估期后，那些随机用柠檬酸铁治疗的患者进入四周、随机化、开放标签、安慰剂对照疗效评估期。进入疗效评估期的患者按 1:1 重新随机分配到用柠檬酸铁或安慰剂治疗。

[0278] 在洗脱期期间或在随机化访视 (Randomization Visit) 时，营养师向患者提供富含维生素 D 的食物的研究供应清单，并且教导患者在整个试验中尽可能保持他们的饮食始终如一的是富含维生素 D 的食物。在疗效评估期开始之前的 30 天以内，营养师与患者一起再次审核富含维生素 D 的食物清单并提醒患者设法保持他们的饮食始终如一的是富含维生素 D 的食物直到试验结束为止，如果可能的话。在疗效评估期的期间，营养师采用盲法向柠檬酸铁或安慰剂分配。

[0279] 为了评估安全性和疗效，在整个研究中进行了多次实验室测量。所给予的剂量和具体静脉内铁制剂（必要时）是由 PI 决定。不允许使用口服铁疗法。含钙药物如果在食物摄入的两个小时以内服用不被允许（含钙药物在食物摄入之前或之后两个小时或更长时间或者在睡觉时为了升高血清钙的目的则被允许使用）。不允许使用维生素 C 补充剂。允许患者每天服用包括少量维生素 C 的水溶性维生素（例如，善存 (Centrum)、Nephrocaps、Renaphro)，但是教导那些患者要在食物摄入之前或之后两个小时或更长时间或者在睡觉时才准服用它们。如果铁蛋白水平 >1000 微克 /L 或 TSAT>30％，不允许使用静脉内铁剂疗法。如果在这些参数以外接受静脉内铁剂被认为在患者的最大利益之中，则向临床协作中心 (CCC) 咨询，并且当被批准和记录时，不被临床协作中心 (CCC) 认为是协议例外。

[0280] 研究持续期间

[0281] 本试验的持续期间是大约 18 到 24 个月，其中大约六到八个月分配给患者筛选、洗脱期和随机化，12 个月分配给安全性评估期，和一 (1) 个月分配给疗效评估期。

[0282] 研究人群

[0283] 以下 ESRD 患者符合条件报名：在筛选访视（访视 0）之前正在接受一周三次血液透析或正在接受腹膜透析持续至少三个月，目前正在服用≥ 3 粒和≤ 18 粒丸剂 / 天的醋酸钙、碳酸钙、碳酸镧和 / 或司维拉姆（碳酸盐或盐酸盐或司维拉姆粉末（相当于司维拉姆片剂））或任何起到磷酸盐结合剂作用的其它药剂或这些药剂的任何组合。可以预料在美国有大约 20 到 40 个中心和在以色列有大约 5 到 10 个中心。筛选了多达大约 775 例患者，将大约 350 例患者随机分到柠檬酸铁组或活性剂对照组。询问了大约 25 到 50 个地点中的每一个以随机分配不超过大约 35 例患者。

[0284] 纳入标准：

[0285] ●男性或未怀孕、未哺乳的女性

[0286] ●年龄≥ 18 岁

[0287] ●在筛选访视（访视 0）之前至少前三个月，正在接受一周三次血液透析或正在接受腹膜透析

[0288] ●在筛选访视（访视 0）时，血清磷水平≥ 2.5mg/dL 和≤ 8.0mg/dL

[0289] ●在洗脱期（访视 2 或 3）的期间，血清磷≥ 6.0mg/dL

[0290] ●服用 3 至 18 粒丸剂 / 天的醋酸钙、碳酸钙、碳酸镧和 / 或司维拉姆（碳酸盐或盐酸盐或等同的司维拉姆粉末）或任何起到磷酸盐结合剂作用的其它药剂或这些药剂的任何组合，由患者在筛选访视（访视 0）时报告

[0291] ●在筛选访视（访视 0）时，血清铁蛋白 <1000 微克 /L 和 TSAT<50％

[0292] ●愿意中断目前的磷酸盐结合剂并愿意随机分到柠檬酸铁组或活性剂对照组

[0293] ●自愿且能够签署知情同意书

[0294] ●预期寿命 >1 年

[0295] 排除标准：

[0296] ●在筛选访视（访视 0）之前六个月以内做了甲状旁腺切除术

[0297] ●活动性有症状的胃肠出血或炎症性肠疾病

[0298] ●在筛选访视（访视 0）之前 3 个月以内，在每月三次实验室测量（在透析单位常规做的）的全部测量中记录有血清磷水平≥ 10.0mg/dL

[0299] ●最近五年内有恶性肿瘤病史（经治疗的宫颈癌或非黑素瘤性皮肤癌如果经 CCC 批准可被允许）

[0300] ●绝对需要口服铁疗法

[0301] ●绝对需要维生素 C（复合维生素 [Nephrocaps, Renaphro 等] 被允许）

[0302] ●绝对需要用餐时含有钙、镁或铝的药物

[0303] ●不耐受口服含铁产品

[0304] ●不耐受口服给予的醋酸钙和司维拉姆碳酸盐

[0305] 研究药物

[0306] KRX-0502（柠檬酸铁）是在本研究中被调查的药物。该药物作为小胶囊剂给予，每

一个小胶囊剂包含 1 克 (1,000mg) 含有大约 210mg 三价铁的柠檬酸铁。

[0307] 研究药物给药

[0308] 血清磷的靶目标是 3.5 到 5.5mg/dL。

[0309] 柠檬酸铁、活性剂对照和安慰剂都被认为是研究药物。在洗脱期后，血清磷水平 ≥ 6.0mg/dL 的合格患者以 2:1 的比例随机分到柠檬酸铁组或活性剂对照组。对于随机分到柠檬酸铁组的患者，开始剂量为 6 粒小胶囊剂 / 天。对于随机分到活性剂对照组的患者，磷酸盐结合剂的开始剂量为正好在洗脱期开始之前给予的最后剂量 (如果患者仍保留同一种磷酸盐结合剂)，或由 PI 决定，按包装插页说明书指导进行，如果患者改变结合剂的话。然而，对于磷酸盐结合剂之前的剂量超过了 12 粒丸剂 / 天的患者，如果被随机分到活性剂对照组，活性剂对照药物的开始剂量是由 PI 决定，但不要超过 12 粒丸剂 / 天。在试验的持续期间，使用醋酸钙 667mg 胶囊剂和司维拉姆碳酸盐 800mg 片剂并且均由 Keryx Biopharmaceuticals,Inc.(Keryx) 供应。

[0310] 血清磷和钙在访视 5(第 1 周) 时和在访视 4(随机化访视) 后前 12 周期间每两周和在安全性评估期的休息时每个月做检查。在疗效评估期的期间，血清磷和钙每周获取。这些值指导研究药物的给药。使用研究药物的同时，其它磷酸盐结合剂的使用不被许可。柠檬酸铁的剂量调整由滴定时间表指导。在整个 52 周安全性评估期，醋酸钙和司维拉姆碳酸盐的滴定根据这些药剂的现行包装插页说明书来进行和 / 或由该地点 PI 决定。

[0311] 患者在吃完正餐或点心时或 1 小时以内经口服服用研究药物。如果自患者吃完正餐或点心起时间过去了超过 1 个小时，告诉他们不要服用研究药物。在每个地点的 PI 或设计者将研究药物分配给患者并告诉患者如何用药。人们应该认识到，一些患者需要在给定的一天因吃点心或漏吃正餐所致的丸剂的不同分布。如果患者接受了用餐时在任何分布中按协议所需要的每天丸剂的总数，这不需要经过 CCC 批准 (例如，在开始剂量为柠檬酸铁 6g/ 天的患者可以吃早餐时服用 1 粒小胶囊剂、吃点心时 1 粒、吃午餐时 2 粒和吃晚餐时 2 粒)。

[0312] 实验室评估

[0313] 对于进行血液透析的患者，血样在该周的第二或第三个透析期的透析前获取，如果可能的话。对于在星期一、星期三或星期五透析的正在接受血液透析的患者，所有血样都在星期三或星期五时透析前抽取，如果可能的话。对于在星期二、星期四或星期六透析的患者，所有血样都在星期四或星期六时透析前抽取，如果可能的话。在以色列各采集地点，这些采集方法被允许不相同。从各患者采集的用于试验相关分析的血液总量是每次访视大约 15ml。

