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(54) Title: USE OF FERRIC CITRATE IN THE TREATMENT OF IRON-DEFICIENCY ANEMIA

(57) Abstract: Described herein are methods for treating patients with iron-deficiency anemia (IDA), comprising administering ferric citrate to such patients. In certain aspects, the patients treated for iron-deficiency anemia have a gastrointestinal disorder, such as inflammatory bowel disease, inflammatory bowel syndrome, Crohn' s disease, microscopic colitis (such as collagenous or lymphocytic colitis), or chemically-induced colitis (e.g., NSAID (nonsteroidal anti-inflammatory drug)-induced colitis). In certain aspects, the patients treated for iron-deficiency anemia have blood loss associated with childbirth, menstruation or infection. In some aspects, the patients treated for iron-deficiency anemia have insufficient dietary intake of iron and/or insufficient absorption of iron.

USE OF FERRIC CITRATE IN THE TREATMENT OF IRON-DEFICIENCY ANEMIA

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional application No. 62/127,963, filed on March 4, 2015, which is incorporated by reference herein in its entirety.

1. FIELD

[0002] Described herein are methods for treating patients with iron-deficiency anemia (IDA), comprising administering ferric citrate to such patients. In certain aspects, the patients treated for iron-deficiency anemia have a gastrointestinal disorder, such as inflammatory bowel disease, inflammatory bowel syndrome, Crohn's disease, microscopic colitis (such as collagenous or lymphocytic colitis), or chemically-induced colitis (*e.g.*, NSAID (nonsteroidal anti-inflammatory drug)-induced colitis). In certain aspects, the patients treated for iron-deficiency anemia have blood loss associated with childbirth, menstruation or infection. In some aspects, the patients treated for iron-deficiency anemia have insufficient dietary intake of iron and/or insufficient absorption of iron.

2. BACKGROUND

[0003] About 2 billion people have anemia world-wide, and iron deficiency is the most prevalent cause of anemia, affecting millions of children, women, and men in both developed and less developed countries (Baltussen *et al.*, Journal of Nutrition (2004) 134, 2678-2684; McLean *et al.*, Public Health Nutr. (2009) 12, 444–454). Although the impact of iron-deficiency anemia (IDA) on human health is significant, it is either frequently overlooked or insufficiently treated (Miller *et al.*, Cold Spring Harb. Perspect. Med. (2013) 3, a011866).

[0004] Most well-nourished, non-iron deficient 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 IDA patients. Symptoms of iron deficiency can occur in the patients before the condition has progressed to IDA, and 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.

[0005] IDA is typically characterized by pallor (pale color resulting from reduced oxyhemoglobin in the skin and mucous membranes), fatigue, lightheadedness, and weakness. However, signs of IDA can vary among patients. Because iron deficiency in IDA patients tends to develop slowly, adaptation to the disease can occur and it can go unrecognized for some time, even years. In some instances, patients with IDA can develop dyspnea (trouble breathing), pica (unusual obsessive food cravings), anxiety often resulting in obsessive-compulsive disorder (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), insomnia, and restless legs syndrome, among others.

[0006] IDA can be caused by insufficient dietary intake of iron, insufficient absorption of iron, insufficient storage of iron, and/or iron loss from bleeding which can originate from a number of sources such as the gastrointestinal, uterine or urinary tract. Therefore it is commonly associated with conditions and disorders such as acute blood loss, chronic blood loss, childbirth, menstruation, gastrointestinal disorders (*e.g.*, inflammatory bowel disease (IBD)), Chronic Kidney Disease (CKD), parasitic infections, insufficient dietary intake of iron, and insufficient absorption of iron.

[0007] There are typically three means by which IDA 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 the patients, which leads to patient non-compliance. In those instances where an IDA patient cannot take oral iron supplements, he or she may have to have intravenous iron supplementation.

[0008] Intravenous (IV) iron supplementation is a method of delivering iron by injection with a needle, either through a muscle or into a vein. IDA patients who are receiving IV iron

usually do so because they cannot tolerate oral iron. Intravenous iron is delivered into the IDA 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 patient usually receives iron injections over the course of several visits until his or her iron levels are correct. In some instances, an IDA patient may require chronic IV iron supplementation.

[0009] However, IV iron is also associated with short-term side effects such as gastrointestinal pains (*e.g.*, nausea and cramps), breathing problems, skin problems (*e.g.*, rash), chest pain, low blood pressure, anaphylaxis, and death, as well as long-term toxicity, including the development of atherosclerosis, infection, and increased mortality (Quinibi, Arzneimittelforschung (2010) 60, 399-412). Further, many clinics, particularly community sites, are ill-equipped to administer intravenous iron. This has left a majority of IDA patients without intravenous iron treatment.

[0010] IDA patients may also take one or more erythropoiesis-stimulating agents (ESAs) in an effort to control anemia. However, side effects can occur with ESA use. The most often side effects 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. In addition, ESAs may in certain cases worsen iron depletion and lead to an increase in thrombocytosis.

[0011] Thus, there is need to develop improved methods for oral iron treatment of IDA patients.

3. SUMMARY

[0012] In one aspect, provided herein are methods for treating iron-deficiency anemia (IDA) comprising administering ferric citrate or a pharmaceutical composition thereof to a subject in need thereof. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In one embodiment, provided herein is a method for treating iron

deficiency anemia comprising orally administering a low dose of ferric citrate or a pharmaceutical composition thereof at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, every 5 days, etc. for a certain period of time) to a subject in need thereof. In particular embodiments, the low dose is administered once a day, every other day, or every two days for a period of time, such as 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 9 months, 12 months or more. In certain embodiments, the ferric citrate or pharmaceutical composition thereof is administered to a subject who has not ingested food within a certain timeframe. *See*, *e.g.*, Section 4.3, *infra*, for examples of such timeframes for not having ingested food. In some embodiments, one or more iron storage parameters, such as hemoglobin concentration, transferrin saturation (TSAT) value, serum ferritin level, serum iron level, hematocrit level, total iron-binding capacity (TIBC) value, plasma erythropoietin level, and/or free erythrocyte protoporphyrin (FEP) level, of the subject are monitored (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more) and, in certain embodiments, the frequency of administration of ferric citrate or a pharmaceutical composition thereof and/or the amount of ferric citrate or a pharmaceutical composition thereof that the subject receives is altered based on the one or more iron storage parameters (*e.g.*, the amount of ferric citrate or a pharmaceutical composition thereof is increased if the hemoglobin concentration has increased by less than 1 g/dl after a certain period of time, and the amount of ferric citrate or a pharmaceutical composition thereof is decreased if the hemoglobin concentration has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl or 1.5 g/dl). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia. In some embodiments, the patient has a gastrointestinal disorder, such as inflammatory bowel disease, inflammatory bowel syndrome, Crohn's disease, microscopic colitis (such as collagenous or lymphocytic colitis), and/or chemically-induced colitis (*e.g.*, NSAID (nonsteroidal anti-inflammatory drug)-induced colitis). In certain embodiments, the patients treated for iron-deficiency anemia have blood loss (for example, blood loss associated with childbirth or menstruation, or blood loss associated with an infection). In some embodiments, the patients treated for iron-deficiency anemia have insufficient dietary intake of iron. In certain embodiments, the patients treated for iron-deficiency anemia have insufficient absorption of iron.

[0013] In a specific embodiment, provided herein is a method for treating iron deficiency anemia in a patient (*e.g.*, a human patient), wherein the patient has not been diagnosed with chronic kidney disease, the method comprising orally administering a ferric citrate tablet containing approximately 210 mg of ferric iron to the patient, wherein the ferric citrate in the tablet is a complex of iron (+3), 0.70 – 0.87 (1, 2, 3-propanetricarboxylic acid, 2-hydroxy-), 1.9 – 3 (H_2O). In some embodiments, the patient has a serum ferritin level of between 5 ng/ml to 300 ng/ml (*e.g.*, between 5 ng/ml to 250 ng/ml, between 5 ng/ml to 150 ng/ml, between 5 ng/ml to 100 ng/ml, between 5 ng/ml to 75 ng/ml, between 5 ng/ml to 50 ng/ml, between 5 ng/ml to 25 ng/ml, between 5 ng/ml to 15 ng/ml, or between 5 ng/ml to 10 ng/ml). In certain embodiments, the ferric citrate is not administered with food. In some embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more) and, in certain embodiments, the frequency of administration of ferric citrate or a pharmaceutical composition thereof and/or the amount of ferric citrate or a pharmaceutical composition thereof that the subject receives is altered based on the one or more iron storage parameters (*e.g.*, the amount of ferric citrate or a pharmaceutical composition thereof is increased if the hemoglobin concentration has increased by less than 1 g/dl after a certain period of time, and the amount of ferric citrate or a pharmaceutical composition thereof is decreased if the hemoglobin concentration has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl or 1.5 g/dl). In certain embodiments, the patient has a gastrointestinal disorder, such as inflammatory bowel disease, inflammatory bowel syndrome, Crohn's disease, ulcerative colitis, microscopic colitis (such as collagenous colitis or lymphocytic colitis), and/or chemically-induced colitis (*e.g.*, NSAID-induced colitis). In certain embodiments, the patients treated for iron-deficiency anemia have blood loss (for example, blood loss associated with childbirth or menstruation, or blood loss associated with an infection). In some embodiments, the patients treated for iron-deficiency anemia have insufficient dietary intake of iron. In certain embodiments, the patients treated for iron-deficiency anemia have insufficient absorption of iron.

[0014] In another specific embodiment, provided herein is a method for treating iron deficiency anemia in a patient (*e.g.*, a human patient), wherein the patient has not been diagnosed

with chronic kidney disease and the patient has a serum ferritin level of between 5 ng/ml to 300 ng/ml (*e.g.*, between 5 ng/ml to 250 ng/ml, between 5 ng/ml to 150 ng/ml, between 5 ng/ml to 100 ng/ml, between 5 ng/ml to 75 ng/ml, between 5 ng/ml to 50 ng/ml, between 5 ng/ml to 25 ng/ml, between 5 ng/ml to 15 ng/ml, or between 5 ng/ml to 10 ng/ml), the method comprising orally administering a ferric citrate tablet containing approximately 210 mg of ferric iron to the patient, wherein the ferric citrate is not administered within 2 hours of food being ingested by the patient, and wherein the ferric citrate in the tablet is a complex of iron (+3), 0.70 – 0.87 (1, 2, 3-propanetricarboxylic acid, 2-hydroxy-), 1.9 – 3 (H_2O). In some embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more) and, in certain embodiments, the frequency of administration of ferric citrate or a pharmaceutical composition thereof and/or the amount of ferric citrate or a pharmaceutical composition thereof that the subject receives is altered based on the one or more iron storage parameters (*e.g.*, the amount of ferric citrate or a pharmaceutical composition thereof is increased if the hemoglobin concentration has increased by less than 1 g/dl after a certain period of time, and the amount of ferric citrate or a pharmaceutical composition thereof is decreased if the hemoglobin concentration has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl or 1.5 g/dl). In certain embodiments, the patient has a gastrointestinal disorder, such as inflammatory bowel disease, inflammatory bowel syndrome, Crohn's disease, ulcerative colitis, microscopic colitis (such as collagenous colitis or lymphocytic colitis), and/or chemically-induced colitis (*e.g.*, NSAID-induced colitis). In certain embodiments, the patients treated for iron-deficiency anemia have blood loss (for example, blood loss associated with childbirth or menstruation, or blood loss associated with an infection). In some embodiments, the patients treated for iron-deficiency anemia have insufficient dietary intake of iron. In certain embodiments, the patients treated for iron-deficiency anemia have insufficient absorption of iron.

[0015] In another specific embodiment, provided herein is a method for treating iron deficiency anemia in a human patient that has not been diagnosed with chronic kidney disease, the method comprising: (a) orally administering to the patient one ferric citrate tablet containing approximately 210 mg of ferric iron per day, wherein the ferric citrate is not administered within

2 hours of food being ingested by the patient, and wherein the ferric citrate in the tablet is a complex of iron (+3), 0.70 – 0.87 (1, 2, 3-propanetricarboxylic acid, 2-hydroxy-), 1.9 – 3 (H_2O); and (b) decreasing the dose of ferric citrate after 4 weeks if the hemoglobin concentration of the subject has increased by more than 5 g/dl, 4g/dl, 3 g/dl or 2 g/dl and increasing the dose of ferric citrate after 4 weeks if the hemoglobin concentration of the subject has increased by less than 1 g/dl. In some embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, the patient has a gastrointestinal disorder, such as inflammatory bowel disease, inflammatory bowel syndrome, Crohn's disease, ulcerative colitis, microscopic colitis (such as collagenous colitis or lymphocytic colitis), and/or chemically-induced colitis (*e.g.*, NSAID-induced colitis). In certain embodiments, the patients treated for iron-deficiency anemia have blood loss (for example, blood loss associated with childbirth or menstruation, or blood loss associated with an infection). In some embodiments, the patients treated for iron-deficiency anemia have insufficient dietary intake of iron. In certain embodiments, the patients treated for iron-deficiency anemia have insufficient absorption of iron.

[0016] In a specific embodiment of any of the foregoing embodiments, the patients treated for iron-deficiency anemia are monitored for one or more iron storage parameters. The one or more iron storage parameters can be selected from the group consisting of hemoglobin concentration, serum ferritin level, TSAT value, serum iron level, hematocrit level, TIBC value, plasma erythropoietin level, and FEP level.

4. DETAILED DESCRIPTION

[0017] The present disclosure provides methods of using ferric citrate to treat a patient having iron-deficiency anemia (IDA). The present disclosure also provides pharmaceutical compositions, which may be administered to iron deficiency patients. Methods of assessing patients before and/or after administering ferric citrate are also provided.

4.1. Methods for Treating IDA

[0018] In one aspect, provided herein are methods for treating IDA comprising administering ferric citrate or a pharmaceutical composition thereof to a subject in need thereof. In one embodiment, provided herein is a method for treating IDA comprising administering an effective amount of ferric citrate or a pharmaceutical composition thereof to a subject in need thereof. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In another embodiment, provided herein is a method for treating IDA comprising orally administering an effective amount of ferric citrate or a pharmaceutical composition thereof to a subject in need thereof. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In certain embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT (transferring saturation) value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, total iron-binding capacity (TIBC) value, plasma erythropoietin level, and/or free erythrocyte protoporphyrin (FEP) level, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0019] In a specific embodiment, provided herein is a method for treating IDA comprising orally administering a low dose of ferric citrate or a pharmaceutical composition thereof at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, every 5 days, etc. for a certain period of time) to a subject in need thereof. In particular embodiments, the low dose is administered once a day, every other day, or every two days for a

period of time, such as 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 9 months, 12 months or more. In certain embodiments, the ferric citrate or pharmaceutical composition thereof is administered to a subject who has not ingested food within a certain timeframe. *See*, *e.g.*, Section 4.3, *infra*, for examples of such timeframes for not having ingested food. In some embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more) and, in certain embodiments, the frequency of administration of ferric citrate or a pharmaceutical composition thereof and/or the amount of ferric citrate or a pharmaceutical composition thereof that the subject receives is altered based on the one or more iron storage parameters (*e.g.*, the amount of ferric citrate or a pharmaceutical composition thereof is increased if the hemoglobin concentration has increased by less than 1 g/dl after a certain period of time, and the amount of ferric citrate or a pharmaceutical composition thereof is decreased if the hemoglobin concentration has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl or 1.5 g/dl). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0020] As used herein, the term "low dose" in the context of ferric citrate or a pharmaceutical composition thereof is equivalent to a dose of 1100 mg of ferric iron or less but above 50 mg of ferric iron (in certain embodiments, above 100 mg or 200 mg of ferric iron). In one embodiment, a low dose of ferric citrate or a pharmaceutical composition thereof is equivalent to a dose of 1050 mg, 840 mg, 630 mg, 420 mg, or 210 mg of ferric iron. In another embodiment, a low dose of ferric citrate or a pharmaceutical composition thereof is equivalent to a dose of 1050 mg to 1100 mg, 840 mg to 1050 mg, 840 mg to 1100 mg, 630 mg to 840 mg, 630 mg to 1050 mg, 630 mg to 1100 mg, 420 mg to 630 mg, 420 mg to 840 mg, 420 mg to 1050 mg, 210 mg to 420 mg, 210 mg to 630 mg, 210 mg to 840 mg, or 210 mg to 1050 mg of ferric iron. In a specific embodiment, a low dose of ferric citrate or a pharmaceutical composition thereof is equivalent to 1, 2, 3, 4 or 5 tablets of Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) per day or every other day.