[0314] 对于正在接受腹膜透析的患者，按照研究协议，血样或在透析单位或在诊所采集。

[0315] 血清磷和钙如下进行 :在筛选 (访视 0) 时 ;每周在洗脱期的期间在访视 1 之后 (第 2 周) ;在访视 4(随机化访视) 时 ;在 52 周安全性评估期的访视 5(第 1 周)、6(第 2 周)、7(第 4 周)、8(第 6 周)、9(第 8 周)、10(第 10 周)、11(第 12 周)、12(第 16 周)、13(第 20 周)、14(第 24 周)、15(第 28 周)、16(第 32 周)、17(第 36 周)、18(第 40 周)、19(第 44 周)、20(第 48 周) 和 21(第 52 周) 时 ;和在疗效评估期的访视 22(第 53 周)、23(第 54 周)、24(第 55 周) 和 25(第 56 周) 时。

[0316] 完全血计数 (CBC)(白细胞 [WBC] 计数、白细胞类型 [WBC 分类]、红细胞 [RBC] 计

数、红细胞比容[HCT]、血红蛋白[Hgb]、红细胞指数、血小板[凝血细胞]计数)如下进行:在随机化访视(访视4)时;在52周安全性评估期的访视11(第12周)、14(第24周)、17(第36周)、20(第48周)和21(第52周)时;和在疗效评估期的访视25(第56周)时。

[0317] 完全化学概况分析(Complete Chemistry Profile)(钠、钾、氯离子、血液尿素氮(BUN)、肌酸酐、葡萄糖[随机]、天冬氨酸转氨酸[AST]、丙氨酸转氨酸[ALT]、碱性磷酸盐[ALP]、总胆红素、总蛋白、白蛋白和调节白蛋白的钙)如下进行:在随机化访视(访视4)时;在52周安全性评估期的访视11(第12周)、14(第24周)、17(第36周)、20(第48周)和21(第52周)时;和在疗效评估期的访视25(第56周)时。

[0318] 铁研究包括血清铁、铁蛋白、TSAT和总铁结合能力如下进行:在筛选(访视0)时;在随机化访视(访视4)时;在52周安全性评估期的访视7(第4周)、9(第8周)、11(第12周)、12(第16周)、13(第20周)、14(第24周)、15(第28周)、16(第32周)、17(第36周)、18(第40周)、19(第44周)、20(第48周)和21(第52周)时;和在疗效评估期的访视25(第56周)时。

[0319] 完整甲状旁腺激素(iPTH)水平如下进行:在随机化访视(访视4)时;在安全性评估期的期间在访视11(第12周)、17(第36周)和21(第52周)时;和在疗效评估期的访视25(第56周)时。

[0320] 血清维生素(25-二羟基-维生素D3、维生素A、维生素B-12、维生素E、维生素K和叶酸)如下进行:在随机化访视(访视4)时;和在安全性评估期的期间在访视11(第12周)、17(第36周)和21(第52周)时。

[0321] 脂质概况分析(lipid profile)(总胆固醇、低密度脂蛋白[LDL]、高密度脂蛋白[HDL]和甘油三酯)如下进行:在随机化访视(访视4)时;在安全性评估期的期间在访视11(第12周)、17(第36周)和21(第52周)时。

[0322] 血清铝如下进行:在随机化访视(访视4)时和在访视21(第52周)。

[0323] 血清碳酸氢盐如下进行:在地方实验室和在随机化访视(访视4)时;在安全性评估期的期间在访视11(第12周)、14(第24周)、17(第36周)、20(第48周)和21(第52周)时;和在疗效评估期的访视25(第56周)时。

[0324] 除了在地方采集和测量的血清碳酸氢盐以外,所有实验室项目都由Spectra Clinical Research,Rockleigh,NJ,USA完成。

[0325] 统计学考虑:疗效

[0326] 除非另有说明,否则所有假设都在0.05的双侧显著性水平上检验,该95%置信区间是双侧的。所有分析都采用SAS Version 9进行。

[0327] 在数据库锁定之前,详细的统计学分析计划(Statistical Analysis Plan,SAP)要完成并置于文档上。数据分析计划(Data Analysis Plan)含有比以下描述的统计学分析中使用的方法更加全面的解释。数据分析计划也含有进行分析所用的规则和数据处理规范,并且该程序用于说明缺失数据。

[0328] 总结制表展示观察数、平均值、标准偏差、中值、最小值、最大值和连续变量的适当百分位,及分类数据的分类数目和百分比。适当的时候,总结给出了治疗臂和总体的数据。这些数据列表包括所有可利用的疗效数据和安全性数据。

[0329] 疗效分析基于全分析 (FA) 人群，该 FA 人群由服用至少一个剂量的研究药物并提供基线和至少一个基线后疗效评估的所有患者组成。安全性分析基于安全性人群，安全性人群由服用至少一个剂量的研究药物的所有患者组成。

[0330] 有两种独特的和区别性的基线评估。安全性评估期的基线是随机化访视（访视 4）并定义为“第 0 周基线 (Week-0-baseline)”。疗效评估期的基线是安全性评估期的最后一次访视（访视 21，第 52 周）并定义为“研究基线 (study-baseline)”。

[0331] 本试验的主要疗效结果是柠檬酸铁 vs. 安慰剂对从研究基线（访视 21，第 52 周）到疗效评估期结束（访视 25，第 56 周）的血清磷变化的影响。主要的疗效变量通过用治疗作为固定效应和研究基线作为协变量的 ANCOVA 模型进行分析。估计治疗间差异并给出该差异的双侧 95％置信区间。

[0332] 本试验的次要终点包括以下终点：

[0333] 1. 在第 52 周时铁蛋白基线的变化

[0334] 与基线（访视 4）相比，在第 52 周时铁蛋白基线的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。使用 MMRM 方法进行灵敏度分析。

[0335] 2. 在第 52 周时 TSAT 基线的变化

[0336] 与基线（访视 4）相比，在第 52 周时 TSAT 基线的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。使用 MMRM 方法进行灵敏度分析。

[0337] 3. 在 52 周内静脉内铁剂的累积使用量

[0338] 从随机化到第 52 周的累积静脉内铁剂摄入量在治疗组之间进行比较。这个变量使用 ANCOVA 方法像主要的疗效变量一样进行类似分析。对于所有以上比较将给出治疗差异的双侧 95％置信区间。

[0339] 4. 在 52 周内 EPO(ESA) 的累积使用量

[0340] 从随机化到第 52 周给予的累积 EPO(ESA) 在治疗组之间进行比较。这个变量使用 ANCOVA 方法像主要的疗效变量一样进行类似分析。对于所有以上比较将给出治疗差异的双侧 95％置信区间。

[0341] 在血清磷、磷乘以钙之积中和在血清钙中，在第 12 周（访视 11）相对于访视 -4 基线的变化，对在柠檬酸铁和所有活性剂对照结合剂之间的治疗差异以及在柠檬酸铁和作为单个药剂的司维拉姆碳酸盐之间的治疗差异进行分析。这些变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和访视 -4 基线（协变量）。使用 MMRM 方法进行分析作为灵敏度分析。获取治疗效应的最小平水平均估计以及治疗效应的双侧 95％置信区间 (CI)。如果治疗差异的双侧 95％置信区间的下边界是在对照的最小平方平均值的 20％以内，非劣效性 (Non-inferiority) 将请求被保护。

[0342] 5. 达到磷目标的患者百分比

[0343] 1). 在第 12、24、36、48、52 和 56 周达到磷目标（≤ 5.5mg/dL）的患者百分比 - 这些变量将通过 x^2 检验 (chi-square test) 进行分析。估计在治疗之间百分比的差异，采用不伴有连续性校正的正态大约法计算各差异的双侧 95％置信区间。

[0344] 2). 对于在四周疗效评估期的期间仍保留在研究药物上的患者，在第 56 周达到磷

目标（≤ 5.5mg/dL）的患者百分比－这些变量将通过 x^2检验进行分析。估计在治疗之间百分比的差异，采用不伴有连续性校正的正态大约法计算各差异的双侧 95％置信区间。

[0345] 3). 在四周疗效评估期的期间，在任何时间获得血清磷≥ 9.0mg/dL 的患者百分比－这些变量将通过 x^2检验进行分析。估计在治疗之间百分比的差异，采用不伴有连续性校正的正态大约法计算各差异的双侧 95％置信区间。

[0346] 6. 血清磷浓度的变化

[0347] 1). 与基线（访视 4）相比，在第 12、24、36、48 和 52 周，在血清磷浓度中的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。

[0348] 7. 在其它实验室测量中的变化

[0349] 1). 与基线（访视 4）相比，在第 12、24、36、48 和 52 周，在血清钙浓度中的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。

[0350] 2). 与基线（访视 4）相比，在第 12、24、36 和 48 周，在铁蛋白和 TSAT 中的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。

[0351] 3). 与基线（访视 4）相比，在第 12、24、36、48 和 52 周，在血清铁和 TIBC 中的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。

[0352] 4). 与基线（访视 4）相比，在第 12、24、36、48 和 52 周，在 Ca x P 之积中的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。

[0353] 5). 与基线（访视 4）相比，在第 12、36、52 和 56 周，在 iPTH 中的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。

[0354] 6). 与基线（访视 4）相比，在第 12、36 和 52 周，在血清 25- 二羟基－维生素 D3、维生素 A、维生素 B-12、维生素 E、维生素 K 和叶酸中的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。

[0355] 7). 与基线（访视 4）相比，在第 12、36 和 52 周，在血清碳酸氢盐浓度中的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。

[0356] 8). 与基线（访视 4）相比，在第 12、24、36、48 和 52 周，在静脉内铁剂摄入量中的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。

[0357] 9). 与基线（访视 4）相比，在第 12、24、36、48 和 52 周，在给予的 EPO(ESA) 使用中的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。

[0358] 10). 与基线（访视 4）相比，在第 12、24、36、48 和 52 周，在使用维生素 D 补充剂（及其类似物）和 Sensipar（西那卡塞特 (cinacalcet)）中的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。

[0359] 11). 与基线（访视 4）相比，在第 12、36 和 52 周，在 LDL、HDL 和甘油三酯中的变化。这个变量采用 LOCF 方法进行分析。使用 ANCOVA。该模型包括治疗（固定效应）和基线（协变量）。

[0360] 统计学考虑：安全性

[0361] 通过记录并监测不良事件、同时使用的药物、身体检查和按治疗分配 (treatment assignment) 的序贯血液来评估安全性。不良事件率概括为总体和按器官系统分类、优选的项目 (preferred term)、严重程度和按治疗分配怀疑与研究药物的关系。AEs 概括为用治疗分配分开的洗脱期、安全性评估期和疗效评估期。实验室参数相对于基线随时间的变化按治疗分配进行总结。

[0362] 统计学考虑：效力

[0363] 在安全性评估期的期间，大约 434 例患者以 2:1 的比例随机分到柠檬酸铁（大约 288 例患者）或活性剂对照（大约 146 例患者）进行治疗。这个样本文小提供至少 90％效力以检测在 5％显著性水平上柠檬酸铁和安慰剂之间的治疗差异，假定治疗差异是 1.2，普通的标准偏差是 2。

[0364] 结果

[0365] 在第 12 周，在血清磷、磷乘以钙之积和血清钙相对于研究基线的变化方面，在柠檬酸铁和作为单个药剂的司维拉姆碳酸盐之间的治疗差异 (ANCOVA 方法)、全分析人群 (Full Analysis Population) 的总结 - - 见表 12：

[0366] 表 12:

[0367]

统计学	安全性评估期中的 KRX-0502 (N=288)	安全性评估期中的 司维拉姆碳酸盐 (N=73)	治疗差异[1]
磷(MG/DL)			
基线			
N	277	72	
平均值(SD)	7.39 (1.557)	7.51 (1.633)	
中值	7.20	7.40	
(最小值, 最大值)	(2.7, 12.3)	(4.3, 12.9)	
第 12 周			
N	277	72	
平均值(SD)	5.38 (1.374)	5.23 (1.713)	
中值	5.10	5.00	
(最小值, 最大值)	(2.4, 9.9)	(2.5, 14.1)	
第 12 周相对于基线的变化			
N			
平均值(SD)	277	72	
中值	-2.01 (1.887)	-2.28 (2.169)	
(最小值, 最大值)	-2.00	-2.45	
95% CI	(-7.6, 4.6)	(-8.9, 6.7)	(-0.21, 0.54)
LS 平均值(SE)	(5.21, 5.55)	(4.89, 5.55)	0.16 (0.19)
p-值	5.38 (0.09)	5.22 (0.17)	0.3900
钙和磷之积			
基线			
N	277	72	
平均值(SD)	65.4075 (15.47697)	68.0872 (16.29263)	
中值	62.7000	66.2700	
(最小值, 最大值)	(25.920, 123.210)	(36.660, 123.840)	
第 12 周			
N	277	72	
平均值(SD)	48.8440 (12.93765)	48.0251 (14.36518)	
中值	47.5000	46.2800	
(最小值, 最大值)	20.440, 92.650)	(22.500, 109.980)	
第 12 周相对于基线的变化			
N	277	72	

[0368]

平均值(SD)	-16.5635	-20.0621 (19.17393)	
中值	(16.97535)	-19.8500	
(最小值, 最大值)	-16.7400	86.200, 46.340)	(-1.87, 4.77)
95% CI	(-78.660, 42.700)	(44.57, 50.48)	1.45 (1.69)
LS 平均值(SE)	(47.47, 50.48)	47.52 (1.50)	0.3903
p-值	48.97 (0.77)		
钙(MG/DL)			
基线			
N	278	72	
平均值(SD)	8.843 (0.8048)	9.056 (0.7291)	
中值	8.900	9.150	
(最小值, 最大值)	(6.30, 11.10)	(6.70, 10.30)	
第 12 周			
N	278	72	
平均值(SD)	9.089 (0.7568)	9.231 (0.7210)	
中值	9.100	9.400	
(最小值, 最大值)	(6.30, 12.00)	(7.00, 10.60)	
第 12 周相对于基线的变化			
N			
平均值(SD)	278	72	
中值	0.245 (0.7486)	0.175 (0.7509)	
(最小值, 最大值)	0.200	0.100	
95% CI	(-2.80, 3.00)	(-1.50, 2.30)	(-0.20, 0.13)
LS 平均值(SE)	(9.04, 9.19)	(9.00, 9.29)	-0.04 (0.08)
p-值	9.11 (0.04)	9.15 (0.08)	0.6765

[0369] 注释 :[1].LS 平均治疗差异和在血清磷、Ca x P 和 Ca 中变化的 p- 值通过用治疗作为固定效应和第 0 天基线作为协变量的 ANCOVA 模型来创建。治疗间的差异计算为 LS 平均值 (KRX-0502)-LS 平均值 (对照)。仅包括对于感兴趣参数具有基线和基线后观察二者的受试者。

[0370] 在第 12、24、36、48 和 52 周的平均血清磷值和相对于通过治疗的研究基线的变化 (ANCOVA 方法)、全分析人群的总结 - - 见表 13 :

[0371] 表 13:

[0372]

统计学	安全性评估期中的 KRX-0502 (N=288)	安全性评估期中的 对照 (N=146)	治疗差异[1]
第 0 天基线			
N	277	144	
平均值(SD)	7.39 (1.557)	7.55 (1.750)	
中值	7.20	7.40	
(最小值, 最大值)	(2.7, 12.3)	(4.3, 12.9)	
第 12 周			
N	277	144	
平均值(SD)	5.38 (1.374)	5.34 (1.652)	
中值	5.10	5.05	
(最小值, 最大值)	(2.4, 9.9)	(2.5, 14.1)	
第 12 周相对于基线的变化			
N	277	144	
平均值(SD)	-2.01 (1.887)	-2.21 (2.086)	
中值	-2.00	-2.25	
(最小值, 最大值)	(-7.6, 4.6)	(-8.9, 6.7)	(-0.23, 0.36)
95% CI	(5.22, 5.56)	(5.08, 5.56)	0.07 (0.15)
LS 平均值(SE)	5.39 (0.09)	5.30 (0.12)	0.6594
p-值			
第 24 周			
N	277	144	

[0373]