[0021] In a specific embodiment, provided herein is a method for treating IDA comprising orally administering a low dose of ferric citrate or a pharmaceutical composition thereof at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, every 5 days, etc. for a certain period of time) to a subject in need thereof without food. In another specific embodiment, provided herein is a method for treating IDA comprising orally administering a low dose of ferric citrate or a pharmaceutical composition thereof at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, every 5 days, etc. for a certain period of time) to a subject in need thereof without food being ingested by the subject within 3 hours, 2 hours or 1 hour of ingestion of the ferric citrate or a pharmaceutical composition thereof. In particular embodiments, the low dose is administered once a day, every other day, or every two days for a period of time, such as 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 9 months, 12 months or more. In certain embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more) and, in certain embodiments, the frequency of administration of ferric citrate or a pharmaceutical composition thereof and/or the amount of ferric citrate or a pharmaceutical composition thereof that the subject receives is altered based on the one or more iron storage parameters (*e.g.*, the amount of ferric citrate or a pharmaceutical composition thereof is increased if the hemoglobin concentration has increased by less than 1 g/dl after a certain period of time, and the amount of ferric citrate or a pharmaceutical composition thereof is decreased if the hemoglobin concentration has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl or 1.5 g/dl). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0022] In another embodiment, provided herein is a method for treating IDA in a subject, comprising: (a) assessing one or more of the following iron storage parameters: (i) the hemoglobin concentration, (ii) the TSAT value, (iii) the serum ferritin level, (iv) the serum iron level, (v) the tissue iron level (*e.g.*, stainable tissue iron level), (vi) the hematocrit level, (vii) the TIBC value, (viii) the plasma erythropoietin level, and/or (ix) the FEP level of the subject; and (b) administering (*e.g.*, orally administering) ferric citrate or a pharmaceutical composition thereof to a subject that has a certain hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level. *See*, *e.g.*, Section 4.2, *infra*, for hemoglobin concentrations, TSAT values, serum ferritin levels, serum iron levels, tissue iron levels (*e.g.*, stainable tissue iron levels), hematocrit levels, TIBC values, plasma erythropoietin levels, and/or FEP levels of subjects that may be administered ferric citrate or a pharmaceutical composition in accordance with the methods described herein. In certain embodiments, a subject treated in accordance with the methods disclosed herein has one, two or all of the following prior to administration of ferric citrate or a pharmaceutical composition: (i) a hemoglobin concentration of approximately 6 grams/dl to approximately 8 grams/dl, approximately 6 grams/dl to approximately 10 grams/dl, approximately 6 grams/dl to approximately 12 grams/dl, approximately 7 grams/dl to approximately 9 grams/dl, approximately 7 grams/dl to approximately 11 grams/dl, approximately 7 grams/dl to approximately 13 grams/dl, approximately 8 grams/dl to approximately 10 grams/dl, approximately 8 grams/dl to approximately 12 grams/dl, approximately 9 grams/dl to approximately 11 grams/dl, approximately 9 grams/dl to approximately 12 grams/dl, approximately 9 grams/dl to approximately 13 grams/dl, approximately 10 grams/dl to approximately 11 grams/dl, approximately 10 grams/dl to approximately 12 grams/dl, approximately 10 grams/dl to approximately 13 grams/dl, approximately 11 grams/dl to approximately 12 grams/dl, approximately 11 grams/dl to approximately 13 grams/dl, or approximately 12 grams/dl to approximately 13 grams/dl; (ii) TSAT value of 10% to 45%, 12% to 45%, 20% to 45%, 20% to 40%, 10% to 35%, 20% to 25%, 15% to 50%, 10% to 30%, or 10% to 25%; (iii) a serum ferritin level of approximately 5 ng/ml to approximately 25 ng/ml, approximately 25 ng/ml to approximately 50 ng/ml, approximately 50 ng/ml to approximately 100 ng/ml, approximately 100 ng/ml to approximately 150 ng/ml, approximately 150 ng/ml to approximately 200 ng/ml,

approximately 150 ng/ml to approximately 250 ng/ml, approximately 100 ng/ml to approximately 300 ng/ml, approximately 200 ng/ml to approximately 300 ng/ml, or approximately 250 ng/ml to approximately 300 ng/ml; (iv) serum iron level of approximately 10 μg/dl to approximately 20 μg/dl, approximately 10 μg/dl to approximately 30 μg/dl, approximately 10 μg/dl to approximately 40 μg/dl, approximately 10 μg/dl to approximately 50 μg/dl, approximately 10 μg/dl to approximately 60 μg/dl, approximately 20 μg/dl to approximately 30 μg/dl, approximately 20 μg/dl to approximately 40 μg/dl, approximately 20 μg/dl to approximately 50 μg/dl, approximately 20 μg/dl to approximately 60 μg/dl, approximately 30 μg/dl to approximately 40 μg/dl, approximately 30 μg/dl to approximately 50 μg/dl, approximately 30 μg/dl to approximately 60 μg/dl, approximately 40 μg/dl to approximately 50 μg/dl, or approximately 40 μg/dl to approximately 60 μg/dl; (v) tissue iron level (*e.g.*, stainable tissue iron level) of grade 2, grade 1, or grade 0; (vi) hematocrit level of 10% to 15%, 10% to 20%, 10% to 25%, 10% to 30%, 10% to 35%, 10% to 40%, 10% to 45%, 15% to 20%, 15% to 25%, 15% to 30%, 15% to 35%, 15% to 40%, 15% to 45%, 20% to 25%, 20% to 30%, 20% to 35%, 20% to 40%, 25% to 45%, 25% to 30%, 25% to 35%, 25% to 40%, 25% to 45%, 30% to 35%, 30% to 40%, 30% to 45%, 35% to 40%, 35% to 45%, or 40% to 45%; (vii) TIBC value of approximately 390 μg/dl to approximately 600 μg/dl, approximately 390 μg/dl to approximately 800 μg/dl, approximately 390 μg/dl to approximately 1000 μg/dl, approximately 390 μg/dl to approximately 1200 μg/dl, approximately 500 μg/dl to approximately 700 μg/dl, approximately 500 μg/dl to approximately 900 μg/dl, approximately 500 μg/dl to approximately 1100 μg/dl, approximately 600 μg/dl to approximately 800 μg/dl, approximately 600 μg/dl to approximately 1000 μg/dl, approximately 600 μg/dl to approximately 1200 μg/dl, approximately 700 μg/dl to approximately 900 μg/dl, approximately 700 μg/dl to approximately 1100 μg/dl, approximately 800 μg/dl to approximately 1000 μg/dl, approximately 800 μg/dl to approximately 1200 μg/dl, approximately 900 μg/dl to approximately 1100 μg/dl, approximately 1000 μg/dl to approximately 1200 μg/dl; (viii) plasma erythropoietin level of approximately 20 mU/ml to approximately 30 mU/ml, approximately 20 mU/ml to approximately 40 mU/ml, approximately 20 mU/ml to approximately 50 mU/ml, approximately 20 mU/ml to approximately 60 mU/ml, approximately 30 mU/ml to approximately 40 mU/ml, approximately 30 mU/ml to approximately 50 mU/ml, approximately 30 mU/ml to approximately 60 mU/ml, approximately 40 mU/ml to approximately 50 mU/ml, approximately 40 mU/ml to

approximately 60 mU/ml, or approximately 50 mU/ml to approximately 60 mU/ml; and/or (ix) FEP level of approximately 50 μg/dl to approximately 60 μg/dl, approximately 50 μg/dl to approximately 70 μg/dl, approximately 50 μg/dl to approximately 80 μg/dl, approximately 50 μg/dl to approximately 90 μg/dl, approximately 50 μg/dl to approximately 100 μg/dl, approximately 60 μg/dl to approximately 70 μg/dl, approximately 60 μg/dl to approximately 80 μg/dl, approximately 60 μg/dl to approximately 90 μg/dl, approximately 60 μg/dl to approximately 100 μg/dl, approximately 70 μg/dl to approximately 80 μg/dl, approximately 70 μg/dl to approximately 90 μg/dl, approximately 70 μg/dl to approximately 100 μg/dl, approximately 80 μg/dl to approximately 90 μg/dl, approximately 80 μg/dl to approximately 100 μg/dl, or approximately 90 μg/dl to approximately 100 μg/dl. In certain embodiments wherein the subject treated in accordance with the methods disclosed herein is a female, the subject has a TSAT value of 5% to 45%, 5% to 35%, 5% to 25%, 5% to 15%, 5% to 12%, 5% to 10%, 10% to 45%, 10% to 35%, 10% to 25%, 10% to 15%, 10% to 12%, 12% to 45%, 12% to 35%, 12% to 25%, 12% to 15%, 20% to 45%, 20% to 35%, 20% to 25%, 30% to 45%, 30% to 35%, or 40% to 45% prior to administration of ferric citrate or a pharmaceutical composition thereof. In certain embodiments wherein the subject treated in accordance with the methods disclosed herein is a male, the subject has a TSAT value of 5% to 50%, 5% to 40%, 5% to 30%, 5% to 20%, 5% to 15%, 5% to 10%, 10% to 50%, 10% to 40%, 10% to 30%, 10% to 20%, 10% to 15%, 15% to 50%, 15% to 40%, 15% to 30%, 15% to 25%, 15% to 20%, 20% to 50%, 20% to 40%, 20% to 30%, 20% to 25%, 30% to 50%, 30% to 40%, 30% to 35%, 40% to 50%, 40% to 45%, or 45% to 50% prior to administration of ferric citrate or a pharmaceutical composition thereof. In a specific embodiment, the subject is administered a low dose of ferric citrate or a pharmaceutical composition thereof at a certain frequency (*e.g.*, every day, every other day, every two days, every three days, every four days, or every five days). In another specific embodiment, the ferric citrate or pharmaceutical composition thereof is administered orally to the subject without food or not within a few hours, *e.g.*, within less than 3 hours, of the ingestion of food by the subject. In some embodiments, the frequency of administration of ferric citrate or a pharmaceutical composition thereof and/or the amount of ferric citrate or a pharmaceutical composition thereof that the subject receives is altered based on the one or more iron storage parameters (*e.g.*, the amount of ferric citrate or a pharmaceutical composition thereof is increased if the hemoglobin concentration has increased by less than 1 g/dl after a certain period of time, and the amount of

ferric citrate or a pharmaceutical composition thereof is decreased if the hemoglobin concentration has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl or 1.5 g/dl). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0023] In another embodiment, provided herein is a method for treating IDA in a subject, comprising: (a) orally administering ferric citrate or a pharmaceutical composition thereof to a subject at a dose equivalent to 210 mg to 1100 mg of ferric iron per day or every other day; and (b) increasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by less than 1 g/dl. In certain embodiments, the dose of ferric citrate or a pharmaceutical composition thereof is titrated up in increments, such as increments of 210 mg of ferric iron. In another embodiment, provided herein is a method for treating IDA in a subject, comprising: (a) orally administering ferric citrate or a pharmaceutical composition thereof to a subject at a dose equivalent to 210 mg of ferric iron per day or every other day; and (b) increasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by less than 1 g/dl. In certain embodiments, the dose is increased to 420 mg of ferric iron per day or every other day. In other embodiments, the dose is increased to 210 mg of ferric iron per day from 210 mg of ferric iron every other day. In a specific embodiment, the ferric citrate or pharmaceutical composition thereof is administered orally to the subject without food or not within a few hours, *e.g.*, within less than 3 hours, of the ingestion of food by the subject. In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0024] In another embodiment, provided herein is a method for treating IDA in a subject, comprising: (a) orally administering ferric citrate or a pharmaceutical composition thereof to a subject at a dose equivalent to 210 mg to 1100 mg of ferric iron per day or every other day; (b) monitoring the subject after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more); and (c) increasing the dose

of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by less than 1 g/dl. In certain embodiments, the dose of ferric citrate or a pharmaceutical composition thereof is titrated up in increments, such as increments of 210 mg of ferric iron. In another embodiment, provided herein is a method for treating IDA in a subject, comprising: (a) orally administering ferric citrate or a pharmaceutical composition thereof to a subject at a dose equivalent to 210 mg of ferric iron per day or every other day; (b) monitoring the subject after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more); and (c) increasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by less than 1 g/dl. In certain embodiments, the dose is increased to 420 mg of ferric iron per day or every other day. In other embodiments, the dose is increased to 210 mg of ferric iron per day from 210 mg of ferric iron every other day. In a specific embodiment, the ferric citrate or pharmaceutical composition thereof is administered orally to the subject without food or not within a few hours, *e.g.*, within less than 3 hours, of the ingestion of food by the subject. In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0025] In another embodiment, provided herein is a method for treating IDA in a subject, comprising: (a) orally administering ferric citrate or a pharmaceutical composition thereof to a subject at a dose equivalent to 210 mg to 1100 mg of ferric iron per day or every other day; and (b) decreasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl, or 1.5 g/dl. In certain embodiments, the dose of ferric citrate or a pharmaceutical composition thereof is titrated down in increments, such as increments of 210 mg of ferric iron. In another embodiment, provided herein is a method for treating IDA in a subject, comprising: (a) orally administering ferric citrate or a pharmaceutical composition thereof to a subject at a dose equivalent to 210 mg of ferric iron per day; and (b)

decreasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl, or 1.5 g/dl. In certain embodiments, the dose is decreased to 210 mg of ferric iron every other day from 210 mg of ferric iron per day. In a specific embodiment, the ferric citrate or pharmaceutical composition thereof is administered orally to the subject without food or not within a few hours, *e.g.*, within less than 3 hours, of the ingestion of food by the subject. In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0026] In another embodiment, provided herein is a method for treating IDA in a subject, comprising: (a) orally administering ferric citrate or a pharmaceutical composition thereof to a subject at a dose equivalent to 210 mg to 1100 mg of ferric iron per day or every other day; (b) monitoring the subject after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more); and (c) decreasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl, or 1.5 g/dl. In certain embodiments, the dose of ferric citrate or a pharmaceutical composition thereof is titrated down in increments, such as increments of 210 mg of ferric iron. In another embodiment, provided herein is a method for treating IDA in a subject, comprising: (a) orally administering ferric citrate or a pharmaceutical composition thereof to a subject at a dose equivalent to 210 mg of ferric iron per day; (b) monitoring the subject after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more); and (c) decreasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl or 1.5 g/dl. In certain embodiments, the dose is decreased to 210 mg of ferric iron every other day from 210 mg of ferric iron per day. In a specific embodiment, the ferric citrate or pharmaceutical composition thereof is administered orally to the subject without food or not within a few hours,

e.g., within less than 3 hours, of the ingestion of food by the subject. In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0027] In another embodiment, provided herein is a method for treating IDA in a subject, comprising: (a) orally administering ferric citrate or a pharmaceutical composition thereof to a subject at a dose equivalent to 210 mg to 1100 mg of ferric iron per day or every other day; and (b) decreasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl, or 1.5 g/dl and increasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by less than 1 g/dl. In certain embodiments, the dose of ferric citrate or a pharmaceutical composition thereof is titrated down or up in increments, such as increments of 210 mg of ferric iron. In another embodiment, provided herein is a method for treating IDA in a subject, comprising: (a) orally administering ferric citrate or a pharmaceutical composition thereof to a subject at a dose equivalent to 210 mg of ferric iron per day; and (b) decreasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl, or 1.5 g/dl and increasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by less than 1 g/dl. In certain embodiments, the dose is decreased to 210 mg of ferric iron every other day from 210 mg of ferric iron per day. In other embodiments, the dose is increased to 420 mg of ferric iron per day or every other day. In a specific embodiment, the ferric citrate or pharmaceutical composition thereof is administered orally to the subject without food or not within a few hours, *e.g.*, within less than 3 hours, of the ingestion of food by the subject. In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition

thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0028] In another embodiment, provided herein is a method for treating IDA in a subject, comprising: (a) orally administering ferric citrate or a pharmaceutical composition thereof to a subject at a dose equivalent to 210 mg to 1100 mg of ferric iron per day; (b) monitoring the subject after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more); and (c) decreasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl, or 1.5 g/dl and increasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by less than 1 g/dl. In certain embodiments, the dose of ferric citrate or a pharmaceutical composition thereof is titrated down or up in increments, such as increments of 210 mg of ferric iron. In another embodiment, provided herein is a method for treating IDA in a subject, comprising: (a) orally administering ferric citrate or a pharmaceutical composition thereof to a subject at a dose equivalent to 210 mg of ferric iron per day; (b) monitoring the subject after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more); and (c) decreasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by more than 5 g/dl, 4 g/dl, 3 g/dl, 2 g/dl, or 1.5 g/dl and increasing the dose of ferric citrate or a pharmaceutical composition thereof after a certain period of time (*e.g.*, 2 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, or more) if the hemoglobin concentration of the subject has increased by less than 1 g/dl. In certain embodiments, the dose is decreased to 210 mg of ferric iron every other day from 210 mg of ferric iron per day. In other embodiments, the dose is increased to 420 mg of ferric iron per day or every other day. In a specific embodiment, the ferric citrate or pharmaceutical composition thereof is administered orally to the subject without food or not within a few hours, *e.g.*, within less than 3 hours, of the ingestion of food by the

subject. In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0029] In certain embodiments, a subject treated for IDA in accordance with the methods described herein experiences a therapeutic benefit. In specific embodiments, a subject treated for IDA in accordance with the methods described herein experiences one, two, three or more, or all of the following effects: (i) an improvement in one or more symptoms of IDA; (ii) a reduction in the number of symptoms associated with IDA; (iii) a reduction in the duration of one or more symptoms; (iv) an improvement (*e.g.*, an increase) in one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level; (v) a reduction in the administration of intravenous iron and/or an erythropoiesis stimulating agent; (vi) a decrease in iron deficiency; and/or (vii) a decrease or elimination of one, two, three, four or more symptoms of IDA. Symptoms of IDA include, but are not limited to, fatigue, dizziness, lightheadedness, pallor, hair loss, irritability, weakness, pica, brittle or grooved nails, dyspnea, anxiety, sadness, angina, constipation, sleepiness, tinnitus, mouth ulcers, Plummer-Vinson syndrome (painful atrophy of the mucous membrane covering the tongue, pharynx and esophagus), palpitations, hair loss, fainting or feeling faint, depression, twitching muscles, pale yellow skin, tingling (numbness) or burning sensations, missed menstrual cycle(s), heavy menstrual period(s), slow social development, glossitis, angular cheilitis, koilonychias, poor appeitite, prurius, insomnia, dizziness, strange cravings for non-food items (*e.g.*, dirt, ice, and clay), fast or irregular heartbeat, headaches, shortness of breath, cold hands and feet, impaired immune function, pagophagia, restless legs syndrome and combinations of the foregoing. In certain embodiments, a decrease in iron deficiency occurs as the total amount of iron in the body of the IDA patient is increased through the administration of the ferric citrate or a pharmaceutical composition thereof.

[0030] In specific aspects, provided herein are methods for increasing iron absorption in a subject with and/or diagnosed with IDA, comprising orally administering ferric citrate or a pharmaceutical composition thereof to the subject. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric

citrate and pharmaceutical compositions thereof. In specific embodiments, the subject is administered a low dose of ferric citrate at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days). In certain embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP leve, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0031] In specific aspects, provided herein are methods for maintaining or increasing iron stores in a subject with and/or diagnosed with IDA, comprising orally administering ferric citrate or a pharmaceutical composition thereof to the subject. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In specific embodiments, the subject is administered a low dose of ferric citrate at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days). There are several markers of systemic iron status that may be measured to determine whether an IDA 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), TSAT, serum iron level, tissue iron level (*e.g.*, liver iron level, spleen iron level) measured as stainable tissue iron level or tissue iron concentration, serum ferritin level, plasma erythropoietin level, and FEP level. Of these, the hematocrit, hemoglobin concentration (Hb), total iron-binding capacity (TIBC), TSAT and

serum iron level are commonly known as circulating iron stores. The liver iron level, spleen iron level, and serum ferritin level are commonly referred to as stored iron or iron stored in iron-binding complexes. In certain embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0032] In specific aspects, provided herein are methods for improving one or more iron storage parameters in a subject with and/or diagnosed with IDA, comprising orally administering ferric citrate or a pharmaceutical composition thereof to the subject. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In some embodiments, the one or more iron storage parameters are selected from hematocrit, hemoglobin concentration (Hb), total iron-binding capacity (TIBC), TSAT, serum iron level, tissue iron level (*e.g.*, liver iron level, spleen iron level) measured as stainable tissue iron level or tissue iron concentration, serum ferritin level, plasma erythropoietin level and FEP level. In specific embodiments, the subject is administered a low dose of ferric citrate at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days). In certain embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the

subject. In some embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0033] In specific aspects, provided herein are methods for increasing or maintaining serum ferritin level in a subject with and/or diagnosed with IDA, comprising orally administering ferric citrate or a pharmaceutical composition thereof to the subject. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In specific embodiments, the subject is administered a low dose of ferric citrate at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days). In certain embodiments, the serum ferritin level of the subject is assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, the serum ferritin level of the subject is monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In

certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0034] 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. 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 an IDA 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/or store iron.