平均值(SD)	5.24 (1.455)	5.49 (1.536)	
中值	5.10	5.30	
(最小值, 最大值)	(1.3, 10.7)	(2.0, 14.1)	
第 24 周相对于基线的变化			
N			
平均值(SD)	277	144	
中值	-2.14 (1.844)	-2.06 (2.125)	
(最小值, 最大值)	-2.10	-2.00	
95% CI	(-7.5, 3.9)	(-8.4, 6.7)	(-0.51, 0.08)
LS 平均值(SE)	(5.08, 5.43)	(5.23, 5.71)	-0.21 (0.15)
p-值	5.26 (0.09)	5.47 (0.12)	0.1510
第 36 周			
N	277	144	
平均值(SD)	5.22 (1.348)	5.32 (1.557)	
中值	5.10	5.10	
(最小值, 最大值)	(1.1, 9.5)	(2.2, 14.1)	
第 36 周相对于基线的变化			
N			
平均值(SD)	277	144	
中值	-2.16 (1.748)	-2.24 (2.037)	
(最小值, 最大值)	-2.10	-2.10	
95% CI	(-7.4, 3.2)	(-8.1, 6.7)	(-0.33, 0.22)
LS 平均值(SE)	(5.08, 5.40)	(5.07, 5.52)	-0.05 (0.14)
p-值	5.24 (0.08)	5.29 (0.11)	0.7075
第 48 周			
N	277	144	
平均值(SD)	5.32 (1.468)	5.48 (1.563)	
中值	5.20	5.35	
(最小值, 最大值)	(2.2, 10.8)	(2.2, 14.1)	
第 48 周相对于基线的变化			
N			
平均值(SD)	277	144	
中值	-2.07 (1.828)	-2.07 (2.036)	
(最小值, 最大值)	-2.10	-1.90	
95% CI	(-8.4, 4.6)	(-7.8, 6.7)	(-0.42, 0.17)
LS 平均值(SE)	(5.16, 5.50)	(5.22, 5.69)	-0.12 (0.15)
p-值	5.33 (0.09)	5.46 (0.12)	0.4086
第 52 周			
N	277	144	
平均值(SD)	5.32 (1.437)	5.36 (1.572)	
中值	5.20	5.10	
(最小值, 最大值)	(1.1, 10.7)	(2.6, 14.1)	
第 52 周相对于基线的变化			
N			
平均值(SD)	277	144	
中值	-2.06 (1.834)	-2.19 (2.220)	
(最小值, 最大值)	-2.20	-2.10	
95% CI	(-7.1, 3.7)	(-9.8, 6.7)	(-0.30, 0.29)
LS 平均值(SE)	(5.16, 5.51)	(5.10, 5.58)	-0.01 (0.15)
p-值	5.33 (0.09)	5.34 (0.12)	0.9696

[0374] 注释 :[1].LS 平均治疗差异和在铁蛋白中变化的 p- 值通过用治疗作为固定效应和第 0 天基线作为协变量的 ANCOVA 模型来创建。治疗间的差异计算为 LS 平均值 (KRX-0502)-LS 平均值 (对照)。仅包括对于感兴趣参数具有基线和基线后观察二者的受试者。

[0375] 平均血清磷值和相对于通过治疗的第 52 周基线和在疗效评估期期间的访视的变

化 (ANCOVA 方法)、全分析人群的总结 - - 见表 14 :

[0376] 表 14:

[0377]

统计学	疗效评估期中的 KRX-0502 (N=92)	疗效评估期中的 安慰剂 (N=91)	治疗差异[1]
第 52 周基线			
N	85	82	
平均值(SD)	5.16 (1.259)	5.25 (1.475)	
中值	5.10	5.30	
(最小值, 最大值)	(2.2, 8.7)	(1.1, 8.8)	
第 53 周			
N	76	79	
平均值(SD)	4.90 (1.152)	6.66 (1.611)	
中值	4.95	6.50	
(最小值, 最大值)	(2.0, 7.7)	(2.4, 10.6)	
第 53 周相对于基线的变化			
N			
平均值(SD)	76	79	
中值	-0.31 (1.432)	1.39 (1.626)	
(最小值, 最大值)	-0.30	1.30	
95% CI	(-4.6, 2.9)	(-2.1, 5.5)	(-2.15, -1.32)
LS 平均值(SE)	(4.62, 5.21)	(6.36, 6.94)	-1.73 (0.21)
p-值	4.92 (0.15)	6.65 (0.15)	<0.0001
第 54 周			
N	84	81	
平均值(SD)	4.78 (1.309)	6.91 (1.724)	
中值	4.70	6.80	
(最小值, 最大值)	(2.1, 8.9)	(3.4, 10.6)	
第 54 周相对于基线的变化			
N			
平均值(SD)	84	81	
中值	-0.36 (1.404)	1.65 (1.847)	
(最小值, 最大值)	-0.40	1.60	
95% CI	(-3.9, 3.8)	(-2.3, 6.5)	(-2.52, -1.64)
LS 平均值(SE)	(4.50, 5.11)	(6.57, 7.20)	-2.08 (0.22)
p-值	4.80 (0.16)	6.88 (0.16)	<0.0001
第 55 周			
N	85	82	
平均值(SD)	4.75 (1.237)	6.96 (1.808)	
中值	4.60	7.00	
(最小值, 最大值)	(2.8, 9.5)	(2.7, 10.6)	
第 55 周相对于基线的变化			
N			
平均值(SD)	85	82	
中值	-0.41 (1.444)	1.71 (1.967)	
(最小值, 最大值)	-0.50	1.85	
95% CI	(-3.2, 4.6)	(-2.6, 6.5)	(-2.63, -1.73)
LS 平均值(SE)	(4.45, 5.08)	(6.65, 7.26)	-2.18 (0.23)
p-值	4.76 (0.16)	6.94 (0.16)	<0.0001
第 56 周			
N	85	82	
平均值(SD)	4.92 (1.323)	7.24 (1.812)	
中值	4.60	7.25	
(最小值, 最大值)	(2.3, 9.5)	(3.0, 10.6)	
第 56 周相对于基线的变化			
N	85	82	
平均值(SD)	-0.23 (1.484)	1.99 (1.979)	
中值	-0.50	2.20	
(最小值, 最大值)	(-2.9, 4.6)	(-2.7, 6.5)	(-2.74, -1.82)

[0378]

95% CI	(4.62, 5.26)	(6.89, 7.55)	-2.28 (0.23)
LS 平均值(SE)	4.94 (0.16)	7.22 (0.17)	
p-值			<0.0001

[0379] 注释：[1].LS 平均治疗差异和在血清磷中变化的 p- 值通过用治疗作为固定效应和第 52 周基线作为协变量的 ANCOVA 模型来创建。治疗间的差异计算为 LS 平均值 (KRX-0502)-LS 平均值（安慰剂）。仅包括对于感兴趣参数具有基线和基线后观察二者的受试者。

[0380] 在第 12、24、36、48 和 52 周的平均铁蛋白和相对于通过治疗的研究基线的变化 (ANCOVA 方法)、全分析人群的总结 - - 见表 15：

[0381] 表 15:

[0382]

统计学	安全性评估期中的 KRX-0502 (N=288)	安全性评估期中的 对照 (N=146)	治疗差异[1]
第 0 天基线			
N	249	134	
平均值(SD)	595.00 (293.896)	615.76 (307.842)	
中值	587.00	574.00	
(最小值, 最大值)	(22.0, 1612.0)	(11.0, 1548.0)	
第 12 周			
N	243	134	
平均值(SD)	751.19 (379.766)	656.68 (321.518)	
中值	718.00	646.50	
(最小值, 最大值)	(25.0, 2691.0)	(13.0, 1664.0)	
第 12 周相对于基线的变化			
N			
平均值(SD)	243	134	
中值	158.88 (283.314)	40.92 (273.201)	
(最小值, 最大值)	123.00	26.50	
95% CI	(-882.0, 1660.0)	(-794.0, 920.0)	(55.22, 170.68)
LS 平均值(SE)	(723.34, 792.15)	(598.46, 691.14)	112.95 (29.36)
p-值	757.75 (17.50)	644.80 (23.57)	<0.0001
第 24 周			
N	247	134	
平均值(SD)	846.90 (414.672)	658.44 (301.698)	
中值	830.00	675.00	
(最小值, 最大值)	(91.0, 2413.0)	(11.0, 1525.0)	
第 24 周相对于基线的变化			
N			
平均值(SD)	247	134	
中值	252.49 (326.299)	42.68 (291.868)	
(最小值, 最大值)	220.00	35.50	
95% CI	(-628.0, 1594.0)	(-997.0, 757.0)	(139.87, 269.00)
LS 平均值(SE)	(814.24, 890.79)	(596.11, 700.06)	204.43 (32.84)
p-值	852.52 (19.47)	648.08 (26.43)	<0.0001
第 36 周			
N	247	134	
平均值(SD)	863.18 (444.094)	635.96 (326.652)	
中值	818.00	612.00	
(最小值, 最大值)	(51.0, 3181.0)	(13.0, 2080.0)	
第 36 周相对于基线的变化			
N	247	134	
平均值(SD)	268.77 (391.292)	20.20 (328.820)	
中值	223.00	11.00	
(最小值, 最大值)	(-754.0, 2193.0)	(-958.0, 1589.0)	(165.99, 316.49)
95% CI	(823.50, 912.72)	(566.30, 687.45)	241.24 (38.27)