[0035] In certain embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean increase in serum ferritin level of 5-15 ng/ml, 5-25 ng/ml, 5-50 ng/ml, 5-100 ng/ml, 5-200 ng/ml, 5- 300 ng/ml, 5-400 ng/ml, 25-50 ng/ml, 25-100 ng/ml, 25-200 ng/ml, 25-300 ng/ml, 25-400 ng/ml, 50-100 ng/ml, 50-200 ng/ml, 50-300 ng/ml, 50-400 ng/ml, 100-200 ng/ml, 100-300 ng/ml, 100-400 ng/ml, 200-300 ng/ml, or 200-400 ng/ml. In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean increase in serum ferritin level of about 5 ng/ml or more, about10 ng/ml or more, about 25 ng/ml or more, about 50 ng/ml or more, about 100 ng/ml or more, about 110 ng/ml or more, about 120 ng/ml or more, about 130 ng/ml or more, about 140 ng/ml or more, about 150 ng/ml or more, about 160 ng/ml or more, about 170 ng/ml or more, about 180 ng/ml or more, about 190 ng/ml or more, about 200 ng/ml or more, about 210 ng/ml or more, about 220 ng/ml or more, about 230 ng/ml or more, about 240 ng/ml or more, about 250 ng/ml or more, about 260 ng/ml or more, about 270 ng/ml or more, about 280 ng/ml or more, about 290 ng/ml or more, about 300 ng/ml or more, about 310 ng/ml or more, about 320 ng/ml or more, about 330 ng/ml or more, about 340 ng/ml or more, about 350 ng/ml or more, about 360 ng/ml or more, about 370 ng/ml or more, about 380 ng/ml or more, or about 390 ng/ml or more. In certain embodiments, a subject treated for IDA in accordance with the methods described herein

experiences mean increase in serum ferritin level of about 1-100%, 1-95%, 10-95%, 10-90%, 10-85%, 10-80%, 10-75%, 10-70%, 10-65%, 10-60%, 10-50%, 10-45%, 10-40%, 10-35%, 10-30%, 10-25%, 10-20%, 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 30-90%, 30-80%, 30-70%, 30-60%, 30-50%, 30-40%, 40-90%, 40-80%, 40-70%, 40-60%, 40-50%, 50-90%, 50-80%, 50-70%, 50-65%, 50-60%, 60-90%, 60-80%, 60-75%, 60-70%, 70-90%, 70%-80%, or 80-90%. In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean increase in serum ferritin level of 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more. In certain embodiments, a mean increase of serum ferritin level results after the ferric citrate or a pharmaceutical composition thereof is administered to the subject for a certain period of time (*e.g.*, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or more). In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences maintenance of their serum ferritin level such that their serum ferritin level remains substantially unchanged during administration of the ferric citrate or a pharmaceutical composition.

[0036] As used herein, the term "substantially unchanged" in the context of the level of an iron storage parameter, means that the level of the iron storage parameter is changed less than 5%.

[0037] In specific aspects, provided herein are methods for increasing or maintaining tissue iron level (*e.g.*, liver iron level, spleen iron level) measured as stainable tissue iron levels or tissue iron concentrations in a subject with and/or diagnosed with IDA, comprising orally administering ferric citrate or a pharmaceutical composition thereof to the subject. In a specific embodiment, the tissue iron level is measured as stainable tissue iron level. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In specific embodiments, the subject is administered a low dose of ferric citrate at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days). In certain embodiments, the tissue iron level (*e.g.*, stainable tissue iron level) of the subject is assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, the tissue iron level (*e.g.*, stainable tissue iron level) of the subject is

monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0038] Tissue iron levels reflect the iron content in tissues (*e.g.*, liver, spleen), and can be measured as stainable tissue iron levels or tissue iron concentrations. Stainable tissue iron levels and serum ferritin levels are the most sensitive laboratory indicators of mild iron deficiency and are particularly useful in differentiating iron deficiency from the anemia of chronic disorders. Stainable tissue iron levels are determined by histological grading of stainable iron. A normal stainable liver iron level is usually greater than grade 3. In an IDA patient, however, the stainable liver iron level is typically markedly reduced as the body loses its ability to absorb and/or store iron.

[0039] In certain embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean increase in tissue iron level (*e.g.*, stainable tissue iron level) of about 1-100%, 1-95%, 10-95%, 10-90%, 10-85%, 10-80%, 10-75%, 10-70%, 10-65%, 10-60%, 10-50%, 10-45%, 10-40%, 10-35%, 10-30%, 10-25%, 10-20%, 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 30-90%, 30-80%, 30-70%, 30-60%, 30-50%, 30-40%, 40-90%, 40-80%, 40-70%, 40-60%, 40-50%, 50-90%, 50-80%, 50-70%, 50-65%, 50-60%, 60-90%, 60-80%, 60-75%, 60-70%, 70-90%, 70%-80%, or 80-90%. In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean increase in tissue iron level (*e.g.*, stainable tissue iron level) of 10%, 15%, 20%, 25%, 30%, 35%, 40%,

45%, 50%, 55%, 60%, 65%, 70%. 75%, 80%, 85%, 90%, 95% or more. In certain embodiments, a mean increase of tissue iron level (*e.g.*, stainable tissue iron level) results after the ferric citrate or a pharmaceutical composition thereof is administered to the subject for a certain period of time (*e.g.*, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or more). In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences maintenance of their tissue iron level (*e.g.*, stainable tissue iron level) such that their tissue iron level (*e.g.*, stainable tissue iron level) remains substantially unchanged during administration of the ferric citrate or a pharmaceutical composition.

[0040] In specific aspects, provided herein are methods for increasing or maintaining TSAT value in a subject with and/or diagnosed with IDA, comprising orally administering ferric citrate or a pharmaceutical composition thereof to the subject. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In specific embodiments, the subject is administered a low dose of ferric citrate at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days). In certain embodiments, the TSAT value of the subject is assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, the TSAT value of the subject is monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, one or more other iron storage parameters, such as hemoglobin concentration, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more other iron storage parameters, such as hemoglobin concentration, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6

months or more). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0041] 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 Fe3+) 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 non-IDA patients, typical TSAT values are approximately 15–50% for males and 12–45% for females. In an IDA 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/or store iron.

[0042] In certain embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean increase in TSAT value of about 1-10%, 1-15%, 1-20%, 1-25%, 1-50%, 1-75%, 1-100%, 5-15%, 5-20%, 5-25%, 5-50%, 5-75%, 5-100%, 10-15%, 10-20%, 10-25%, 10-50%, 10-75%, 10-100%, 15-20%, 15-25%, 15-50%, 15-75%, 15-100%, 20-25%, 20-50%, 20-75%, 20-100%, 25-50%, 25-75%, 25-100%, 50-75%, or 50-100%. In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean increase in TSAT values of 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 50%, 75%, 100% or more. In certain embodiments, a mean increase of TSAT value results after the ferric citrate or a pharmaceutical composition thereof is administered to the subject for a certain period of time (*e.g.*, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or more). In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences maintenance of

their TSAT value such that their TSAT value remains substantially unchanged during administration of the ferric citrate or a pharmaceutical composition.

[0043] In specific aspects, provided herein are methods for increasing or maintaining hemoglobin concentration in a subject with and/or diagnosed with IDA, comprising orally administering ferric citrate or a pharmaceutical composition thereof to the subject. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In specific embodiments, the subject is administered a low dose of ferric citrate at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days). In certain embodiments, the hemoglobin concentration of the subject is assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, the hemoglobin concentration of the subject is monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, one or more other iron storage parameters, such as TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more other iron storage parameters, such as TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0044] Hemoglobin concentration is the measure of the concentration of hemoglobin (grams) per volume (deciliter) of whole blood. Hemoglobin concentration may also be measured as a mass or weight fraction and presented as a percentage (%). For non-IDA patients, a typical hemoglobin concentration ranges from 13.8-18.0 g/dl (*i.e.*, 8.56-11.17 mmol/L) for men, from

12.1-15.1 g/dl (*i.e.*, 7.51-9.37 mmol/L) for women, from 11.0-16.0 g/dl (*i.e.*, 6.83-9.93 mmol/L) for children, and from 11.0-14.0 g/dl (*i.e.*, 6.83-8.69 mmol/L) for pregnant women. In an IDA patient, however, the hemoglobin concentration can be reduced below the normal range as the body loses its ability to absorb and/or store iron.

[0045] In certain embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean increase in hemoglobin concentration of 0.1-0.5 g/dl, 0.1-1 g/dl, 0.1-1.5 g/dl, 0.1-2 g/dl, 0.1-2.5 g/dl, 0.1-3 g/dl, 0.1-3.5 g/dl, 0.1-4 g/dl, 0.1-4.5 g/dl, 0.1-5 g/dl, 0.4-0.8 g/dl, 0.4-1 g/dl, 0.4-1.5 g/dl, 0.4-2 g/dl, 0.4-2.5 g/dl, 0.4-3 g/dl, 0.4-3.5 g/dl, 0.4-4 g/dl, 0.4-4.5 g/dl, 0.4-5 g/dl, 0.5-0.8 g/dl, 0.5-1g/dl, 0.5-1.5 g/dl, 0.5-2 g/dl, 0.5-2.5 g/dl, 0.5 - 3g/dl, 0.5-3.5 g/dl, 0.5-4 g/dl, 0.5-4.5 g/dl, 0.5-5 g/dl. 1-1.5 g/dl, 1-2 g/dl, 1-2.5 g/dl, 1-3 g/dl, 1-3.5 g/dl, 1-4 g/dl, 1-4.5 g/dl, 1-5 g/dl, 1.5-2 g/dl, 1.5-2.5 g/dl, 1.5-3 g/dl, 1.5-3.5 g/dl, 1.5-4 g/dl, 1.5-4.5 g/dl, 1.5-5 g/dl, 2-2.5 g/dl, 2-3 g/dl, 2-3.5 g/dl, 2-4 g/dl, 2-4.5 g/dl or 2-5 g/dl. In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean increase in hemoglobin concentration of about 0.1 g/dl or more, about 0.2 g/dl or more, about 0.3 g/dl or more, about 0.4 g/dl or more, about 0.5 g/dl or more, about 1g/dl or more, about 1.5 g/dl or more, about 2 g/dl or more, about 2.5 g/dl or more, about 3 g/dl or more, about 3.5 g/dl or more, about 4 g/dl or more, about 4.5 g/dl or more, or about 5 g/dl or more. In certain embodiments, the hemoglobin concentration does not increase by more than 2 g/dl, 3 g/dl, 4 g/dl or 5 g/dl. In some embodiments, a mean increase hemoglobin concentration results after the ferric citrate or a pharmaceutical composition thereof is administered to the subject for a certain period of time (*e.g.*, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or more). In certain embodiments, a subject treated for IDA in accordance with the methods described herein experiences maintenance of their hemoglobin concentration such that their hemoglobin concentration remains substantially unchanged during administration of the ferric citrate or a pharmaceutical composition.

[0046] In specific aspects, provided herein are methods for increasing or maintaining hematocrit level in a subject with and/or diagnosed with IDA, comprising orally administering ferric citrate or a pharmaceutical composition thereof to the subject. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*,

regarding forms of ferric citrate and pharmaceutical compositions thereof. In specific embodiments, the subject is administered a low dose of ferric citrate at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days). In certain embodiments, the hematocrit level of the subject is assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, the hematocrit level of the subject is monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0047] 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-IDA patients, the hematocrit is typically about 45% of blood volume for men and about 40% of blood volume for women. In IDA patients, however, the hematocrit is often significantly depleted due to poor iron absorption and/or poor iron storage capacity.

[0048] In certain embodiments, a subject treated for IDA in accordance with the methods described herein experiences an increase in hematocrit level of about 1-25%, 1-20%, 1-15%, 1-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25%. In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences an increase in hematocrit level of 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25% or more.

In certain embodiments, an increase of hematocrit level results after the ferric citrate or a pharmaceutical composition thereof is administered to the subject for a certain period of time (*e.g.*, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or more). In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences maintenance of their hematocrit level such that their hematocrit remains substantially unchanged during administration of the ferric citrate or a pharmaceutical composition.

[0049] In specific aspects, provided herein are methods for decreasing or maintaining total iron-binding capacity (TIBC) value in a subject with and/or diagnosed with IDA, comprising orally administering ferric citrate or a pharmaceutical composition thereof to the subject. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In specific embodiments, the subject is administered a low dose of ferric citrate at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days). In certain embodiments, the TIBC value of the subject is assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, the TIBC value of the subject is monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, plasma erythropoietin level, and/or FEP level, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, plasma erythropoietin level, and/or FEP level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, the subject administered the ferric citrate

or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0050] 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-IDA 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 IDA 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.

[0051] In certain embodiments, a subject treated for IDA in accordance with the methods described herein experiences a decrease in TIBC value of about 1-25%, 1-20%, 1-15%, 1-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, or 20-25%. In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences a decrease in TIBC value of 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25% or more. In certain embodiments, a decrease of TIBC value results after the ferric citrate or a pharmaceutical composition thereof is administered to the subject for a certain period of time (*e.g.*, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or more). In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences maintenance of their TIBC value such that their TIBC value remains substantially unchanged during administration of the ferric citrate or a pharmaceutical composition.

[0052] In specific aspects, provided herein are methods for increasing or maintaining serum iron level in a subject with and/or diagnosed with IDA, comprising orally administering ferric citrate or a pharmaceutical composition thereof to the subject. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In specific embodiments, the subject is administered a low dose of ferric citrate at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days). In certain

embodiments, the serum iron level is assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, the serum iron level of the subject is monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0053] The serum pool of iron is the fraction of all iron in the body that circulates in the blood and bound primarily to transferrin. The iron in this pool turns over very quickly and represents iron in transit from one location to another. Serum iron level is a measure of the amount of this pool of circulating iron in the blood. A normal serum iron level is usually 65-176 μg/dl for men, 50-170 μg/dl for women, and 50-120 μg/dl for children. In an IDA patient, however, the serum iron level is typically reduced below the normal range as the body loses its ability to absorb and/or store iron.

[0054] In certain embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean increase in serum iron level of about 1-100%, 1-95%, 10-95%, 10-90%, 10-85%, 10-80%, 10-75%, 10-70%, 10-65%, 10-60%, 10-50%, 10-45%, 10-40%, 10-35%, 10-30%, 10-25%, 10-20%, 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 30-90%, 30-80%, 30-70%, 30-60%, 30-50%, 30-40%, 40-90%, 40-80%, 40-70%, 40-60%, 40-50%, 50-90%, 50-80%, 50-70%, 50-65%, 50-60%, 60-90%, 60-80%, 60-75%, 60-70%, 70-90%, 70%-80%, or 80-90%. In some embodiments, a subject treated for IDA in accordance with

the methods described herein experiences mean increase in serum iron level of 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, *50%*, 55%, 60%, 65%, 70%. 75%, 80%, 85%, 90%, 95% or more. In certain embodiments, a mean increase of serum iron level results after the ferric citrate or a pharmaceutical composition thereof is administered to the subject for a certain period of time (*e.g.*, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or more). In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences maintenance of their serum iron level such that their serum iron level remains substantially unchanged during administration of the ferric citrate or a pharmaceutical composition.

[0055] In specific aspects, provided herein are methods for decreasing or maintaining plasma erythropoietin level in a subject with and/or diagnosed with IDA, comprising orally administering ferric citrate or a pharmaceutical composition thereof to the subject. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In specific embodiments, the subject is administered a low dose of ferric citrate at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days). In certain embodiments, the plasma erythropoietin level of the subject is assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, the plasma erythropoietin level of the subject is monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, and/or FEP level, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, and/or FEP level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain

embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0056] Erythropoietin is a renal glycoprotein hormone that is an obligatory growth factor for the proliferation and differentiation of committed erythroid progenitor cells. Plasma erythropoietin level usually increases as the hematocrit level decreases. A normal plasma erythropoietin level is usually 4.1-19.5 mU/ml for adults, and 9-28 mU/ml for children. In an IDA patient, however, the plasma erythropoietin level is typically increased above the normal range as the body loses its ability to absorb and/or store iron.

[0057] In certain embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean decrease in plasma erythropoietin level of about 1-100%, 1-95%, 10-95%, 10-90%, 10-85%, 10-80%, 10-75%, 10-70%, 10-65%, 10-60%, 10-50%, 10-45%, 10-40%, 10-35%, 10-30%, 10-25%, 10-20%, 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 30-90%, 30-80%, 30-70%, 30-60%, 30-50%, 30-40%, 40-90%, 40-80%, 40-70%, 40-60%, 40-50%, 50-90%, 50-80%, 50-70%, 50-65%, 50-60%, 60-90%, 60-80%, 60-75%, 60-70%, 70-90%, 70%-80%, or 80-90%. In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean decrease in plasma erythropoietin level of 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%. 75%, 80%, 85%, 90%, 95% or more. In certain embodiments, a mean increase of plasma erythropoietin level results after the ferric citrate or a pharmaceutical composition thereof is administered to the subject for a certain period of time (*e.g.*, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or more). In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences maintenance of their plasma erythropoietin level such that their plasma erythropoietin level remains substantially unchanged during administration of the ferric citrate or a pharmaceutical composition.