[0383]

LS 平均值(SE)	868.11 (22.69)	626.87 (30.81)	<0.0001
p-值			
第 48 周			
N	247	134	
平均值(SD)	882.10 (461.772)	626.63 (353.836)	
中值	850.00	597.00	
(最小值, 最大值)	(44.0, 3188.0)	(84.0, 1784.0)	
第 48 周相对于基线的变化			
N	247	134	
平均值(SD)	287.69 (395.752)	10.87 (352.066)	
中值	233.00	13.50	
(最小值, 最大值)	(-667.0, 2032.0)	(-1184.0, 1409.0)	(192.20, 348.93)
95% CI	(840.95, 933.86)	(553.76, 679.93)	270.56 (39.85)
LS 平均值(SE)	887.41 (23.63)	616.85 (32.08)	<0.0001
p-值			
第 52 周			
N	249	134	
平均值(SD)	897.12 (485.296)	625.30 (359.018)	
中值	858.00	576.00	
(最小值, 最大值)	(44.0, 3144.0)	(33.0, 1789.0)	
第 52 周相对于基线的变化			
N	249	134	
平均值(SD)	302.11 (435.183)	9.54 (360.411)	
中值	224.00	21.50	
(最小值, 最大值)	(-785.0, 2032.0)	(-1165.0, 1409.0)	(201.58, 369.71)
95% CI	(852.25, 951.66)	(548.54, 684.08)	285.65 (42.76)
LS 平均值(SE)	901.95 (25.28)	616.31 (34.47)	<0.0001
p-值			

[0384] 注释：[1].LS 平均治疗差异和在铁蛋白中变化的 p- 值通过用治疗作为固定效应和第 0 天基线作为协变量的 ANCOVA 模型来创建。治疗间的差异计算为 LS 平均值 (KRX-0502)-LS 平均值（对照）。仅包括对于感兴趣参数具有基线和基线后观察二者的受试者。

[0385] 在第 12、24、36、48 和 52 周的平均 TSAT 和相对于通过治疗的研究基线的变化 (ANCOVA 方法)、全分析人群的总结 - - 见表 16：

[0386] 表 16:

[0387]

统计学	安全性评估期中的 KRX-0502 (N=288)	安全性评估期中的 对照 (N=146)	治疗差异[1]
第 0 天基线			
N	244	131	
平均值(SD)	31.0 (10.99)	31.0 (11.75)	
中值	29.5	29.0	
(最小值, 最大值)	(10, 83)	(10, 73)	
第 12 周			
N	238	131	
平均值(SD)	40.2 (16.00)	31.4 (12.13)	
中值	37.0	29.0	
(最小值, 最大值)	(12, 85)	(10, 79)	
第 12 周相对于基线的变化			
N	238	131	
平均值(SD)	9.2 (17.95)	0.5 (15.91)	
中值	7.0	1.0	
(最小值, 最大值)	(-61, 62)	(-54, 51)	(5.61, 11.87)
95% CI	(38.31, 42.03)	(28.92, 33.94)	8.74 (1.59)
LS 平均值(SE)	40.17 (0.95)	31.43 (1.28)	<0.0001

[0388]

p-值			
第 24 周			
N	242	131	
平均值(SD)	39.9 (15.52)	31.6 (11.96)	
中值	38.0	29.0	
(最小值, 最大值)	(13, 92)	(11, 79)	
第 24 周相对于基线的变化			
N			
平均值(SD)	242	131	
中值	8.9 (17.49)	0.6 (15.40)	
(最小值, 最大值)	7.0	0.0	
95% CI	(-43, 63)	(-52, 49)	(5.25, 11.31)
LS 平均值(SE)	(38.11, 41.70)	(29.18, 34.06)	8.28 (1.54)
p-值	39.90 (0.91)	31.62 (1.24)	<0.0001
第 36 周			
N	242	131	
平均值(SD)	39.8 (15.66)	30.4 (10.88)	
中值	37.0	28.0	
(最小值, 最大值)	(14, 86)	(13, 67)	
第 36 周相对于基线的变化			
N			
平均值(SD)	242	131	
中值	8.8 (17.47)	-0.6 (14.99)	
(最小值, 最大值)	7.0	-1.0	
95% CI	(-57, 63)	(-45, 49)	(6.45, 12.43)
LS 平均值(SE)	(38.03, 41.57)	(27.95, 32.76)	9.44 (1.52)
p-值	39.80 (0.90)	30.36 (1.22)	<0.0001
第 48 周			
N	242	131	
平均值(SD)	40.6 (16.94)	29.4 (10.71)	
中值	38.0	28.0	
(最小值, 最大值)	(13, 86)	(10, 74)	
第 48 周相对于基线的变化			
N			
平均值(SD)	242	131	
中值	9.6 (19.25)	-1.5 (14.48)	
(最小值, 最大值)	7.0	-2.0	
95% CI	(-45, 67)	(-48, 42)	(7.98, 14.37)
LS 平均值(SE)	(38.71, 42.49)	(26.85, 32.00)	11.17 (1.62)
p-值	40.60 (0.96)	29.43 (1.31)	<0.0001
第 52 周			
N	244	131	
平均值(SD)	39.4 (16.81)	29.7 (11.49)	
中值	35.0	28.0	
(最小值, 最大值)	(7, 88)	(10, 72)	
第 52 周相对于基线的变化			
N			
平均值(SD)	244	131	
中值	8.3 (17.97)	-1.3 (14.94)	
(最小值, 最大值)	6.0	0.0	
95% CI	(-60, 62)	(-53, 43)	(6.49, 12.83)
LS 平均值(SE)	(37.48, 41.23)	(27.14, 32.25)	9.66 (1.61)
p-值	39.35 (0.95)	29.69 (1.30)	<0.0001

[0389] 注释 :[1].LS 平均治疗差异和在铁蛋白中变化的 p- 值通过用治疗作为固定效应和第 0 天基线作为协变量的 ANCOVA 模型来创建。治疗间的差异计算为 LS 平均值 (KRX-0502)-LS 平均值 (对照)。仅包括对于感兴趣参数具有基线和基线后观察二者的受

试者。

[0390] 第 12、24、36、48 和 52 周的平均血红蛋白和相对于通过治疗的研究基线的变化(ANCOVA 方法)、全分析人群的总结 - - 见表 17 :

[0391] 表 17:

[0392]