[0058] In specific aspects, provided herein are methods for decreasing or maintaining free erythrocyte protoporphyrin (FEP) level in a subject with and/or diagnosed with IDA, comprising orally administering ferric citrate or a pharmaceutical composition thereof to the subject. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof,

and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In specific embodiments, the subject is administered a low dose of ferric citrate at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days). In certain embodiments, the FEP level of the subject is assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, the FEP level of the subject is monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, and/or plasma erythropoietin level, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more other iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, and/or plasma erythropoietin level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, the one or more iron storage parameters are monitored every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0059] When there is a lack of iron in the bone marrow for incorporation into the heme group during hemoglobin synthesis, zinc is incorporated instead and forms a compound called zinc protoporphyrin (ZPP). Free erythrocyte protoporphyrin (FEP) is the compound left over after the zinc ion has been removed during the extraction and chemical measurement process. A rise in the FEP level is one of the first indicators of insufficient iron in the bone marrow. A normal FEP level is usually 30-40 μg/dl red blood cells. In an IDA patient, however, the serum iron level is typically increased above the normal range as the body loses its ability to absorb and/or store iron.

[0060] In certain embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean decrease in FEP level of about 1-100%, 1-95%, 10-95%, 10-90%, 10-85%, 10-80%, 10-75%, 10-70%, 10-65%, 10-60%, 10-50%, 10-45%, 10-40%, 10-35%,

10-30%, 10-25%, 10-20%, 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 30-90%, 30-80%, 30-70%, 30-60%, 30-50%, 30-40%, 40-90%, 40-80%, 40-70%, 40-60%, 40-50%, 50-90%, 50-80%, 50-70%, 50-65%, 50-60%, 60-90%, 60-80%, 60-75%, 60-70%, 70-90%, 70%-80%, or 80-90%. In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences mean decrease in FEP level of 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%. 75%, 80%, 85%, 90%, 95% or more. In certain embodiments, a mean increase of FEP level results after the ferric citrate or a pharmaceutical composition thereof is administered to the subject for a certain period of time (*e.g.*, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or more). In some embodiments, a subject treated for IDA in accordance with the methods described herein experiences maintenance of their FEP level such that their FEP level remains substantially unchanged during administration of the ferric citrate or a pharmaceutical composition.

[0061] There are typically three means by which IDA 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 or intravenous (IV) iron supplements. Intravenous (IV) iron supplementation is a method of delivering iron by injection with a needle, either through a muscle or into a vein. IDA patients who are receiving IV iron usually do so because they cannot tolerate oral iron. Intravenous iron is delivered into the IDA 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 patient usually receives iron injections over the course of several visits until his or her iron levels are correct. In some instances, an IDA patient may require permanent IV iron supplementation. IV iron is associated with short-term side effects such as gastrointestinal pains (*e.g.*, nausea and cramps), breathing problems, skin problems (*e.g.*, rash), chest pain, low blood pressure, anaphylaxis, and death, as well as long-term toxicity, including the development of atherosclerosis, infection, and increased mortality (Quinibi, Arzneimittelforschung (2010) 60, 399-412). Further, many clinics, particularly community sites, are ill-equipped to administer intravenous iron. This has left a majority of IDA patients without intravenous iron treatment.

[0062] In addition, IDA patients 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).

[0063] 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. In addition, ESAs may in certain cases worsen iron depletion and lead to an increase in thrombocytosis.

[0064] In specific aspects, provided herein are methods for decreasing or maintaining the intravenous iron and/or erythropoeisis-stimulating agent(s) intake by a subject with and/or diagnosed with IDA, comprising orally administering ferric citrate or a pharmaceutical composition thereof to the subject. *See*, *e.g.*, Sections 4.2, *infra*, regarding the patient population treated, Section 4.3, *infra*, regarding the dosing and administration of ferric citrate or a pharmaceutical composition thereof, and Section 4.5, *infra*, regarding forms of ferric citrate and pharmaceutical compositions thereof. In specific embodiments, the subject is administered a low dose of ferric citrate at a certain frequency (*e.g.*, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days). In certain embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC value, plasma erythropoietin level, and/or FEP level, of the subject are assessed prior to administration of ferric citrate or a pharmaceutical composition thereof to the subject. In some embodiments, one or more iron storage parameters, such as hemoglobin concentration, TSAT value, serum ferritin level, serum iron level, tissue iron level (*e.g.*, stainable tissue iron level), hematocrit level, TIBC

value, plasma erythropoietin level, and/or FEP level, of the subject are monitored after the administration of ferric citrate or a pharmaceutical composition thereof to the subject (*e.g.*, every month, 2 months, 3 months, 4 months, 5 months, 6 months or more). In certain embodiments, the subject administered the ferric citrate or pharmaceutical composition thereof does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0065] In certain embodiments, a subject treated for IDA in accordance with the methods described herein experiences a mean reduction in average cumulative IV iron intake of about 1-25%, 1-20%, 1-15%, 1-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, 20-25%, 1-100%, 20-25%, 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 25-30%, 25-45%, 25-50%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-60%, 30-70%, 30-80%, 30-90%, 40-50%, 40-80%, 40-95%, 50-60%, 50-75%, 50-95%, 60-70%, 60-90%, 60-95%, 75-85%, 75-95%, or 75-100%. In some embodiments, a subject treated for IDA in accordance with the methods described herein a mean reduction in average cumulative IV iron intake of 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 30%, 35%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more. In certain embodiments, a mean reduction in average cumulative IV iron intake results after the ferric citrate or a pharmaceutical composition thereof is administered to the subject for a certain period of time (*e.g.*, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or more).

[0066] In certain embodiments, a subject treated for IDA in accordance with the methods described herein experiences a decrease in median ESA intake of about 1-25%, 1-20%, 1-15%, 1-10%, 5-15%, 5-20%, 5-25%, 10-15%, 10-20%, 10-25%, 15-20%, 15-25%, 20-25%, 1-100%, 20-25%, 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 25-30%, 25-45%, 25-50%, 25-75%, 25-80%, 25-85%, 25-90%, 25-95%, 30-40%, 30-60%, 30-70%, 30-80%, 30-90%, 40-50%, 40-80%, 40-95%, 50-60%, 50-75%, 50-95%, 60-70%, 60-90%, 60-95%, 75-85%, 75-95%, or 75-100%. In some embodiments, a subject treated for IDA in accordance with the methods described herein a decrease in median ESA intake of 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 30%, 35%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more. In certain embodiments, a decrease in median ESA intake results after the ferric citrate or a

pharmaceutical composition thereof is administered to the subject for a certain period of time (*e.g.*, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or more).

4.2. Patient Population

[0067] The terms "patient" and "subject" are used herein interchangeably to refer to an animal. In certain embodiments, a patient treated in accordance with the methods disclosed herein is a mammal, such as a non-primate (*e.g.*, a cow, pig, horse, cat, dog, rat, etc.) or a primate (*e.g.*, a monkey or human). In a preferred embodiment, a patient treated in accordance with the methods disclosed herein is a human.

[0068] In certain embodiments, a patient treated in accordance with the methods disclosed herein is male or non-pregnant, non-breastfeeding female. In some embodiments, a patient treated in accordance with the methods disclosed herein is a human 18 years of age or older.

[0069] In certain embodiments, a patient treated in accordance with the methods disclosed herein does not have and/or has not been diagnosed with hyperphosphatemia. In other embodiments, a patient treated in accordance with the methods disclosed herein is hyperphospatemic.

[0070] In some embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed as having IDA associated with chronic kidney disease (CKD). CKD is a condition characterized by a gradual loss of kidney function over time, and IDA is a common complication of CKD. All individuals with a glomerular filtration rate (GFR) <60 ml/min/1.73 m2 for 3 months are classified as having CKD, irrespective of the presence or absence of kidney damage. Based on the severity, CKD can be classified in five stages. Stage 1 is the mildest and usually causing few symptoms. Stage 2 is characterized by mild reduction in GFR (60–89 ml/min/1.73 m^2) with kidney damage. Stage 3 is characterized by moderate reduction in GFR (30–59 ml/min/1.73 m^2). Stage 4 is characterized by severe reduction in GFR (15–29 ml/min/1.73 m^2). Stage 5 is characterized by established kidney failure (GFR <15 ml/min/1.73 m^2). Stage 5 is a severe illness with poor life expectancy if untreated. 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 (ND-CKD) patients. Typically, patients progress through stages 1 through 4 before dialysis is medically necessary. However, patients at stage 5 who have not yet started dialysis or who have not been recommended for transplantation are also non-dialysis dependent CKD patients. In various embodiments, the IDA patients are stage 3-5 CKD patients.

[0071] In some embodiments, a patient treated in accordance with the methods disclosed herein does not have and/or has not been diagnosed with chronic kidney disease. In certain embodiments, a patient treated in accordance with the methods disclosed herein does not have and/or has not been diagnosed with stage 1, 2, 3, 4, or 5 chronic kidney disease. In some embodiments, a patient treated in accordance with the methods disclosed herein does not have and/or has not been diagnosed with end-stage chronic kidney disease. In certain embodiments, a patient treated in accordance with the methods disclosed herein does not have and/or has not been diagnosed with chronic kidney disease and/or hyperphosphatemia.

[0072] In certain other embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with chronic kidney disease. In some embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with stage 1, 2, 3, 4, or 5 chronic kidney disease. In certain embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with end-stage chronic kidney disease. In some embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with chronic kidney disease and is receiving dialysis. In other embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with chronic kidney disease and is not receiving dialysis.

[0073] In certain embodiments, a patient treated in accordance with the methods disclosed herein has a hemoglobin concentration of approximately 9 grams/dl or greater, such as approximately 9.5 grams/dl, 10 grams/dl, 11 grams/dl, 11.5 grams/dl, or 12 grams/dl, prior to administration of ferric citrate or a pharmaceutical composition thereof. In some embodiments, a patient treated in accordance with the methods disclosed herein has a hemoglobin concentration of approximately 9 grams/dl and less than or equal to approximately 12.5 grams/dl, 12 grams/dl or 11.5 grams/dl prior to administration of ferric citrate or a pharmaceutical composition thereof.

In certain embodiments, a patient treated in accordance with the methods disclosed herein has a hemoglobin concentration of approximately 6 grams/dl to approximately 8 grams/dl, approximately 6 grams/dl to approximately 10 grams/dl, approximately 6 grams/dl to approximately 12 grams/dl, approximately 7 grams/dl to approximately 9 grams/dl, approximately 7 grams/dl to approximately 11 grams/dl, approximately 7 grams/dl to approximately 13 grams/dl, approximately 8 grams/dl to approximately 10 grams/dl, approximately 8 grams/dl to approximately 12 grams/dl, approximately 9 grams/dl to approximately 11 grams/dl, approximately 9 grams/dl to approximately 12 grams/dl, approximately 9 grams/dl to approximately 13 grams/dl, approximately 10 grams/dl to approximately 11 grams/dl, approximately 10 grams/dl to approximately 12 grams/dl, approximately 10 grams/dl to approximately 13 grams/dl, approximately 11 grams/dl to approximately 12 grams/dl, approximately 11 grams/dl to approximately 13 grams/dl, or approximately 12 grams/dl to approximately 13 grams/dl prior to administration of ferric citrate or a pharmaceutical composition thereof.

[0074] In certain embodiments, a patient treated in accordance with the methods disclosed herein has a TSAT value of less than 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15% 12%, or 10% prior to administration of ferric citrate or a pharmaceutical composition thereof. In some embodiments, a patient treated in accordance with the methods disclosed herein has a TSAT value of 5% to 50%, 5% to 45%, 5% to 40%, 5% to 35%, 5% to 30%, 5% to 25%, 5% to 20%, 5% to 15%, 5% to 12%, 5% to 10%, 10% to 50%, 10% to 45%, 10% to 40%, 10% to 35%, 10% to 30%, 10% to 25%, 10% to 20%, 10% to 15%, 10% to 12%, 12% to 50%, 12% to 45%, 12% to 40%, 12% to 35%, 12% to 30%, 12% to 25%, 12% to 20%, 12% to 15%, 15% to 50%, 15% to 45%, 15% to 40%, 15% to 35%, 15% to 30%, 15% to 25%, 15% to 20%, 20% to 50%, 20% to 45%, 20% to 40%, 20% to 35%, 20% to 30%, 20% to 25%, 30% to 50%, 30% to 45%, 30% to 40%, 30% to 35%, 40% to 50%, 40% to 45%, or 45% to 50% prior to administration of ferric citrate or a pharmaceutical composition thereof. In certain embodiments wherein the patient treated in accordance with the methods disclosed herein is a female, the patient has a TSAT value of 5% to 45%, 5% to 35%, 5% to 25%, 5% to 15%, 5% to 12%, 5% to 10%, 10% to 45%, 10% to 35%, 10% to 25%, 10% to 15%, 10% to 12%, 12% to 45%, 12% to 35%, 12% to 25%, 12% to 15%, 20% to 45%, 20% to 35%, 20% to 25%, 30% to 45%, 30% to 35%, or 40% to 45% prior to administration of ferric citrate or a pharmaceutical composition thereof. In

certain embodiments wherein the patient treated in accordance with the methods disclosed herein is a male, the patient has a TSAT value of 5% to 50%, 5% to 40%, 5% to 30%, 5% to 20%, 5% to 15%, 5% to 10%, 10% to 50%, 10% to 40%, 10% to 30%, 10% to 20%, 10% to 15%, 15% to 50%, 15% to 40%, 15% to 30%, 15% to 25%, 15% to 20%, 20% to 50%, 20% to 40%, 20% to 30%, 20% to 25%, 30% to 50%, 30% to 40%, 30% to 35%, 40% to 50%, 40% to 45%, or 45% to 50% prior to administration of ferric citrate or a pharmaceutical composition thereof.

[0075] In certain embodiments, a patient treated in accordance with the methods disclosed herein has a serum ferritin level of less than 300 ng/ml (*e.g.*, less than or equal to 275 ng/ml, less than or equal to 250 ng/ml, less than or equal to 225 ng/ml, less than or equal to 200 ng/ml, less than or equal to 175 ng/ml, less than or equal to 150 ng/ml, less than or equal to 125 ng/ml, less than or equal to 100 ng/ml, less than or equal to 75 ng/ml, less than or equal to 50 ng/ml, less than or equal to 25 ng/ml, less than or equal to 15 ng/ml, less than or equal to 10 ng/ml, or less than or equal to 5 ng/ml) prior to administration of ferric citrate or a pharmaceutical composition thereof. In some embodiments, a patient treated in accordance with the methods disclosed herein has a serum ferritin level of approximately 5 ng/ml, 10 ng/ml, 15 ng/ml, 20 ng/ml, 25 ng/ml, 30 ng/ml, 35 ng/ml, 40 ng/ml, 45 ng/ml, 50 ng/ml, 55 ng/ml, 60 ng/ml, 65 ng/ml, 70 ng/ml, 75 ng/ml, 80 ng/ml, 85 ng/ml, 90 ng/ml, 95 ng/ml, 100 ng/ml, 125 ng/ml, 150 ng/ml, 175 ng/ml, 200 ng/ml, 225 ng/ml, 250 ng/ml, 275 ng/ml, or 300 ng/ml prior to administration of ferric citrate or a pharmaceutical composition thereof. In certain embodiments, a patient treated in accordance with the methods disclosed herein has a serum ferritin level of approximately 5 ng/ml to approximately 15 ng/ml, approximately 5 ng/ml to approximately 25 ng/ml, approximately 5 ng/ml to approximately 50 ng/ml, approximately 15 ng/ml to approximately 25 ng/ml, approximately 15 ng/ml to approximately 50 ng/ml, approximately 15 ng/ml to approximately 75 ng/ml, approximately 25 ng/ml to approximately 50 ng/ml, approximately 25 ng/ml to approximately 75 ng/ml, approximately 25 ng/ml to approximately 100 ng/ml, approximately 50 ng/ml to approximately 75 ng/ml, approximately 50 ng/ml to approximately 100 ng/ml, approximately 50 ng/ml to approximately 150 ng/ml, approximately 75 ng/ml to approximately 100 ng/ml, approximately 75 ng/ml to approximately 150 ng/ml, approximately 100 ng/ml to approximately 150 ng/ml, approximately 150 ng/ml to approximately 200 ng/ml, approximately 150 ng/ml to approximately 250 ng/ml, approximately 100 ng/ml to approximately 300 ng/ml, approximately 200 ng/ml to approximately 300 ng/ml, or

approximately 250 ng/ml to approximately 300 ng/ml prior to administration of ferric citrate or a pharmaceutical composition thereof. In certain embodiments, a patient treated in accordance with the methods disclosed herein has a serum ferritin level of between 5 ng/ml to 300 ng/ml (*e.g.*, between 5 ng/ml to 250 ng/ml, between 5 ng/ml to 150 ng/ml, between 5 ng/ml to 100 ng/ml, between 5 ng/ml to 75 ng/ml, between 5 ng/ml to 50 ng/ml, between 5 ng/ml to 25 ng/ml, between 5 ng/ml to 15 ng/ml, or between 5 ng/ml to 10 ng/ml) prior to administration of ferric citrate or a pharmaceutical composition thereof.

[0076] In certain embodiments, a patient treated in accordance with the methods disclosed herein has a hematocrit level of less than 45%, 40%, 35%, 30%, 25%, 20%, 15% or 10% prior to administration of ferric citrate or a pharmaceutical composition thereof. In some embodiments, a patient treated in accordance with the methods disclosed herein has a hematocrit level of 10% to 15%, 10% to 20%, 10% to 25%, 10% to 30%, 10% to 35%, 10% to 40%, 10% to 45%, 15% to 20%, 15% to 25%, 15% to 30%, 15% to 35%, 15% to 40%, 15% to 45%, 20% to 25%, 20% to 30%, 20% to 35%, 20% to 40%, 25% to 45%, 25% to 30%, 25% to 35%, 25% to 40%, 25% to 45%, 30% to 35%, 30% to 40%, 30% to 45%, 35% to 40%, 35% to 45%, or 40% to 45%, prior to administration of ferric citrate or a pharmaceutical composition thereof.

[0077] In certain embodiments, a patient treated in accordance with the methods disclosed herein has a TIBC value of more than 390 μg/dl (*e.g.*, more than or equal to 390 μg/dl, more than or equal to 400 μg/dl, more than or equal to 450 μg/dl, more than or equal to 450 μg/dl, more than or equal to 500 μg/dl, more than or equal to 550 μg/dl, more than or equal to 600 μg/dl, more than or equal to 650 μg/dl, more than or equal to 700 μg/dl, more than or equal to 800 μg/dl, more than or equal to 900 μg/dl, more than or equal to 1000 μg/dl, more than or equal to 1100 μg/dl, or more than or equal to 1200 μg/dl)prior to administration of ferric citrate or a pharmaceutical composition thereof. In some embodiments, a patient treated in accordance with the methods disclosed herein has a TIBC value of approximately 390 μg/dl, 400 μg/dl, 450 μg/dl, 500 μg/dl, 550 μg/dl, 600 μg/dl, 650 μg/dl, 700 μg/dl, 800 μg/dl, 900 μg/dl, 1000 μg/dl, 1100 μg/dl, or 1200 μg/dl prior to administration of ferric citrate or a pharmaceutical composition thereof. In certain embodiments, a patient treated in accordance with the methods disclosed herein has a TIBC value of approximately approximately 390 μg/dl to approximately 600 μg/dl, approximately 390 μg/dl to approximately 800 μg/dl, approximately 390 μg/dl to approximately 1000 μg/dl, approximately 390 μg/dl to approximately 1200 μg/dl, approximately

500 μg/dl to approximately 700 μg/dl, approximately 500 μg/dl to approximately 900 μg/dl, approximately 500 μg/dl to approximately 1100 μg/dl, approximately 600 μg/dl to approximately 800 μg/dl, approximately 600 μg/dl to approximately 1000 μg/dl, approximately 600 μg/dl to approximately 1200 μg/dl, approximately 700 μg/dl to approximately 900 μg/dl, approximately 700 μg/dl to approximately 1100 μg/dl, approximately 800 μg/dl to approximately 1000 μg/dl, approximately 800 μg/dl to approximately 1200 μg/dl, approximately 900 μg/dl to approximately 1100 μg/dl, or approximately 1000 μg/dl to approximately 1200 μg/dl ml prior to administration of ferric citrate or a pharmaceutical composition thereof.

[0078] In certain embodiments, a patient treated in accordance with the methods disclosed herein has a tissue iron level (*e.g.*, stainable tissue iron level) of grade 2 prior to administration of ferric citrate or a pharmaceutical composition thereof. In certain embodiments, a patient treated in accordance with the methods disclosed herein has a tissue iron level (*e.g.*, stainable tissue iron level) of grade 1 prior to administration of ferric citrate or a pharmaceutical composition thereof. In certain embodiments, a patient treated in accordance with the methods disclosed herein has a tissue iron level (*e.g.*, stainable tissue iron level) of grade 0 prior to administration of ferric citrate or a pharmaceutical composition thereof.

[0079] In certain embodiments, a patient treated in accordance with the methods disclosed herein has a serum iron level of less than 60 μg/dl (*e.g.*, less than or equal to 50 μg/dl, less than or equal to 40 μg/dl, less than or equal to 30 μg/dl, less than or equal to 20 μg/dl, or less than or equal to 10 μg/dl) prior to administration of ferric citrate or a pharmaceutical composition thereof. In some embodiments, a patient treated in accordance with the methods disclosed herein has a serum iron level of approximately 5 μg/dl, 10 μg/dl, 15 μg/dl, 20 μg/dl, 25 μg/dl, 30 μg/dl, 40 μg/dl, 50 μg/dl, or 60 μg/dl prior to administration of ferric citrate or a pharmaceutical composition thereof. In certain embodiments, a patient treated in accordance with the methods disclosed herein has a serum iron level of approximately 10 μg/dl to approximately 20 μg/dl, approximately 10 μg/dl to approximately 30 μg/dl, approximately 10 μg/dl to approximately 40 μg/dl, approximately 10 μg/dl to approximately 50 μg/dl, approximately 10 μg/dl to approximately 60 μg/dl, approximately 20 μg/dl to approximately 30 μg/dl, approximately 20 μg/dl to approximately 40 μg/dl, approximately 20 μg/dl to approximately 50 μg/dl, approximately 20 μg/dl to approximately 60 μg/dl, approximately 30 μg/dl to approximately 40 μg/dl, approximately 30 μg/dl to approximately 50 μg/dl, approximately 30 μg/dl to

approximately 60 μg/dl, approximately 40 μg/dl to approximately 50 μg/dl, or approximately 40 μg/dl to approximately 60 μg/dl prior to administration of ferric citrate or a pharmaceutical composition thereof.

[0080] In certain embodiments, a patient treated in accordance with the methods disclosed herein has a plasma erythropoietin level of more than 20 mU/ml (*e.g.*, more than or equal to 20 mU/ml, more than or equal to 25 mU/ml, more than or equal to 30 mU/ml, more than or equal to 40 mU/ml, more than or equal to 50 mU/ml, or more than or equal to 60 mU/ml) prior to administration of ferric citrate or a pharmaceutical composition thereof. In some embodiments, a patient treated in accordance with the methods disclosed herein has a plasma erythropoietin level of approximately 20 mU/ml, 25 mU/ml, 30 mU/ml, 35 mU/ml, 40 mU/ml, 45 mU/ml, 50 mU/ml, 55 mU/ml, or 60 mU/ml prior to administration of ferric citrate or a pharmaceutical composition thereof. In certain embodiments, a patient treated in accordance with the methods disclosed herein has a plasma erythropoietin level of approximately 20 mU/ml to approximately 30 mU/ml, approximately 20 mU/ml to approximately 40 mU/ml, approximately 20 mU/ml to approximately 50 mU/ml, approximately 20 mU/ml to approximately 60 mU/ml, approximately 30 mU/ml to approximately 40 mU/ml, approximately 30 mU/ml to approximately 50 mU/ml, approximately 30 mU/ml to approximately 60 mU/ml, approximately 40 mU/ml to approximately 50 mU/ml, approximately 40 mU/ml to approximately 60 mU/ml, or approximately 50 mU/ml to approximately 60 mU/ml prior to administration of ferric citrate or a pharmaceutical composition thereof.

[0081] In certain embodiments, a patient treated in accordance with the methods disclosed herein has a FEP of more than 50 μg/dl (*e.g.*, more than or equal to 50 μg/dl, more than or equal to 60 μg/dl, more than or equal to 70 μg/dl, more than or equal to 80 μg/dl, more than or equal to 90 μg/dl, or more than or equal to 100 μg/dl) prior to administration of ferric citrate or a pharmaceutical composition thereof. In some embodiments, a patient treated in accordance with the methods disclosed herein has a FEP level of approximately50 μg/dl, 60 μg/dl, 70 μg/dl, 80 μg/dl, 90 μg/dl, or 100 μg/dl prior to administration of ferric citrate or a pharmaceutical composition thereof. In certain embodiments, a patient treated in accordance with the methods disclosed herein has a FEP level of approximately 50 μg/dl to approximately 60 μg/dl, approximately 50 μg/dl to approximately 70 μg/dl, approximately 50 μg/dl to approximately 80 μg/dl, approximately 50 μg/dl to approximately 90 μg/dl, approximately 50 μg/dl to

approximately 100 μg/dl, approximately 60 μg/dl to approximately 70 μg/dl, approximately 60 μg/dl to approximately 80 μg/dl, approximately 60 μg/dl to approximately 90 μg/dl, approximately 60 μg/dl to approximately 100 μg/dl, approximately 70 μg/dl to approximately 80 μg/dl, approximately 70 μg/dl to approximately 90 μg/dl, approximately 70 μg/dl to approximately 100 μg/dl, approximately 80 μg/dl to approximately 90 μg/dl, approximately 80 μg/dl to approximately 100 μg/dl, or approximately 90 μg/dl to approximately 100 μg/dl prior to administration of ferric citrate or a pharmaceutical composition thereof.

[0082] In some embodiments, a patient treated in accordance with the methods disclosed herein has one, two, three or more, or all of the following prior to administration of ferric citrate or a pharmaceutical composition: (i) a hemoglobin concentration of less than or equal to approximately 12.5 grams/dl, 12 grams/dl or 11.5 grams/dl; (ii) a TSAT value of less than 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 12%, or 10%; (iii) a serum ferritin level of less than 300 ng/ml (*e.g.*, less than or equal to 275 ng/ml, less than or equal to 250 ng/ml, less than or equal to 225 ng/ml, less than or equal to 200 ng/ml, less than or equal to 175 ng/ml, less than or equal to 150 ng/ml, less than or equal to 125 ng/ml, less than or equal to 100 ng/ml, less than or equal to 75 ng/ml, less than or equal to 50 ng/ml, less than or equal to 25 ng/ml, less than or equal to 15 ng/ml, less than or equal to 10 ng/ml, or less than or equal to 5 ng/ml); (iv) serum iron level of less than 60 μg/dl (*e.g.*, less than or equal to 50 μg/dl, less than or equal to 40 μg/dl, less than or equal to 30 μg/dl, less than or equal to 20 μg/dl, or less than or equal to 10 μg/dl); (v) tissue iron level (*e.g.*, stainable tissue iron level) of grade 2, grade 1, or grade 0; (vi) hematocrit level of less than 45%, 40%, 35%, 30%, 25%, 20%, 15%, or 10%; (vii) TIBC value of more than 390 μg/dl (*e.g.*, more than or equal to 390 μg/dl, more than or equal to 400 μg/dl, more than or equal to 450 μg/dl, more than or equal to 450 μg/dl, more than or equal to 500 μg/dl, more than or equal to 550 μg/dl, more than or equal to 600 μg/dl, more than or equal to 650 μg/dl, more than or equal to 700 μg/dl, more than or equal to 800 μg/dl, more than or equal to 900 μg/dl, more than or equal to 1000 μg/dl, more than or equal to 1100 μg/dl, or more than or equal to 1200 μg/dl); (viii) plasma erythropoietin level of more than 20 mU/ml (*e.g.*, more than or equal to 20 mU/ml, more than or equal to 25 mU/ml, more than or equal to 30 mU/ml, more than or equal to 40 mU/ml, more than or equal to 50 mU/ml, or more than or equal to 60 mU/ml); and/or (ix) FEP of more than 50 μg/dl (*e.g.*, more than or equal to 50 μg/dl, more than or equal to 60 μg/dl, more than or equal to 70 μg/dl, more than or equal to 80 μg/dl, more than or equal to 90 μg/dl, or more

than or equal to 100 μg/dl). In certain embodiments wherein the patient treated in accordance with the methods disclosed herein is a female, the patient has a TSAT value of less than 45% , 40%, 35%, 30%, 25%, 20%, 15%, or 12% prior to administration of ferric citrate or a pharmaceutical composition thereof. In certain embodiments wherein the patient treated in accordance with the methods disclosed herein is a male, the patient has a TSAT value of less than 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, or 10% prior to administration of ferric citrate or a pharmaceutical composition thereof.

[0083] In certain embodiments, a patient treated in accordance with the methods disclosed herein has one, two, three or more, or all of the following prior to administration of ferric citrate or a pharmaceutical composition: (i) a hemoglobin concentration of approximately 6 grams/dl to approximately 8 grams/dl, approximately 6 grams/dl to approximately 10 grams/dl, approximately 6 grams/dl to approximately 12 grams/dl, approximately 7 grams/dl to approximately 9 grams/dl, approximately 7 grams/dl to approximately 11 grams/dl, approximately 7 grams/dl to approximately 13 grams/dl, approximately 8 grams/dl to approximately 10 grams/dl, approximately 8 grams/dl to approximately 12 grams/dl, approximately 9 grams/dl to approximately 11 grams/dl, approximately 9 grams/dl to approximately 12 grams/dl, approximately 9 grams/dl to approximately 13 grams/dl, approximately 10 grams/dl to approximately 11 grams/dl, approximately 10 grams/dl to approximately 12 grams/dl, approximately 10 grams/dl to approximately 13 grams/dl, approximately 11 grams/dl to approximately 12 grams/dl, approximately 11 grams/dl to approximately 13 grams/dl, or approximately 12 grams/dl to approximately 13 grams/dl; (ii) TSAT value of 10% to 45%, 12% to 45%, 20% to 45%, 20% to 40%, 10% to 35%, 20% to 25%, 15% to 50%, or 10% to 30%; (iii) a serum ferritin level of approximately 5 ng/ml to approximately 15 ng/ml, approximately 5 ng/ml to approximately 25 ng/ml, approximately 5 ng/ml to approximately 50 ng/ml, approximately 15 ng/ml to approximately 25 ng/ml, approximately 15 ng/ml to approximately 50 ng/ml, approximately 15 ng/ml to approximately 75 ng/ml, approximately 25 ng/ml to approximately 50 ng/ml, approximately 25 ng/ml to approximately 75 ng/ml, approximately 25 ng/ml to approximately 100 ng/ml, approximately 50 ng/ml to approximately 75 ng/ml, approximately 50 ng/ml to approximately 100 ng/ml, approximately 50 ng/ml to approximately 150 ng/ml, approximately 75 ng/ml to approximately 100 ng/ml, approximately 75 ng/ml to approximately 150 ng/ml, approximately 100 ng/ml to

approximately 150 ng/ml, approximately 150 ng/ml to approximately 200 ng/ml, approximately 150 ng/ml to approximately 250 ng/ml, approximately 100 ng/ml to approximately 300 ng/ml, approximately 200 ng/ml to approximately 300 ng/ml, or approximately 250 ng/ml to approximately 300 ng/ml; (iv) serum iron level of approximately 10 μg/dl to approximately 20 μg/dl, approximately 10 μg/dl to approximately 30 μg/dl, approximately 10 μg/dl to approximately 40 μg/dl, approximately 10 μg/dl to approximately 50 μg/dl, approximately 10 μg/dl to approximately 60 μg/dl, approximately 20 μg/dl to approximately 30 μg/dl, approximately 20 μg/dl to approximately 40 μg/dl, approximately 20 μg/dl to approximately 50 μg/dl, approximately 20 μg/dl to approximately 60 μg/dl, approximately 30 μg/dl to approximately 40 μg/dl, approximately 30 μg/dl to approximately 50 μg/dl, approximately 30 μg/dl to approximately 60 μg/dl, approximately 40 μg/dl to approximately 50 μg/dl, or approximately 40 μg/dl to approximately 60 μg/dl; (v) tissue iron level (*e.g.*, stainable tissue iron level) of grade 2, grade 1, or grade 0; (vi) hematocrit level of 10% to 15%, 10% to 20%, 10% to 25%, 10% to 30%, 10% to 35%, 10% to 40%, 10% to 45%, 15% to 20%, 15% to 25%, 15% to 30%, 15% to 35%, 15% to 40%, 15% to 45%, 20% to 25%, 20% to 30%, 20% to 35%, 20% to 40%, 25% to 45%, 25% to 30%, 25% to 35%, 25% to 40%, 25% to 45%, 30% to 35%, 30% to 40%, 30% to 45%, 35% to 40%, 35% to 45%, or 40% to 45%; (vii) TIBC value of approximately approximately 390 μg/dl to approximately 600 μg/dl, approximately 390 μg/dl to approximately 800 μg/dl, approximately 390 μg/dl to approximately 1000 μg/dl, approximately 390 μg/dl to approximately 1200 μg/dl, approximately 500 μg/dl to approximately 700 μg/dl, approximately 500 μg/dl to approximately 900 μg/dl, approximately 500 μg/dl to approximately 1100 μg/dl, approximately 600 μg/dl to approximately 800 μg/dl, approximately 600 μg/dl to approximately 1000 μg/dl, approximately 600 μg/dl to approximately 1200 μg/dl, approximately 700 μg/dl to approximately 900 μg/dl, approximately 700 μg/dl to approximately 1100 μg/dl, approximately 800 μg/dl to approximately 1000 μg/dl, approximately 800 μg/dl to approximately 1200 μg/dl, approximately 900 μg/dl to approximately 1100 μg/dl, or approximately 1000 μg/dl to approximately 1200 μg/dl; (viii) plasma erythropoietin level of approximately 20 mU/ml to approximately 30 mU/ml, approximately 20 mU/ml to approximately 40 mU/ml, approximately 20 mU/ml to approximately 50 mU/ml, approximately 20 mU/ml to approximately 60 mU/ml, approximately 30 mU/ml to approximately 40 mU/ml, approximately 30 mU/ml to approximately 50 mU/ml, approximately 30 mU/ml to approximately 60 mU/ml, approximately

40 mU/ml to approximately 50 mU/ml, approximately 40 mU/ml to approximately 60 mU/ml, or approximately 50 mU/ml to approximately 60 mU/ml; and/or (ix) FEP level of approximately 50 μg/dl to approximately 60 μg/dl, approximately 50 μg/dl to approximately 70 μg/dl, approximately 50 μg/dl to approximately 80 μg/dl, approximately 50 μg/dl to approximately 90 μg/dl, approximately 50 μg/dl to approximately 100 μg/dl, approximately 60 μg/dl to approximately 70 μg/dl, approximately 60 μg/dl to approximately 80 μg/dl, approximately 60 μg/dl to approximately 90 μg/dl, approximately 60 μg/dl to approximately 100 μg/dl, approximately 70 μg/dl to approximately 80 μg/dl, approximately 70 μg/dl to approximately 90 μg/dl, approximately 70 μg/dl to approximately 100 μg/dl, approximately 80 μg/dl to approximately 90 μg/dl, approximately 80 μg/dl to approximately 100 μg/dl, or approximately 90 μg/dl to approximately 100 μg/dl. In certain embodiments wherein the patient treated in accordance with the methods disclosed herein is a female, the patient has a TSAT value of 5% to 45%, 5% to 35%, 5% to 25%, 5% to 15%, 5% to 12%, 5% to 10%, 10% to 45%, 10% to 35%, 10% to 25%, 10% to 15%, 10% to 12%, 12% to 45%, 12% to 35%, 12% to 25%, 12% to 15%, 20% to 45%, 20% to 35%, 20% to 25%, 30% to 45%, 30% to 35%, or 40% to 45% prior to administration of ferric citrate or a pharmaceutical composition thereof. In certain embodiments wherein the patient treated in accordance with the methods disclosed herein is a male, the patient has a TSAT value of 5% to 50%, 5% to 40%, 5% to 30%, 5% to 20%, 5% to 15%, 5% to 10%, 10% to 50%, 10% to 40%, 10% to 30%, 10% to 20%, 10% to 15%, 15% to 50%, 15% to 40%, 15% to 30%, 15% to 25%, 15% to 20%, 20% to 50%, 20% to 40%, 20% to 30%, 20% to 25%, 30% to 50%, 30% to 40%, 30% to 35%, 40% to 50%, 40% to 45%, or 45% to 50% prior to administration of ferric citrate or a pharmaceutical composition thereof.