统计学	安全性评估期中的 KRX-0502 (N=288)	安全性评估期中的 对照 (N=146)	治疗差异[1]
第 0 天基线			
N	244	130	
平均值(SD)	11.61 (1.213)	11.72 (1.265)	
中值	11.45	11.70	
(最小值, 最大值)	(8.7, 15.8)	(8.7, 15.7)	
第 12 周			
N	231	128	
平均值(SD)	11.82 (1.375)	11.55 (1.268)	
中值	11.70	11.60	
(最小值, 最大值)	(7.5, 17.4)	(6.7, 14.5)	
第 12 周相对于基线的变化			
N			
平均值(SD)	231	128	
中值	0.19 (1.397)	-0.16 (1.522)	
(最小值, 最大值)	0.10	-0.05	
95% CI	(-4.6, 4.0)	(-4.3, 3.5)	(0.03, 0.57)
LS 平均值(SE)	(11.67, 11.99)	(11.31, 11.75)	0.30 (0.14)
p-值	11.83 (0.08)	11.53 (0.11)	0.0291
第 24 周			
N	241	130	
平均值(SD)	11.55 (1.401)	11.47 (1.165)	
中值	11.30	11.40	
(最小值, 最大值)	(6.6, 17.3)	(9.2, 15.4)	
第 24 周相对于基线的变化			
N			
平均值(SD)	241	130	
中值	-0.08 (1.405)	-0.25 (1.394)	
(最小值, 最大值)	-0.10	-0.30	
95% CI	(-6.3, 3.8)	(-2.9, 3.5)	(-0.14, 0.38)
LS 平均值(SE)	(11.41, 11.72)	(11.23, 11.65)	0.12 (0.13)
p-值	11.56 (0.08)	11.44 (0.11)	0.3756
第 36 周			
N	241	130	
平均值(SD)	11.54 (1.432)	11.31 (1.205)	
中值	11.20	11.20	
(最小值, 最大值)	(8.6, 17.4)	(8.9, 14.9)	
第 36 周相对于基线的变化			
N			
平均值(SD)	241	130	
中值	-0.08 (1.359)	-0.41 (1.577)	
(最小值, 最大值)	-0.10	-0.50	
95% CI	(-5.1, 3.9)	(-3.8, 4.6)	(0.00, 0.54)
LS 平均值(SE)	(11.39, 11.71)	(11.06, 11.50)	0.27 (0.14)
p-值	11.55 (0.08)	11.28 (0.11)	0.0482
第 48 周			
N	241	130	
平均值(SD)	11.50 (1.502)	11.25 (1.296)	
中值	11.20	11.10	
(最小值, 最大值)	(6.7, 18.2)	(7.9, 16.1)	
第 48 周相对于基线的变化			
N	241	130	

[0393]

平均值(SD)	-0.12 (1.395)	-0.47 (1.498)	
中值	-0.20	-0.30	
(最小值, 最大值)	(-4.8, 4.9)	(-4.2, 3.5)	(0.03, 0.58)
95% CI	(11.35, 11.68)	(10.99, 11.44)	0.30 (0.14)
LS 平均值(SE)	11.52 (0.08)	11.21 (0.11)	0.0322
p-值			
第 52 周			
N	244	130	
平均值(SD)	11.42 (1.474)	11.11 (1.403)	
中值	11.20	11.00	
(最小值, 最大值)	(8.3, 16.6)	(7.1, 15.3)	
第 52 周相对于基线的变化			
N			
平均值(SD)	244	130	
中值	-0.20 (1.326)	-0.61 (1.581)	
(最小值, 最大值)	-0.20	-0.60	
95% CI	(-3.9, 3.7)	(-4.9, 4.6)	(0.09, 0.64)
LS 平均值(SE)	(11.27, 11.60)	(10.85, 11.30)	0.36 (0.14)
p-值	11.44 (0.08)	11.07 (0.11)	0.0105

[0394] 注释 :[1].LS 平均治疗差异和在铁蛋白中变化的 p- 值通过用治疗作为固定效应和第 0 天基线作为协变量的 ANCOVA 模型来创建。治疗间的差异计算为 LS 平均值 (KRX-0502)-LS 平均值 (对照)。仅包括对于感兴趣参数具有基线和基线后观察二者的受试者。

[0395] 在第 12、24、36、48 和 52 周的平均血清碳酸氢盐浓度和相对于通过治疗的研究基线的变化 (ANCOVA 方法)、全分析人群的总结 - - 见表 18 :

[0396] 表 18:

[0397]

统计学	安全性评估期中的 KRX-0502 (N=288)	安全性评估期中的 对照 (N=146)	治疗差异[1]
第 0 天基线			
N	214	117	
平均值(SD)	23.92 (3.408)	23.65 (3.393)	
中值	24.00	23.00	
(最小值, 最大值)	(13.0, 34.0)	(11.0, 32.0)	
第 12 周			
N	190	101	
平均值(SD)	25.63 (3.358)	26.25 (3.481)	
中值	25.00	26.00	
(最小值, 最大值)	(15.0, 36.0)	(16.0, 34.0)	
第 12 周相对于基线的变化			
N			
平均值(SD)	190	101	
中值	1.57 (3.364)	2.41 (3.813)	
(最小值, 最大值)	1.05	2.00	
95% CI	(-7.0, 13.0)	(-10.0, 14.0)	(-1.45, 0.01)
LS 平均值(SE)	(25.17, 26.03)	(25.73, 26.91)	-0.72 (0.37)
p-值	25.60 (0.22)	26.32 (0.30)	0.0522
第 24 周			
N	200	113	
平均值(SD)	25.39 (3.424)	25.66 (3.953)	
中值	25.45	26.00	
(最小值, 最大值)	(16.0, 36.0)	(16.0, 34.0)	
第 24 周相对于基线的变化			
N	200	113	
平均值(SD)	1.48 (3.499)	1.99 (3.854)	

[0398]

中值	1.00	2.00	
(最小值, 最大值)	(-13.0, 13.0)	(-6.0, 14.0)	(-1.13, 0.35)
95% CI	(24.90, 25.79)	(25.15, 26.33)	-0.39 (0.38)
LS 平均值(SE)	25.35 (0.23)	25.74 (0.30)	0.2974
p-值			
第 36 周			
N	212	117	
平均值(SD)	25.27 (3.152)	25.29 (3.700)	
中值	25.00	25.00	
(最小值, 最大值)	(17.0, 33.0)	(17.0, 36.0)	
第 36 周相对于基线的变化			
N			
平均值(SD)	212	117	
中值	1.36 (3.441)	1.64 (3.555)	
(最小值, 最大值)	1.00	1.00	
95% CI	(-10.0, 16.0)	(-7.0, 14.0)	(-0.82, 0.53)
LS 平均值(SE)	(24.82, 25.62)	(24.83, 25.91)	-0.15 (0.34)
p-值	25.22 (0.20)	25.37 (0.27)	0.6706
第 48 周			
N	212	117	
平均值(SD)	24.81 (3.177)	25.24 (3.643)	
中值	25.00	25.20	
(最小值, 最大值)	(15.0, 33.0)	(15.0, 34.0)	
第 48 周相对于基线的变化			
N			
平均值(SD)	212	117	
中值	0.91 (3.614)	1.59 (4.081)	
(最小值, 最大值)	1.00	1.00	
95% CI	(-12.0, 14.0)	(-9.0, 14.0)	(-1.23, 0.18)
LS 平均值(SE)	(24.36, 25.20)	(24.74, 25.87)	-0.52 (0.36)
p-值	24.78 (0.21)	25.30 (0.29)	0.1458
第 52 周			
N	214	117	
平均值(SD)	24.63 (4.049)	25.25 (3.871)	
中值	25.00	25.00	
(最小值, 最大值)	(-9.0, 33.0)	(15.0, 35.0)	
第 52 周相对于基线的变化			
N			
平均值(SD)	214	117	
中值	0.71 (4.369)	1.59 (4.668)	
(最小值, 最大值)	1.00	1.00	
95% CI	(-37.0, 15.0)	(-9.0, 14.0)	(-1.57, 0.16)
LS 平均值(SE)	(24.08, 25.11)	(24.60, 26.00)	-0.70 (0.44)
p-值	24.60 (0.26)	25.30 (0.36)	0.1117

[0399] 注释 :[1].LS 平均治疗差异和在铁蛋白中变化的 p- 值通过用治疗作为固定效应和第 0 天基线作为协变量的 ANCOVA 模型来创建。治疗间的差异计算为 LS 平均值 (KRX-0502)-LS 平均值 (对照)。仅包括对于感兴趣参数具有基线和基线后观察二者的受试者。

[0400] 通过治疗到第 52 周的累积静脉内铁剂摄入量、全分析人群、处理重叠剂量 (Overlapping Doses) 的方法 1 的总结 - - 见表 19 :

[0401] 表 19:

[0402]

统计学	安全性评估期中的 KRX-0502 (N=288)	安全性评估期中的 对照 (N=146)	治疗差异[1]
到第 52 周基于累积静脉内			

[0403]

铁剂摄入量的平均每日静脉内铁剂摄入量(访视 4 - 21) [2, 3]			
N	278	138	
平均值(SD)	2.96 (4.260)	4.86 (4.374)	
中值	1.86	3.84	
(最小值, 最大值)	(0.0, 44.3)	(0.0, 24.2)	
p-值[4]			<0.0001

[0404] 注释 :[1].LS 平均治疗差异和针对累积静脉内铁剂摄入量的 p- 值通过用治疗作为固定效应的 ANCOVA 模型来创建。治疗间的差异计算为 LS 平均值 (KRX-0502)-LS 平均值 (对照)。

[0405] 注释 :[2]. 到第 52 周基于累积静脉内铁剂摄入量的平均每日静脉内铁剂摄入量计算为把总的累积静脉内铁剂摄入量除以在研究药物上的总天数。

[0406] 注释 :[3]. 处理重叠剂量的方法 1 如下 :对于重叠剂量将基于仅包括在安全性评估期的期间在研究药物上的时间周期的剂量的天数进行按比例分配。

[0407] 注释 :[4]. 在基本假设不满足 ANCOVA 的情况下, 采用 Wilcoxon 秩和检验 (Wilcoxon Rank Sum Test) 计算 p- 值并去掉 CI 和 LS 平均值。

[0408] 通过治疗到第 52 周给予的累积 EPO(ESA)、全分析人群、处理重叠剂量的方法 1 的总结 - - 见表 20 :

[0409] 表 20:

[0410]

统计学	安全性评估期中的 KRX-0502 (N=288)	安全性评估期中的 对照 (N=146)	治疗差异[1]
到第 52 周基于累积 EPO (ESA)摄入量的平均每日 EPO (ESA)摄入量(访视 4 - 21) [2, 3]			
N	280	141	
平均值(SD)	1077.67 (1291.384)	1309.85 (1342.258)	
中值	724.24	993.46	
(最小值, 最大值)	(0.0, 11015.0)	(0.0, 8171.9)	
p-值[4]			0.0322

[0411] 注释 :[1].LS 平均治疗差异和针对累积 EPO(ESA) 摄入量的 p- 值通过用治疗作为固定效应的 ANCOVA 模型来创建。治疗间的差异计算为 LS 平均值 (KRX-0502)-LS 平均值 (对照)。

[0412] 注释 :[2]. 到第 52 周基于累积 EPO(ESA) 摄入量的平均每日静脉内铁剂摄入量计算为把总的累积 EPO(ESA) 摄入量除以在研究药物上的总天数。

[0413] 注释 :[3]. 处理重叠剂量的方法 1 如下 :对于重叠剂量将基于仅包括在安全性评

估期的期间在研究药物上的时间周期的剂量的天数进行按比例分配。

[0414] 注释 :[4]. 在基本假设不满足 ANCOVA 的情况下,采用 Wilcoxon 秩和检验计算 p- 值并去掉 CI 和 LS 平均值。

[0415] 实施例 2

[0416] KRX-0502(柠檬酸铁) 在处理患有 III 到 V 期慢性肾脏疾病但没有接受透析的贫血症受试者的血清磷和铁缺乏症中的研究

[0417] 进行 2 期、概念验证 (proof of concept)、多中心、随机化、安慰剂对照、开放标签临床试验。

[0418] 本研究持续大约五到七个月,其中大约八到 12 周分配给受试者筛选,两周给洗脱受试者以将其目前的磷酸盐结合剂 (如果服用它们的话) 洗脱掉,和 12 周分配给用研究药物 (它或是本文公开的柠檬酸铁或是安慰剂) 治疗。对于本实施例的目的,将本文公开的柠檬酸铁称为 KRX-0502(柠檬酸铁)。

[0419] 本研究的目的是为了确定 KRX-0502(柠檬酸铁) 在处理患有非透析依赖的 III 到 V 期慢性肾脏疾病 (CKD) 的贫血症受试者的血清磷和铁缺乏症中的疗效和安全性。

[0420] 为了随机分配大约 140 例受试者,筛选了多达大约 200 例受试者。合格的受试者以 1:1 的比例随机分到 KRX-0502(柠檬酸铁) 或安慰剂。每个治疗臂有随机分配的大约 70 例受试者。在两周洗脱期和 12 周治疗期的期间,退出率大约 20%,因此大约 110 例受试者完成了 12 周用研究药物 (KRX-0502(柠檬酸铁) 或安慰剂) 治疗。完成 12 周用研究药物 (KRX-0502(柠檬酸铁) 或安慰剂) 治疗的受试者有大约 55 例。

[0421] 本试验由三个周期组成 :筛选期、两周洗脱期和 12 周治疗期。在大约 10 到 15 个地点筛选大约 200 例受试者需要花大约八到 12 周。两周洗脱期是仅用于目前服用磷酸盐结合剂的受试者。

[0422] 本试验招募两种不同类型的患贫血症的 III 到 V 期 CKD 受试者。他们是如下的受试者 :1) 血清磷≥ 4.5mg/dL 和 <6.0mg/dL 及低磷酸盐饮食失败但一直尚未开始用任何磷酸盐结合剂 (从头 (de novo) 受试者) 并且有贫血症病史记录的受试者 ;或 2) 目前服用磷酸盐结合剂以处理其血清磷并且有贫血症病史记录的受试者。从头受试者不进入洗脱期,目前服用磷酸盐结合剂的受试者进入两周洗脱期。洗脱两周后,这些受试者的血清磷≥ 4.5mg/dL 和 <6.0mg/dL 以便进入 12 周的治疗期

[0423] 招募对从头受试者 vs. 目前服用磷酸盐结合剂的受试者来说不分层次。

[0424] 研究设计 / 方法

[0425] 本试验是由筛选期、两周洗脱期和 12 周治疗期组成的三周期临床试验。在确定受试者符合报名条件之后,将受试者随机分到 KRX-0502(柠檬酸铁) 或安慰剂。受试者以 1:1 的比例随机分到 KRX-0502(柠檬酸铁) 或安慰剂。

[0426] 目前服用磷酸盐结合剂的受试者进入两周洗脱期,在两周洗脱期完成之后,随机分到 KRX-0502(柠檬酸铁) 或安慰剂。未曾服用磷酸盐结合剂的合格受试者立即开始研究药物 (KRX-0502(柠檬酸铁) 或安慰剂)。在这个受试者群组中没有洗脱期。所有受试者的血清磷≥ 4.5mg/dL 以便进入 12 周治疗期。

[0427] 在开始用研究药物 (KRX-0502(柠檬酸铁) 或安慰剂) 治疗之后,对受试者滴定治疗目的 (血清磷介于 3.0 到 4.0mg/dL 之间)。如果在 12 周治疗期的期间,受试者的血清磷

≥ 6.0mg/dL 持续至少连续两次访视，那么该受试者被认为是治疗失败，停止研究药物并且离开本研究。

[0428] 在两周洗脱期和 12 周治疗期的期间，不允许使用静脉内铁剂和红细胞生成素刺激剂 (ESA)。如果在两周洗脱期的期间，受试者的血红蛋白水平 (Hgb)<9.0g/dL，那么受试者是筛选失败。如果在 12 周治疗期的期间，受试者的 Hgb<9.0g/dL 持续至少连续两次访视，那么该受试者被认为是治疗失败，停止研究药物并且离开本研究。

[0429] 血清磷、血清钙、血清肌酸酐 (用于估计肾小球滤过率)、完整的成纤维细胞生长因子 23(FGF23)、完整的甲状旁腺激素 (iPTH) 和几种血液学参数 (铁蛋白、TSAT、不饱和铁结合能力 (UIBC)、TIBC、血清铁、红细胞比容 (HCT) 和 Hgb) 在筛选时、在洗脱期的期间、在 12 周治疗期的期间在访视 4(第 0 周) 和每周在研究药物 (KRX-0502(柠檬酸铁) 或安慰剂) 给药之前进行测定。

[0430] 在 12 周治疗期的期间在访视 4(第 0 周)、在访视 7(第 4 周) 和访视 9(第 8 周) 在研究药物 (KRX-0502(柠檬酸铁) 或安慰剂) 给药之前及在 12 周治疗期结束 (访视 11，第 12 周) 时，测定尿磷。