[0084] In certain embodiments, a patient treated in accordance with the methods disclosed herein has not taken a phosphate binder medication within 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months or more of administration of the first dose of ferric citrate or a pharmaceutical composition thereof. In certain embodiments, a patient treated in accordance with the methods disclosed herein has not experienced acute kidney injury within 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months or more of administration of the first dose of ferric citrate or a pharmaceutical composition thereof. In some embodiments, a patient treated in accordance with the methods disclosed herein has not been on dialysis or had a requirement for dialysis within 2

weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months or more of administration of the first dose of ferric citrate or a pharmaceutical composition thereof. In certain embodiments, a patient treated in accordance with the methods disclosed herein is not anticipated to require a kidney transplant or begin dialysis within 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months or more of the first dose of ferric citrate or a pharmaceutical composition thereof.

[0085] In certain embodiments, a patient treated in accordance with the methods disclosed herein is not and/or has not received intravenous iron within 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months or more of administration of the first dose of ferric citrate or a pharmaceutical composition thereof. In some embodiments, a patient treated in accordance with the methods disclosed herein is not and/or has not received an erythropoiesis-stimulating agent (ESA) within 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months or more of administration of the first dose of ferric citrate or a pharmaceutical composition thereof. In certain embodiments, a patient treated in accordance with the methods disclosed herein is not and/or has not received intravenous iron and an erythropoiesis-stimulating agent (ESA) within 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months or more of administration of the first dose of ferric citrate or a pharmaceutical composition thereof. In some embodiments, a patient treated in accordance with the methods disclosed herein is not receiving intravenous iron and/or an erythropoiesis-stimulating agent (ESA).

[0086] In certain embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed IDA associated with one, two or more of the following conditions: chronic blood loss; acute blood loss; childbirth; menstruation; menorrhagia; dialysis; chronic kidney Disease (CKD); dysfunctional uterine bleeding; heavy uterine bleeding; urinary tract bleeding; hemoglobinuria; chronic internal bleeding; gastrointestinal bleeding; angiodysplasia; idiopathic pulmonary haemosiderosis; blood loss from injury, surgery, acute trauma, or frequent blood drawing; bleeding ulcer; gastric ulcer; duodenal ulcer; intravascular hemolysis; chronic recurrent hemoptysis; colon polyp; gastrointestinal cancer (such as colonic cancer, gastric cancer, and intestinal cancer); gastrointestinal disorder (*e.g.*,

inflammatory bowel disease (IBD) and Crohn's disease); celiac disease; post surgical bowel resection; gut resection or bypass; Whipple's disease; chronic heart failure; systemic inflammation; parasitic infections (such as malaria and infections with hookworms, tapeworms, flukes, whipworms, roundworms, *T. trichiura*, or *H. Pylori*); and/or pregnancy. In some embodiments, a patient treated in accordance with the methods disclosed herein has IDA associated with the use of proton pump inhibitors; use of antacids; use of non-steroidal anti-inflammatory drugs (NSAIDs) (*e.g.*, aspirin, anticoagulants such as clopidogrel and warfarin); chronic ingestion of alcohol; chronic ingestion of salicylates; chronic ingestion of steroids; chronic ingestion of non-steroidial anti-inflammatory agents; chronic ingestion of erythropoiesis stimulating agents; insufficient dietary intake of iron and/or insufficient absorption of iron; deficient levels of hemoglobin; childhood development; psychomotor and cognitive development in children; and/or breath holding spells.

[0087] Insufficient dietary intake of iron, blood loss in women, and infectious diseases are also major causes of IDA. In certain embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with IDA associated with insufficient dietary intake of iron. In some embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with IDA associated with insufficient absorption of iron. In certain embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with IDA associated with insufficient dietary intake of iron and/or insufficient absorption of iron. In some embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with IDA associated with menstruation. In some embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with IDA associated with child birth. In some embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with IDA s associated with an infection with hookworms. In some embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with IDA associated with malaria.

[0088] In some embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with IDA associated with one, two or more of the following conditions: gastrointestinal bleeding; angiodysplasia; gastric ulcer; duodenal ulcer; colon polyp; gastrointestinal cancer (such as colonic cancer, gastric cancer, and intestinal

cancer); gastrointestinal disorder (*e.g.*, inflammatory bowel disease (IBD) and Crohn's disease); celiac disease; post surgical bowel resection; gut resection or bypass; and Whipple's disease. In specific embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with IDA associated with gastrointestinal cancer (such as colonic cancer, gastric cancer, and intestinal cancer).

[0089] In certain embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with a gastrointestinal condition. In some embodiments, a patient treated in accordance with the methods disclosed herein has and/or has been diagnosed with inflammatory bowel disease, inflammatory bowel syndrome, ulcerative colitis, Crohn's disease, microscopic colitis (such as collagenous or lymphocytic colitis), and/or chemically-induced colitis (*e.g.*, NSAID-induced colitis). In certain embodiments, a patient treated in accordance with the methods disclosed herein has gastrointestinal bleeding. In specific embodiments, a patient treated in accordance with the methods disclosed herein has gastrointestinal bleeding associated with a gastrointestinal condition, such as inflammatory bowel disease, inflammatory bowel syndrome, Crohn's disease, ulcerative colitis, microscopic colitis (such as collagenous or lymphocytic colitis), or chemically-induced colitis (*e.g.*, NSAID-induced colitis).

[0090] In certain embodiments, a patient treated in accordance with the methods disclosed herein has not received a blood transfusion within 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, or more of initiating administration of ferric citrate. In other embodiments, a patient treated in accordance with the methods disclosed herein has received a blood transfusion within 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, or more of initiating administration of ferric citrate.

[0091] In certain embodiments, a patient treated in accordance with the methods disclosed herein has not been diagnosed with a malignancy within 1 month, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 year or 6 years of initiating administration of ferric citrate. In other embodiments, a patient treated in accordance with the methods disclosed herein has been diagnosed with a malignancy. In some embodiments, a patient treated in accordance with the methods disclosed herein has not been diagnosed with hemochromatosis. In other embodiments, a patient treated in accordance with the methods disclosed herein has been diagnosed with hemochromatosis. In specific embodiments, a patient treated in accordance with the methods

disclosed herein has no known allergies to iron products and/or a previous intolerance to oral ferric citrate.

[0092] In specific embodiments, a patient treated in accordance with the methods disclosed herein fulfills one, two, three or more of the inclusion criteria in Section 5, *infra* and/or does not fulfill one, two, three or more of the exclusion criteria in Section 5, *infra*.

4.3. Dosing and Administration

[0093] In one aspect in accordance with the methods disclosed herein, the ferric citrate or a pharmaceutical composition thereof is administered to a subject as frequently as necessary and/or desired to treat the IDA. In some embodiments in accordance with the methods disclosed herein, the ferric citrate or a pharmaceutical composition thereof is administered to a subject once per day. In certain embodiments in accordance with the methods disclosed herein, the ferric citrate or a pharmaceutical composition thereof is administered to a subject twice per day. In some embodiments in accordance with the methods disclosed herein, the ferric citrate or a pharmaceutical composition thereof is administered to a subject three times per day. In specific embodiments in accordance with the methods disclosed herein, the ferric citrate or a pharmaceutical composition thereof is administered orally to a subject.

[0094] In various aspects, the daily dose of ferric citrate or a pharmaceutical composition thereof administered to a subject 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 is taken in the afternoon, and the final 2 grams is taken in the evening, for a total of 6 grams over the course of a day.

[0095] Pharmaceutical compositions, such as tablets and other oral dosage forms, disclosed herein can be made to accommodate a number of doses of ferric citrate. Pharmaceutical compositions comprising ferric citrate which may be administered to a subject are described in Section 4.5, *infra*. In certain embodiments, the weight of an individual tablet or other oral dosage form depends upon the final dosage to be produced; *e.g.*, 125 mg, 250 mg, 500 mg, 667 mg, 750 mg and 1,000 mg of ferric citrate per tablet. In a specific embodiment, the ferric citrate is provided in a tablet dosage form comprising approximately 1 gram of ferric citrate equivalent to approximately 210 mg of ferric iron. The number of tablets or other oral

dosage forms administered to a subject can be adjusted to conform to the desired amount of ferric citrate to be administered. For example, if a subject is directed to take 4 grams of ferric citrate daily in a single dose, the subject may take 4 tablets or other oral dosage forms, each comprising 1 gram of ferric citrate, or may take 8 tablets or other oral dosage forms, each comprising 500 mg of ferric citrate.

[0096] In some embodiments, a daily dose of ferric citrate administered to a subject in accordance with the methods disclosed herein is from 1 gram to 12 grams, at a dose of ferric iron ranging from 210 mg to 2, 520 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 a subject in accordance with the methods disclosed herein.

[0097] In some embodiments, the ferric citrate is administered to a subject in accordance with the methods disclosed herein 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 certain embodiments, the ferric citrate is administered to a subject in accordance with the methods disclosed herein 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 to a subject in accordance with the methods disclosed herein 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 certain embodiments, the ferric citrate is administered to a subject in accordance with the methods disclosed herein 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 to a subject in accordance with the methods disclosed herein 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 certain embodiments, the ferric citrate is administered to a subject in accordance with the methods disclosed herein 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 to a subject in accordance with the methods disclosed herein 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 certain embodiments, the ferric citrate is administered to a subject in accordance with the methods disclosed herein 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 to a subject in accordance with the methods disclosed herein 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 certain embodiments, the ferric citrate is administered to a subject in accordance with the methods disclosed herein 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 to a subject in accordance with the methods disclosed herein 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 to a subject in accordance with the methods disclosed herein 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. Tablets which may be administered to a subject are described in Section 4.5, *infra*. In a specific embodiment, the tablet is Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.).

[0098] In a specific aspect, each dose of ferric citrate administered to a subject in accordance with the methods is without food. In certain embodiments in accordance with the methods disclosed herein, each dose of ferric citrate is administered to a subject approximately 1 hour prior to the intake of food. In some embodiments in accordance with the methods disclosed herein, each dose of ferric citrate is administered to a subject approximately 2 hours prior to the intake of food. In certain embodiments in accordance with the methods disclosed herein, each dose of ferric citrate is administered to a subject approximately 3 hours prior to the intake of food. In some embodiments in accordance with the methods disclosed herein, each dose of ferric citrate is administered to a subject approximately 4 hours prior to the intake of food. In certain embodiments in accordance with the methods disclosed herein, each dose of ferric citrate is

administered to a subject approximately 1-2, 1-3, 1-4, 2-3, 2-4, or 3-4 hours prior to the intake of food. In accordance with these embodiments, the ferric citrate can be administered as a pharmaceutical composition, such as described in Section 4.5, *infra*.

[0099] In certain embodiments in accordance with the methods disclosed herein, each dose of ferric citrate is administered to a subject approximately 1 hour after the intake of food. In some embodiments in accordance with the methods disclosed herein, each dose of ferric citrate is administered to a subject approximately 2 hours after the intake of food. In certain embodiments in accordance with the methods disclosed herein, each dose of ferric citrate is administered to a subject approximately 3 hours after the intake of food. In some embodiments in accordance with the methods disclosed herein, each dose of ferric citrate is administered to a subject approximately 4 hours after the intake of food. In certain embodiments in accordance with the methods disclosed herein, each dose of ferric citrate is administered to a subject approximately 1-2, 1-3, 1-4, 2-3, 2-4, or 3-4 hours after the intake of food. In accordance with these embodiments, the ferric citrate can be administered as a pharmaceutical composition, such as described in Section 4.5, *infra*.

[00100] In some embodiments in accordance with the methods disclosed herein, no food is ingested by a subject within approximately 1 hour of the administration each dose of ferric citrate. In certain embodiments in accordance with the methods disclosed herein, no food is ingested by a subject within approximately 2 hours of the administration each dose of ferric citrate. In some embodiments in accordance with the methods disclosed herein, no food is ingested by a subject within approximately 3 hours of the administration each dose of ferric citrate. In certain embodiments in accordance with the methods disclosed herein, no food is ingested by a subject within approximately 4 hours of the administration each dose of ferric citrate. In some embodiments in accordance with the methods disclosed herein, no food is ingested by a subject within approximately 1-2, 1-3, 1-4, 2-3, 2-4, or 3-4 hours of the administration each dose of ferric citrate. In accordance with these embodiments, the ferric citrate can be administered as a pharmaceutical composition, such as described in Section 4.5, *infra*.

[00101] In one embodiment, the ferric citrate is administered to a subject at the dose(s) described in the Examples in Section 5, *infra*. In a specific embodiment, the ferric citrate is administered to a subject at the dose(s) and in the tablet form described in the Examples in

Section 5, *infra*. In another specific embodiment, the dose of ferric citrate administered to a subject in accordance with the methods disclosed herein is not sufficient to treat hyperphosphatemia.

[00102] The ferric citrate or a pharmaceutical composition thereof can be administered for any length of time, such as, *e.g.*, the length of time prescribed by a medical professional (*e.g.*, a doctor, nurse practitioner or physician assistant). In any of the methods described herein, ferric citrate or a pharmaceutically acceptable composition thereof can be administered to the patient for a long period of time, for example, up to and including 52 weeks, including up to and including 56 weeks. The ferric citrate may also be administered to the patient for a short period of time, for example, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 9 weeks, 10 weeks, or 12 weeks.

4.4. Combination Therapy

[00103] In certain embodiments, ferric citrate or a pharmaceutical composition thereof described herein may be administered or applied singly, or in combination with other agents. Ferric citrate or a pharmaceutical composition thereof described herein may also be administered or applied singly or in combination with other pharmaceutically active agents, including other agents known to improve one or more iron storage parameters (*e.g.*, increase serum ferritin level, increase transferrin saturation (TSAT), increase hemoglobin concentration, increase serum iron level, increase tissue iron level (*e.g.*, stainable tissue iron level), increase TIBC value, increase plasma erythropoietin level, increase FEP level), increase iron absorption, maintain iron stores, treat iron deficiency, or treat anemia. In specific embodiments, ferric citrate or a pharmaceutical composition thereof described herein is not administered in combination with other pharmaceutically active agents known to improve one or more iron storage parameters (*e.g.*, increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration, increase serum iron level, increase tissue iron level (*e.g.*, stainable tissue iron level), increase TIBC value, increase plasma erythropoietin level, increase FEP level), increase iron absorption, maintain iron stores, treat iron deficiency, or treat anemia. For example, in specific embodiments, ferric citrate or a pharmaceutical composition thereof described herein is not administered in combination with one, two or all of the following: erythropoesis-stimulating agent(s), intravenous iron and/or a blood transfusion.

[00104] As used herein, "in combination" in the context of the administration of agents or therapies refers to the use of more than one agent or therapy. The use of the term "in combination" does not restrict the order in which agents or therapies are administered to a patient with a disease. In certain embodiments, administration of one or more agents or therapies to a patient with a disease includes, without limitation, a first agent or therapy that can be administered prior to (*e.g.*, 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second agent or therapy to a patient which had, has, or is susceptible to a disease.

[00105] In certain embodiment, ferric citrate or a pharmaceutical composition thereof described herein is administered in combination with a pharmaceutically active agent known to treat a gastrointestinal condition, such as colitis or inflammatory bowel disease, or agents known to ameliorate one or more symptoms thereof. For example, in some embodiments, ferric citrate or a pharmaceutical composition thereof described herein is administered in combination with an anti-inflammatory drug (*e.g.*, aminosalicylate or corticosteroid), an immunosuppressent (*e.g.*, azathioprine (Azasan, Imuran), mercaptopurine, cyclosporine, infliximab (Remicade®), adalimumab (Humira®), golimumab (Simponi®), vedolizumab (Entyvio®)), antibiotics, anti-dirraheal agents and/or pain relievers. The ferric citrate and an additional agent(s) may be combined in any manner known in the art such as a unitary dosage form. Alternatively, the ferric citrate and an additional agent(s) may be administered to a subject in separate dosage forms intended for simultaneous or sequential administration to the subject. When administered sequentially, the combination may be administered in two or more administrations. In certain embodiments, the ferric citrate or a pharmaceutical composition thereof described herein and one or more additional agents are administered by different routes. In other embodiments, the ferric citrate or a pharmaceutical composition thereof described herein and one or more additional agents are administered by the same route.

4.5. Ferric Citrate

[00106] Disclosed herein are preparations of ferric citrate and pharmaceutical compositions comprising the ferric citrate for use in accordance with the methods described herein. 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).

[00107] In certain embodiments, the ferric citrate used as described herein is disclosed in U.S. Patent Nos. 7,767,851, 8,093,423, 8,299,298, 8,338,642, 8,754,258, 8,846,976, and/or 8,754,257, and/or International Patent Publication Nos. WO 2004/074444, WO 2007/022435, WO 2007/089571, WO 2007/089577 and/or WO 2011/011541. In some embodiments, the ferric citrate used as described herein has certain characteristics or features of the ferric citrate disclosed in U.S. Patent Nos. 7,767,851, 8,093,423, 8,299,298, 8,338,642, 8,754,258, 8,846,976, and/or 8,754,257, and/or International Patent Publication Nos. WO 2004/074444, WO 2007/022435, WO 2007/089571, WO 2007/089577 and/or WO 2011/011541.

[00108] In specific aspects, the ferric citrate used as described 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.

[00109] In some embodiments, the ferric citrate used as described herein has a BET active surface area exceeding 16 m^2/g. In certain embodiments, the ferric citrate used in accordance with the methods described herein has a BET active surface area exceeding 20 m^2/g. In some embodiments, the ferric citrate used as described herein has a BET active surface area exceeding

25 m^2/g. In certain embodiments, the ferric citrate used as described herein has a BET active surface area exceeding 30 m^2/g. In some embodiments, the ferric citrate used as described herein has a BET active surface area exceeding 35 m^2/g. In certain embodiments, the ferric citrate used as described herein has a BET active surface area exceeding 40 m^2/g. In some embodiments, the ferric citrate used as described herein has a BET active surface area exceeding 45 m^2/g. In certain embodiments, the ferric citrate used as described herein has a BET active surface area exceeding 50 m^2/g.

[00110] In some embodiments, the ferric citrate used as described herein have a BET active surface area ranging from 16.17 m^2/g to 19.85 m^2/g. In certain embodiments, the ferric citrate used as described herein has a BET active surface area selected from 16.17 m^2/g and 19.85 m^2/g. In some embodiments, the ferric citrate used as described herein has a BET active surface area exceeding 27 m^2/g. In some embodiments, the ferric citrate used as described 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 used as described 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 used as described 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 used as described 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. In some embodiments, the ferric citrate preparations used as described herein have a BET active surface area from 30 m^2/g to 40 m^2/g. In some embodiments, the ferric citrate preparations used as described herein have a BET active surface area from 20 m^2/g to 35 m^2/g.

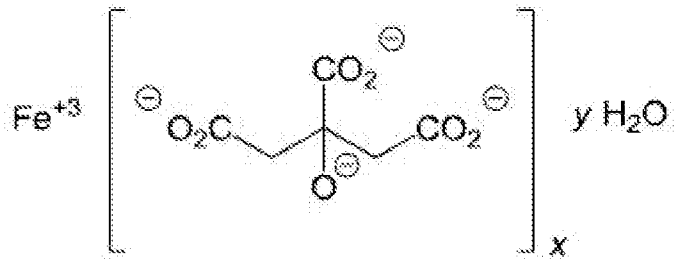
[00111] In certain embodiments, the ferric iron content of the ferric citrate is greater than or exceeds about 19% w/w. In some embodiments, the ferric iron content of the ferric citrate is 21.2% w/w, 22.1% w/w, or 22.4% w/w. In certain embodiments, the ferric iron content of the ferric citrate is between 19.5% w/w and 22.5%. In certain embodiments, the ferric iron content of the ferric citrate is between 21% w/w and 23% w/w. Techniques known to one of skill in the art can be used to determine the iron content of ferric citrate. In a specific embodiment, the ferric iron content is determined as follows: Pre-weighed ferric citrate is mixed with an appropriate amount of water and an appropriate amount of hydrochloric acid. The mixture is heated to boiling, and then cooled. Solid potassium iodide is added into the mixture, and the solution turns to dark-red and almost brown. A sample is removed from the solution and titrated with sodium thiosulfate until the sample turns to olive-green, when starch solution is added, and

the sample then turns to blue-black. Titration with sodium thiosulfate is continued until the blue-black color disappears. Iron content is then calculated using the weight of ferric citrate, the pre-determined titer of sodium thiosulfate, and the total volume of sodium thiosulfate added.

[00112] In a specific embodiment, the ferric citrate used as described herein is a complex comprising iron (III) and citric acid. In specific aspects, the complex of iron (III) and citric acid comprises water. In some embodiments, 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 certain embodiments, the molar ratio of iron (III) to citric acid is from 1: 0.75 to 1: 1.10. In some embodiments, the molar ratio of iron (III) to citric acid is from 1: 0.78 to 1: 0.95. In certain embodiments, the molar ratio of iron (III) to citric acid is from 1: 0.80 to 1: 0.92. In some embodiments, the molar ratio of iron (III) to citric acid is from 1: 0.81 to 1: 0.91. In certain embodiments, the molar ratio of iron (III) to citric acid is from 1: 0.75 to1: 1.15. In some embodiments, the molar ratio of iron (III) to citric acid is from 1: 0.80 to 1: 1.10.

[00113] In some embodiments, the molar ratio of iron (III) to water is from 1: 0.32 to 1: 0.42. In certain embodiments, 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 embodiments, the molar ratio of iron (III) to water is from 1: 1.8 to 1: 3.2. In certain embodiments, the molar ratio of iron (III) to water is from 1: 2.4 to 1: 3.1. In some embodiments, the molar ratio of iron (III) to water is from 1: 2.7 to 1: 3.1.

[00114] In a specific embodiment, the ferric citrate used as described herein is known chemically as iron (+3), *x* (1, 2, 3-propanetricarboxylic acid, 2-hydroxy-), *y* (H_2O)



x=0.70 – 0.87, y = 1.9 – 3.3

[00115] In specific embodiments, the ferric citrate used as described herein is tetraferric tricitrate decahydrate.

[00116] In specific embodiments, the ferric citrate used as described herein is substantially free of impurities, such as beta-iron hydroxide oxide. In particular embodiments, the ferric citrate used as described herein contains less than 6% of impurities, such as beta-iron hydroxide oxide, by weight based on the total weight of the ferric citrate. In some embodiments, the ferric citrate used as described herein contains less than 5% of impurities, such as beta-iron hydroxide oxide, by weight based on the total weight of the ferric citrate. In certain embodiments, the ferric citrate used as described herein contains less than 4% of impurities, such as beta-iron hydroxide oxide, by weight based on the total weight of the ferric citrate. In some embodiments, the ferric citrate used as described herein contains less than 3% of impurities, such as beta-iron hydroxide oxide, by weight based on the total weight of the ferric citrate.

[00117] In specific aspects, the ferric citrate used as described herein is more soluble compared to commercially available or chemical grade forms of ferric citrate. In specific embodiments, in dissolution testing, the percentage of ferric citrate 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. 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.

[00118] In some embodiments, 80% or more of the ferric citrate used as described herein is dissolved within 15 minutes in dissolution testing conducted in USP <711> vessels using Apparatus II. In certain embodiments, 85% or more of the ferric citrate used as described herein is dissolved within 15 minutes in dissolution testing conducted in USP <711> vessels using Apparatus II. In some embodiments, 90% or more of the ferric citrate used as described herein is dissolved within 15 minutes in dissolution testing conducted in USP <711> vessels using Apparatus II. In certain embodiments, 91% or more of the ferric citrate used as described herein is dissolved within 15 minutes in dissolution testing conducted in USP <711> vessels using Apparatus II. In some embodiments, 95% or more of the ferric citrate used as described herein is dissolved within 15 minutes in dissolution testing conducted in USP <711> vessels using Apparatus II. In certain embodiments, 96% or more of the ferric citrate used as described herein is dissolved within 15 minutes in dissolution testing conducted in USP <711> vessels using Apparatus II. In some embodiments, 97% or more of the ferric citrate used as described herein is

dissolved within 15 minutes in dissolution testing conducted in USP <711> vessels using Apparatus II. In certain embodiments, 100% of the ferric citrate used as described herein is dissolved within 15 minutes in dissolution testing conducted in USP <711> vessels using Apparatus II.

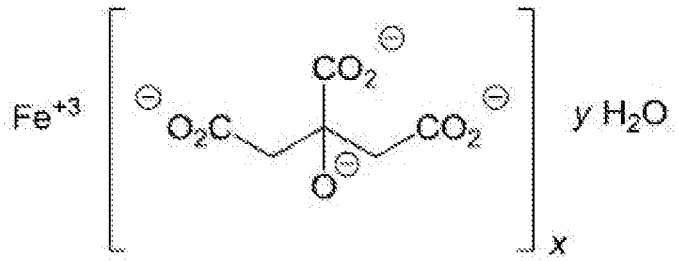
[00119] Without being bound by any theory, the increase in solubility of the ferric citrate is believed to be a result of the unique, significantly large active surface area of the ferric citrate. The intrinsic dissolution rate is defined as the dissolution rate of pure substances under the condition 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.

[00120] In some embodiments, the ferric citrate used as described herein has an intrinsic dissolution rate of between 1.88 mg/cm^2/min to 4 mg/cm^2/min. In certain embodiments, the ferric citrate used as described herein has an intrinsic dissolution rate of greater than 2.28 mg/cm^2/min. In some embodiments, the ferric citrate used as described herein has an intrinsic dissolution rate exceeding 2.28 mg/cm^2/min. In certain embodiments, the ferric citrate used as described herein has an intrinsic dissolution rate of 2.99 mg/cm^2/min. In some embodiments, the ferric citrate used as described herein has an intrinsic dissolution rate ranging from 2.28 mg/cm^2/min to 2.99 mg/cm^2/min. In certain embodiments, the ferric citrate used as described herein has an intrinsic dissolution rate selected from 2.28 mg/cm^2/min and 2.99 mg/cm^2/min. In specific embodiments, the commercial grade preparations of ferric citrate have an intrinsic dissolution rate that is substantially lower than the ferric citrate described herein.

[00121] Exemplary methods of manufacture of preparations of the ferric citrate are disclosed in U.S. Patent Nos. 7,767,851, 8,093,423, 8,299,298, 8,338,642, 8,754,258, 8,846,976, and 8,754,257, U.S. Publication No. 2012/0238622 and International Publication Nos. WO 2004/074444, WO 2007/022435, WO 2007/089571, WO 2007/089577 and WO 2011/011541.

4.5.1. Pharmaceutical Composition of Ferric Citrate

[00122] In a specific embodiment, the ferric citrate is contained in a pharmaceutical composition. In one embodiment, a pharmaceutical composition comprises ferric citrate and a pharmaceutically acceptable excipient or carrier. In a particular embodiment, a pharmaceutical composition comprises ferric citrate and a binder. In some embodiments, the pharmaceutical compositions further comprise a lubricant and/or a disintegrant (which, in certain embodiments, can be the same as the binder). In a specific embodiment, the pharmaceutical compositions include ferric citrate as the active ingredient. In some embodiments, the pharmaceutical compositions are oral tablet dosage forms. In certain embodiments, the pharmaceutical compositions are oral formulations other than tablets, such as capsules, suspensions, syrups, or sachets. In specific embodiment, the ferric citrate used in the pharmaceutical compositions is one or more forms of the ferric citrate described in Section 4.5, *infra*. In a specific embodiment, the ferric citrate used in a pharmaceutical composition described herein is known chemically as iron (+3), *x* (1, 2, 3-propanetricarboxylic acid, 2-hydroxy-), *y* (H_2O)



x=0.70 – 0.87, y = 1.9 – 3.3

In specific embodiments, the ferric citrate used in a pharmaceutical composition described herein is tetraferric tricitrate decahydrate.

[00123] The pharmaceutical compositions described herein may be utilized in the methods described herein.

[00124] In some embodiments, the pharmaceutical compositions and oral tablet dosage forms provided by this disclosure are disclosed in International Publication No. WO 2011/011541 and U.S. Publication No. 2012/0115945.

[00125] In a specific aspect, the pharmaceutical compositions are tablets or other oral formulations that include ferric citrate and a binder. In some embodiments, the tablets or other oral formulations can include ferric citrate, a binder, a lubricant and a disintegrant. In a specific

embodiment, a single tablet comprises 1 gram of ferric citrate having a 210 mg dose of ferric iron.

[00126] In some embodiments, the tablets or other oral formulations are characterized as highly drug loaded with the ferric citrate present in the tablets 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% or approximately 95% 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 or other oral formulations. In some embodiments, the tablets or other oral formulations are characterized as highly drug loaded with the ferric citrate present in the tablets at values of approximately 75% to approximately 92%, approximately 80% to approximately 92%, approximately 85% to approximately 92%, approximately 80% to approximately 90%, approximately 85% to approximately 90%, approximately 90% to approximately 92%, approximately 80% to approximately 95%, approximately 85% to approximately 95%, or approximately 90% to approximately 95%. The characteristics of the tablets produced at these highly loaded weight percentages may be 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 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.

[00127] In various embodiments, the tablets or other oral formulations comprise ferric and one or more components selected from among one or more binders, one or more lubricants, and one or more disintegrants. In certain embodiments, the tablets or other oral formulations comprise ferric citrate and one or more binders. In some embodiments, the tablets or other oral formulations comprise ferric citrate, one or more binders, and one or more lubricants. In certain embodiments, the tablets or other oral formulations comprise ferric citrate, one or more binders, one or more lubricants, and one or more disintegrants.

[00128] Any binder known to one skilled in the art may be used in the tablets or other oral formulations described herein. In certain embodiments, the binder is 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, or methyl cellulose. In some embodiments, the tablet or other oral formulation comprises a combination of two or more of the following binders: comprises 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, or methyl cellulose. The maltodextrin, PVP/VA, and methyl cellulose function as immediate release binders when used in the ferric citrate tablets or other oral formulations. In a specific embodiment, the binder used in a tablet or other oral formulation comprises partially or fully pregelatinized starch.

[00129] 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.

[00130] In various aspects, the tablets or other oral formulations can include a lubricant. Any lubricant known to one skilled in the art can be used in the tablets or other oral formulations. In certain embodiments, the lubricant used in the ferric citrate tablets or other oral formulations is magnesium stearate, calcium stearate, sodium stearyl fumarate. In some embodiments, the ferric citrate tablets comprise a combination of two or more of the following: magnesium stearate, calcium stearate, sodium stearyl fumarate. Other suitable lubricants that can be used in the ferric citrate tablets or other oral formulations include one or more of polyethylene glycol (molecular weight above 3350), sodium lauryl sulfate, talc, mineral oil, leucine, and poloxamer. In a specific embodiment, the lubricant used in the ferric citrate tablets or other oral formulations is calcium stearate.

[00131] In various aspects, the tablets or other oral formulations can include a disintegrant. 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.

[00132] The binder can be present in the tablets or other oral formulations in an amount ranging from approximately 4.5% by weight to approximately 30% by weight. In certain embodiments, the binder is present in the tablets or other oral formulations in an amount ranging from approximately 5% by weight to approximately 15% by weight. In some embodiments, the binder is present in the tablets or other oral formulations in an amount ranging from approximately 10% by weight to approximately 15% by weight. The disintegrant can be present in the tablets or other oral formulations 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 or other oral formulations can be as low as 0.25% in some conditions.

[00133] The lubricant can be present in the tablets or other oral formulations in an amount ranging from approximately 0.5% by weight to approximately 3% by weight. In certain embodiments, the lubricant is present in the tablets or other oral formulations in an amount ranging from approximately 0.5% by weight to 2% by weight. In some embodiments, the lubricant is present in the tablets or other oral formulations in an amount ranging from approximately 0.5% by weight to approximately 1% by weight. It should be understood that some components, such as microcrystalline cellulose, can function with both disintegrant and binder properties.

[00134] The weight of individual tablets or other oral formulations can depend upon the final dosage to be produced; *e.g.*, 125 mg, 250 mg, 500 mg, 667 mg, 750 mg and 1,000 mg of ferric citrate. In some embodiments, the tablets comprise 1 gram of ferric citrate and therefore a dose of 210 mg of ferric iron.

[00135] In various embodiments, the ferric citrate tablets or other oral formulations are coated to a weight gain of approximately 2% to 5%. In a specific embodiment, the ferric citrate tablets are coated using an Opadry suspension or equivalent in a perforated pan coater.

[00136] In a specific aspect, the tablets and/or oral iron supplements have reduced water content. In one embodiment, the water content of the tablet, as measured by loss on drying (LOD) percentage, 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%.

[00137] In certain embodiments, the water content of the tablet, as measured by LOD %, is between 10% and 15%. In some embodiments, the water content of the tablet, as measured by LOD %, is between 5% and 10%. In certain embodiments, the water content of the tablet, as measured by LOD %, is between 5% and 14%. In some embodiments, the water content of the tablet, as measured by LOD %, is between 5% and 12%. In certain embodiments, the water content of the tablet, as measured by LOD %, is between 10% and 14%. In some embodiments, the water content of the tablet, as measured by LOD %, is between 2% and 14%. In certain embodiments, the water content of the tablet, as measured by LOD %, is between 2% and 10%. In some embodiments, the water content of the tablet, as measured by LOD %, is between 2% and 12%. In certain embodiments, the water content of the tablet, as measured by LOD %, is between 8% and 10%. In certain embodiments, the water content of the tablet, as measured by LOD %, is between 6% and 9%. In certain embodiments, the water content of the tablet, as measured by LOD %, is between 7% and 9%.

[00138] 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. Technologies known to one of skill in the art can be used to measure LOD. In a specific embodiment, LOD % of the tablet is measured by Mettler-Toledo's model HB-43-S Moisture Balance using the "Standard" drying program, with temperature set at 105°C, endpoint set at mean weight loss of less than 1 mg in 50 seconds, and using samples of 0.9-1.1 gram.

[00139] In some embodiments, the tablets or other oral formulations 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 a specific embodiment, the tablets or other oral formulations comprise 1 gram (1000 mg) of ferric citrate. In specific embodiments, the tablets or oral formulations comprise 1 gram of ferric citrate containing approximately 210 mg of ferric iron.

[00140] In certain embodiments, the tablets or other oral formulations comprise 1.1 grams of ferric citrate. In some embodiments, the tablets or other oral formulations comprise 1.2 grams of ferric citrate. In certain embodiments, the tablets or other oral formulations comprise 1.3 grams of ferric citrate. In some embodiments, the tablets or other oral formulations comprise 1.5 grams of ferric citrate. In certain embodiments, the tablets or other oral formulations comprise 1.6 grams of ferric citrate. In some embodiments, the tablets or other oral formulations 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 specific embodiments, the tablets or other oral formulations comprise approximately 1 g of ferric citrate. In certain embodiments, the tablets or other oral formulations comprise approximately 1000 mg to 1050 mg, 975 mg to 1050 mg, or 950 mg to 1050 mg of ferric citrate.

[00141] In some embodiments, the tablets or other oral formulations 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 certain embodiments, the tablets or other oral formulations comprise between approximately 80 wt% and approximately 92 wt% ferric citrate; between approximately 5 wt% and approximately 15 wt% binder; and between approximately 0.5 wt% and approximately 2 wt% lubricant. In some embodiments, the tablets or other oral formulations comprise between approximately 85 wt% and approximately 92 wt% ferric citrate; between approximately 5 wt% and approximately 15 wt% binder; and between approximately 0.5 wt% and approximately 1 wt% lubricant. In certain embodiments, the lubricant is selected from one or more of magnesium stearate, calcium stearate, and sodium stearyl fumarate. In a specific embodiment, the lubricant is calcium stearate. In specific embodiments, the binder is pregelatinized starch and the lubricant is calcium stearate.

[00142] In some embodiments, the tablets or other oral formulations 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 certain embodiments, the mean surface area to mass ratio of the tablets or other oral formulations is equal to or greater than 5 m^2 per gram. In some embodiments, the mean surface area to mass ratio of the tablets or other oral formulations is equal to or greater than 10 m^2 per gram. In certain embodiments, the tablets or other oral formulations comprise 70% to 92% by weight of ferric citrate. In some embodiments, the tablets or other oral formulations comprise 80% to 92% by weight of ferric citrate. In certain embodiments, the tablets or other oral formulations comprise 90% to 93% by weight of ferric citrate. In some embodiments, the LOD % water of the tablets or other oral formulations is less than 15% but greater than 2%, 3%, 4% or 5% of water w/w. In some embodiments, the LOD % water of the tablets or other oral formulations is less than 10% but greater than 2%, 3%, 4%, or 5% of water w/w. In some embodiments, the tablets or other oral formulations further comprise a lubricant selected from one or more of magnesium stearate, calcium stearate, and sodium stearyl fumarate. In some embodiments, the tablets or other oral formulations comprise between 0.5% and 3% lubricant. In specific embodiments, the binder comprises pregelatinized starch and the lubricant is calcium stearate. In some embodiments, at least 80% of the ferric citrate in the tablets or other oral formulations is dissolved in a time less than or equal to 60 minutes as measured by test method USP <711>. In certain embodiments, at least 80% of the ferric citrate in the tablets or other oral formulations is

dissolved in a time less than or equal to 45 minutes as measured by test method USP <711>. In some embodiments, the tablets or oral formulations comprise approximately 1000 mg of ferric citrate.