[0431] 本试验的纳入标准如下 :

[0432] 1. 男性和未怀孕、非哺乳期的女性 ;

[0433] 2. 年龄 >18 岁 ;

[0434] 3. 为控制血清磷的低磷酸盐饮食失败和 :(i) 目前正服用磷酸盐结合剂以处理其血清磷并且在筛选时血清磷 >2.5mg/dL 和 <6.0mg/dL，或 (ii) 未曾服用磷酸盐结合剂并且在筛选时血清磷水平≥ 4.5mg/dL 和 <6.0mg/dL 的未接受透析的 III 到 V 期 CKD 受试者 ;

[0435] 4. 有贫血症病史记录 ;

[0436] 5. 血清铁蛋白 <200ng/mL 和 TSAT 20％ ;

[0437] 6. 血红蛋白 >9.5g/dL 和 <11.5g/dL ;

[0438] 7. 肾小球滤过率 (GFR)<60mL/min ;

[0439] 8. 如果目前正服用磷酸盐结合剂，愿意中断目前的磷酸盐结合剂、进入洗脱期和被随机分到 KRX-0502(柠檬酸铁) 或安慰剂 ;和

[0440] 9. 自愿且能够签署知情同意书。

[0441] 本试验的排除标准如下 :

[0442] 1. 在筛选访视 (访视 0) 之前六个月以内做了甲状旁腺切除术 ;

[0443] 2. 在筛选访视 (访视 0) 之前三个月以内有症状的胃肠出血和炎症性肠疾病 ;

[0444] 3. 正在透析 ;

[0445] 4. 在随机化 (访视 4，第 0 周) 之前 60 天以内用过静脉内铁剂 ;

[0446] 5. 在随机化 (访视 4，第 0 周) 之前 60 天以内输过血 ;

[0447] 6. 预期在随机化 (访视 4，第 0 周) 的三 (3) 个月以内做肾脏移植或透析开始 ;

[0448] 7. 除铁缺乏症以外的贫血症原因 ;

[0449] 8. 血清甲状旁腺激素 >1000pg/ml ;

[0450] 9. 多药物变态反应病史 ;

[0451] 10. 最近五年内有恶性肿瘤病史 (经治疗的宫颈癌或皮肤癌经批准后被允许) ;

[0452] 11. 之前不耐受口服柠檬酸铁 ;

[0453] 12. 绝对需要口服铁疗法；

[0454] 13. 绝对需要维生素 C；但是，复合维生素（即，善存 (Centrum)、Nephrocaps、Renaphro 等）被允许。

[0455] 14. 绝对需要用餐时含有钙、镁或铝的药物；

[0456] 15. 干扰受试者遵守本研究协议的能力的精神病障碍；

[0457] 16. 计划在本研究期间做手术或住院（在该计划表以外的患者手术被允许）；

[0458] 17. 使受试者不能够或不喜欢完成本研究或将会干扰本研究中的最佳参与或对受试者造成重大风险的任何其它医学病症；

[0459] 18. 在随机化（访视 4，第 0 周）的 30 天以内接受过任何调查药物；和

[0460] 19. 不能够与研究人员合作或有非依从性历史。

[0461] 研究药物给药

[0462] KRX-0502（柠檬酸铁）作为 1 克含有大约 210mg 三价铁的柠檬酸铁小胶囊剂向那些随机分到柠檬酸铁的受试者供应。

[0463] 匹配的安慰剂向那些随机分到安慰剂的受试者供应。

[0464] 所有受试者以 KRX-0502（柠檬酸铁）的固定剂量为每天 3 粒小胶囊剂（大约 3 克的柠檬酸铁作为大约 630mg 三价铁）或安慰剂（每天大约 3 个匹配的小胶囊剂）开始研究药物。血清磷的目标水平为 3.0 到 4.0mg/dL。受试者如下滴定：

[0465] 1. 如果血清磷是在目标值 (3.0 到 4.0mg/dL) 上，剂量不需要做调整。

[0466] 2. 如果血清磷 <3.0mg/dL，KRX-0502（柠檬酸铁）或安慰剂的剂量每天减少 1 粒小胶囊剂，受试者的血清磷在七天内复查。

[0467] 3. 如果血清磷 >4.0mg/dL，KRX-0502（柠檬酸铁）或安慰剂的剂量每天增加 1 粒小胶囊剂，受试者的血清磷在七天内复查。

[0468] KRX-0502（柠檬酸铁）或安慰剂小胶囊剂的每日最大数量为 12 粒或 12g/ 天的柠檬酸铁。如果在 12 周治疗期的期间，受试者的血清磷≥ 6.0mg/dL 持续至少连续两次访视，那么该受试者被认为是治疗失败，停止研究药物并且离开本研究。

[0469] 如果在两周洗脱的期间，受试者的 Hgb<9.0g/dL，那么受试者是筛选失败。如果在 12 周治疗期的期间，受试者的 Hgb<9.0g/dL 持续至少连续两次访视，那么该受试者被认为是治疗失败，停止研究药物并且离开本研究。

[0470] 受试者在吃正餐或点心时或在他们吃完正餐或点心的 1 小时以内经口服服用 KRX-0502（柠檬酸铁）或安慰剂。如果自受试者吃完正餐或点心起时间过去了超过 1 个小时，告诉他们不要服用 KRX-0502（柠檬酸铁）或安慰剂。

[0471] 统计学考虑：疗效

[0472] 在 12 周后，到治疗结束时，血清磷、铁蛋白和 TSAT 水平相对于基线的变化是主要终点。

[0473] 本研究证明了在不接受透析、需要磷酸盐结合剂的患贫血症的 III 到 V 期 CKD 受试者中，KRX-0502（柠檬酸铁）在处理血清磷和铁缺乏症方面从基线（访视 4，第 0 周）到终点（访视 11，第 12 周）在统计学上优于安慰剂。

[0474] 钙 x 磷之积、血清钙、估计的肾小球滤过率 (eGFR)、尿磷、碳酸氢盐水平、血清铁、UIBC、TIBC、iPTH 和完整的成纤维细胞生长因子 23(FGF23) 从基线（访视 4，第 0 周）到治

疗结束（访视 11，第 12 周）的变化也作为次要终点进行了评估。

[0475] 统计学考虑：样本大小

[0476] 为了随机分配大约 140 例受试者，筛选了多达大约 200 例受试者。合格的受试者以 1:1 的比例随机分到 KRX-0502（柠檬酸铁）或安慰剂。每个治疗臂有随机分配的大约 70 例受试者。在两周洗脱期和 12 周治疗期的期间，退出率大约 20％，因此大约 110 例受试者完成了 12 周用研究药物（KRX-0502（柠檬酸铁）或安慰剂）治疗。完成 12 周用研究药物（KRX-0502（柠檬酸铁）或安慰剂）治疗的受试者有大约 55 例。

[0477] 在访视 11（第 12 周），结束时的血清磷在 KRX-0502（柠檬酸铁）组中是大约 4.3mg/dL 且在安慰剂治疗组中是大约 4.6mg/dL。普通的标准偏差是大约 0.5mg/dL。基于这些参数，本试验具有至少 80％效力来检测两组之间的差异（α ＝ 0.05，双侧）。

[0478] 在访视 11（第 12 周），结束时的铁蛋白水平在 KRX-0502（柠檬酸铁）组中是大约 300ng/mL 且在安慰剂治疗组中是大约 150ng/mL。普通的标准偏差是大约 75ng/mL。基于这些参数，本试验具有至少 80％效力来检测两组之间的差异（α ＝ 0.05，双侧）。

[0479] 在访视 11（第 12 周），结束时的 TSAT 水平在 KRX-0502（柠檬酸铁）组中是大约 25％且在安慰剂治疗组中是大约 17％。普通的标准偏差是大约 5％。基于这些参数，本试验具有至少 80％效力来检测两组之间的差异（α ＝ 0.05，双侧）。

[0480] 最后，应该注意的是，有许多替代方式能实现本文公开的实施方案。因此，本发明的实施方案被认为是说明性的而不是限制性的。此外，权利要求并不限于本文中给出的细节而是涵盖它们的全部范围及其等同方案。

Abstract

Methods of administering ferric citrate to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesisstimulating agents (ESAs) in chronic kidney disease patients, are disclosed