[00143] In certain embodiments, the tablets or other oral formulations comprise between approximately 80 wt% and approximately 92 wt% ferric citrate and between approximately 5 wt% and approximately 15 wt% 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 between 5% to 14%. In some embodiments, the tablets or other oral formulations comprise between approximately 85 wt% and approximately 92 wt% ferric citrate and between approximately 5 wt% and approximately 15 wt% 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 between 5% to 14%. In some embodiments, the mean surface area to mass ratio of the tablets or other oral formulations 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 a or other oral formulations is equal to or greater than 10 m^2 per gram. In some embodiments, the tablets or other oral formulations comprise between approximately 0.5% and approximately 3% lubricant. In certain embodiments, the tablets or other oral formulations comprise between approximately 0.5% and approximately 2% lubricant. In specific embodiments, the binder comprises pregelatinized starch. In another specific embodiment, the lubricant comprises calcium stearate. In some embodiments, at least 80% of the ferric citrate in the tablets or other oral formulations is dissolved in a time less than or equal to 60 minutes as measured by test method USP <711>. In certain embodiments, at least 80% of the ferric citrate in the tablets or other oral formulations is dissolved in a time less than or equal to 45 minutes as measured by test method USP <711>. In some embodiments, the tablets or other oral formulations comprise approximately 1000 mg of ferric citrate. In a specific embodiment, the tablet or other oral formulation comprises a coating.

[00144] In certain embodiments, the tablets or other oral formulations comprise between approximately 80 wt% and approximately 92 wt% ferric citrate; between approximately 5 wt% and approximately 15 wt% binder; and between approximately 0.5 wt% and approximately 2 wt% lubricant, wherein at least 80% of the ferric citrate in the tablets or other oral formulations is dissolved in a time less than or equal to 45 minutes, or less than or equal to 60 minutes as measured by test method USP <711>. In some embodiments, the tablets or other oral

formulations comprise between approximately 85 wt% and approximately 92 wt% ferric citrate; between approximately 5 wt% and approximately 15 wt% binder; and between approximately 0.5 wt% and approximately 1 wt% lubricant, wherein at least 80% of the ferric citrate in the tablets or other oral formulations is dissolved in a time less than or equal to 45 minutes, or less than or equal to 60 minutes as measured by test method USP <711>. In a specific embodiment, the binder is pregelantinized starch and the lubricant is calcium stearate. In another specific embodiment, the tablet or other oral formulation comprises a coating.

[00145] In certain embodiments, the tablets or other oral formulations comprise between approximately 80 wt% and approximately 92 wt% ferric citrate and between approximately 5 wt% and approximately 15 wt% 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 between 5% to 10%. In some embodiments, the tablets or other oral formulations comprise between approximately 85 wt% and approximately 92 wt% ferric citrate and between approximately 5 wt% and approximately 15 wt% 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 between 5% to 10%. In some embodiments, the mean surface area to mass ratio of the tablets or other oral formulations 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 a or other oral formulations is equal to or greater than 10 m^2 per gram. In some embodiments, the tablets or other oral formulations comprise between approximately 0.5% and approximately 3% lubricant. In certain embodiments, the tablets or other oral formulations comprise between approximately 0.5% and approximately 2% lubricant. In specific embodiments, the binder comprises pregelatinized starch. In another specific embodiment, the lubricant comprises calcium stearate. In some embodiments, at least 80% of the ferric citrate in the tablets or other oral formulations is dissolved in a time less than or equal to 60 minutes as measured by test method USP <711>. In certain embodiments, at least 80% of the ferric citrate in the tablets or other oral formulations is dissolved in a time less than or equal to 45 minutes as measured by test method USP <711>. In some embodiments, the tablets or other oral formulations comprise approximately 1000 mg of ferric citrate. In a specific embodiment, the tablet or other oral formulation comprises a coating.

[00146] Table 1 provides a formulation for a ferric citrate tablet according to one embodiment of the present disclosure:

Table 1.

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

[00147] Table 2 provides a formulation for a ferric citrate tablet according to one embodiment of the present disclosure:

Table 2.

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

[00148] Table 3 provides a formulation for a ferric citrate tablet according to one embodiment of the present disclosure:

Table 3.

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

[00149] Table 4 provides a formulation for a ferric citrate oral formulation according to one embodiment of the present disclosure:

Table 4.

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.

[00150] Table 5 provides a formulation for a ferric citrate oral formulation according to one embodiment of the present disclosure:

Table 5.

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.

[00151] In a specific embodiment, the ferric citrate tablet is the ferric citrate tablet referred to as JTT-751 (Japan Tobacco Inc. and Torii Pharmaceutical Co., Ltd.). In another specific embodiment, the ferric citrate tablet is the Auryxia™ tablet sold by Keryx Biopharmaceuticals, Inc.

4.6. Methods of Assessing Iron Storage Parameters

[00152] As stated above, iron storage parameters may be measured to determine whether an IDA patient has sufficient iron stores to maintain adequate health. These iron storage parameters are useful in assessing whether an IDA patient can be suitably treated with ferric citrate and the efficacy of ferric citrate treatment so as to guide health care professionals in determining and/or adjusting a dosage regimen for the patient. To assess the one or more iron storage parameters, a blood sample may be drawn by needle from a vein in the arm and iron tests (*i.e.*, iron studies) as well as complete blood count tests may be performed to determine the amount of circulating iron in the blood, the capacity of the blood to transport iron, and the amount of stored iron in tissues. In some embodiments, the one or more iron storage parameters are selected from hematocrit, hemoglobin (Hb) concentration, total iron-binding capacity (TIBC), TSAT, serum iron levels, liver iron levels, spleen iron levels, and serum ferritin levels. In specific embodiments, the one or more iron storage parameters are hemoglobin concentration, TSAT, or serum ferritin levels.

5. EXAMPLES

[00153] The following examples in this Section (*i.e.*, Section 5) describe the use of ferric citrate to treat IDA. In particular, Example 1 demonstrates the use of ferric citrate to achieve a clinically significant increase in hemoglobin concentration in IDA patients in the absence of erythropoiseis-stimulating agents and intravenous iron. Surprising, a low dose of ferric citrate taken without food was well tolerated and resulted in a clinically significant increase in hemoglobin concentration in IDA patients.

[00154] The examples are offered by way of illustration, and not by way of limitation.

5.1. Example 1: A Phase 2 Pilot Study of KRX-0502 (Ferric Citrate Coordination Complex) in Treating IDA in Patients with Stage 3-5 Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD)

5.1.1. Protocol

[00155] The objective of the study was to evaluate the efficacy and safety of Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) in treating IDA in subjects with stage 3-5 non-dialysis dependent chronic kidney disease (NDD-CKD) as measured by changes in hemoglobin over an 8-week treatment period. The primary endpoint for the study was change in hemoglobin concentration from baseline (Day 0) to end of the 8-week treatment period (Week 8). Secondary endpoints for the study included the mean change from baseline to the highest hemoglobin value; percentage of subjects achieving hemoglobin change ≥1.0 g/dl at any visit during the study; and the percentage of patients achieving hemoglobin ≥12.0 g/dl hemoglobin at any visit during the study.

5.1.1.1. Overall Design

[00156] This was a Phase 2, single-arm, multicenter, open-label clinical trial.

[00157] Following a screening visit, eligible subjects were enrolled and received a fixed starting dose of Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) of 1 tablet/day without food. All subjects had to have a hemoglobin ≥9.0 g/dl and ≤11.5 g/dl at their screening visit to enter the 8-week treatment period.

[00158] After starting treatment at Day 0 with Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) at the starting dose of 1 tablet/day, hemoglobin was measured at every study visit. Subjects who had a hemoglobin increase <1.0 g/dl after the first 4 weeks compared

to baseline (Day 0), were titrated up to 2 tablets/day for the remainder of the trial. Subjects who had a hemoglobin increase >1.5 g/dl after the first 4 weeks, compared to baseline (Day 0) were to be titrated down to a dose of 1 tablet every other day for the remainder of the trial (one subject had a hemoglobin increase >1.5 g/dl after the first 4 weeks compared to baseline (Day 0), however the subject remained on a dose of 1 tablet/day for the remainder of the trial, due to a request by the Principle Investigator (PI) to deviate from the protocol). Otherwise, subjects remained on a dose of 1 tablet/day for the remainder of the trial (two subjects had a hemoglobin increase ≥1.0 g/dl and ≤1.5 g/dl after the first 4 weeks compared to baseline (Day 0); one of the two subjects remained on a dose of 1 table/day for the remainder of the trial, the other subject was titrated up to 2 tablets/day for the remainder of the trial).

[00159] The use of phosphate binders was not permitted at any time during the trial. The use of oral or IV iron and Erythropoiesis-Stimulating Agents (ESAs) and receipt of blood transfusions was not permitted at any time during the trial.

[00160] Blood samples for Complete Chemistry Profile (CCP), iron studies, and Complete Blood Count (CBC) were collected at screening; at Day 0; and at 1, 2, 4, 6 and 8 weeks after treatment began.

5.1.1.2. **Patient Population / Inclusion and Exclusion Criteria**

[00161] Human subjects were screened and 32 human subjects were enrolled in the study. Eligible subjects received a starting fixed dose of 1 tablet/day of Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) without food. Subjects who had a hemoglobin increase <1.0 g/dl after the first 4 weeks compared to baseline (Day 0), were titrated up to 2 tablets/day for the remainder of the trial. One subject who had a hemoglobin increase ≥1.0 g/dl and ≤1.5 g/dl after the first 4 weeks compared to baseline (Day 0) was also titrated up to 2 tablets/day for the remainder of the trial. The other subject who had a hemoglobin increase ≥1.0 g/dl and ≤1.5 g/dl after the first 4 weeks compared to baseline (Day 0) remained on a dose of 1 tablet/day for the remainder of the trial. One subject had a hemoglobin increase >1.5 g/dl after the first 4 weeks compared to baseline (Day 0), and remained on a dose of 1 tablet/day for the remainder of the trial, due to a request by the PI to deviate from the protocol.

[00162] Following a screening visit, eligible subjects enrolled in an 8-week treatment period. Enrollment into the study (Day 0) generally occurred within a week of the screening visit.

[00163] Inclusion Criteria

[00164] Subjects enrolled in the study met the following inclusion criteria:

[00165] 1. Males and non-lactating females with negative serum pregnancy test (for females of child-bearing potential) at screening visit

[00166] 2. Age > 18 years

[00167] 3. Serum ferritin <300 ng/ml and TSAT <25% at screening visit

[00168] 4. Hemoglobin ≥9.0 g/dl and ≤11.5 g/dl at screening visit

[00169] 5. eGFR <60 ml/min at screening visit using the 4-variable Modification of Diet in Renal Disease (MDRD) equation

[00170] Exclusion Criteria

[00171] Subjects who meet any of the following exclusion criteria were not enrolled into this study:

1. Subjects receiving phosphate binder medication(s) at, or within 4 weeks prior to, screening

2. Symptomatic gastrointestinal bleeding, inflammatory bowel disease, inflammatory bowel syndrome and/or Crohn's Disease within 24 weeks prior to screening visit

3. Evidence of acute kidney injury or requirement for dialysis within 8 weeks prior to screening visit

4. Kidney transplant anticipated or start of dialysis expected within 16 weeks of screening visit

5. Intravenous iron administered within 4 weeks prior to screening visit

6. Erythropoiesis-Stimulating Agent (ESA) administered within 4 weeks prior to screening visit

7. Blood transfusion within 4 weeks prior to screening visit

8. Receipt of any investigational drug within 4 weeks prior to screening visit

9. Cause of anemia other than iron deficiency or chronic kidney disease

10. History of malignancy in the last five years (treated cervical or skin cancer may be permitted if approved by Keryx)

11. History of hemochromatosis

12. Active drug or alcohol dependence or abuse (excluding tobacco use) within the 12 months prior to screening visit or evidence of such abuse

13. Subjects with any known allergies to iron products

14. Previous intolerance to oral ferric citrate

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

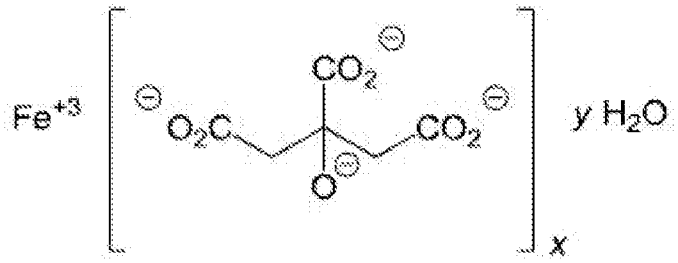
16. Planned surgery or hospitalization during the trial

17. Any other medical condition that, in the opinion of the PI, renders the subject unable to or unlikely to complete the trial or that would interfere with optimal participation in the trial or produce significant risk to the subject

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

5.1.1.3. **Drug Administration and Titration**

[00172] The active ingredient in Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) tablet is chemically known as iron (+3), *x* (1, 2, 3-propanetricarboxylic acid, 2-hydroxy-), *y* (H_2O)



x=0.70 – 0.87, y = 1.9 – 3.3

The Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) is a tablet contains 210 mg of ferric iron, equivalent to 1 gram of ferric citrate.

[00173] Subjects who had a hemoglobin increase of <1.0 g/dl after the first 4 weeks compared to Day 0 were titrated up to 2 tablets/day for the remainder of the study. One subject who had a hemoglobin increase ≥1.0 g/dl and ≤1.5 g/dl after the first 4 weeks compared to Day 0 was also titrated up to 2 tablets/day for the remainder of the trial. The other subject who had a hemoglobin increase ≥1.0 g/dl and ≤1.5 g/dl after the first 4 weeks compared to Day 0 remained

on a dose of 1 tablet/day for the remainder of the trial. One subject had a hemoglobin increase of >1.5 g/dl after the first 4 weeks compared to Day 0, and remained on a dose of 1 tablet/day for the remainder of the trial, due to a request by the Principle Investigator (PI) to deviate from the protocol.

[00174] The maximum number of Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) tablets per day permitted was 2, or 2 g/day. The Principal Investigator (PI) was permitted to reduce the dose of study drug due to an adverse event in consultation with Keryx Biopharmaceuticals, Inc.

[00175] Subjects took Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) orally without meals. Subjects were instructed not to take Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) if less than two hours had passed since the ingestion of their meals or snacks. Subjects were advised to try to take their daily dose at approximately the same time during each day. Daily water-soluble multivitamins (*i.e.*, Centrum, Nephrocaps, Renaphro, etc.) were allowed during the study. Subjects were advised to take multivitamins separately (at least two hours apart) from Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.). Subjects were encouraged to maintain a stable dose and type of multivitamin (if any) throughout the trial. Subjects were advised to take calcium supplements separately (at least two hours apart) from Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.).

5.1.1.4. **Study Drug Discontinuation**

[00176] Subjects were permitted to stop study drug for any of the following reasons:

[00177] 1. Intercurrent illness, medical event or hospitalization necessitating study drug discontinuation

[00178] 2. Investigator's discretion for the best interest of the subject

[00179] If study drug is discontinued due to an intercurrent illness or adverse event that resolves, the subject may be given the study drug again for the remainder of their trial participation.

5.1.1.4.1. **Early Termination**

[00180] Subjects were permitted to discontinue the trial for the following reasons:

1. Subject request

2. Lost to follow-up
3. Sponsor or investigator decision to terminate the trial at any time
4. Start of dialysis
5. Pregnancy
6. Kidney transplantation
7. Meeting the pre-specified early termination criteria (see below)
8. Safety
9. Death
10. Other

[00181] If a subject's Hgb is <9.0 or >13.0 g/dl for two consecutive study visits (at least 7 days apart) during the 8-week treatment period after Day 0, the subject was instructed to stop study drug and exit the trial.

[00182] If a subject early terminates from the trial for any reason, the subject should be encouraged to complete the final visit assessments.

5.1.1.4.2. **Adverse Events**

[00183] All adverse events were to be recorded. An adverse event (AE) was defined to be any reaction, side effect, or other undesirable event that occurs in conjunction with the use of a drug, biologic product or diagnostic agent in humans, whether or not the event is considered drug related. In this trial, this included any illness, sign, symptom or clinically significant laboratory test abnormality that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the drug(s) under study. Following the questioning and examination of the subject, all AEs were required to be noted. If known, the name of the underlying illness or disorder (*i.e.*, the diagnosis) was requested to be recorded, rather than its individual symptoms.

[00184] Subjects experiencing AEs that cause interruption or discontinuation of trial medication, or those experiencing adverse events that are present at the end of their participation in the trial should receive follow-up as appropriate (to resolution or stabilization).

[00185] Severity of an AE was defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the subject. The assessment of severity was made irrespective of drug relationship or seriousness of the event and should be evaluated according to the following scale:

1 = Mild (discomfort noticed, but no disruption of normal daily activity.)

2 = Moderate (discomfort sufficient to reduce or affect normal daily activity.)

3 = Severe (incapacitating, with inability to work or to perform normal daily activity.)

[00186] **Non-Serious Adverse Events**

[00187] Any adverse event that was not designated as serious, as defined below, was required to be recorded.

[00188] **Serious Adverse Events**

[00189] An event that was serious was required to be recorded and marked as "serious." An serious adverse event (SAE) was one that met any one of the following criteria:

Results in death

Is a Life-threatening experience,

Requires or prolongs inpatient hospitalization defined as >24-hour hospitalization

Causes persistent or significant disability/incapacity

Results in congenital anomaly

Is an important medical event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

[00190] Life-threatening experience: Any adverse event that places the subject, in the view of the investigator, at immediate risk of death from the adverse event as it occurred (*i.e.*, does not include an adverse event that had it occurred in a more severe form, might have caused death).

[00191] Persistent or significant disability/incapacity: Any adverse event that may result in a substantial disruption of a person's ability to conduct normal life functions.

[00192] Important medical event: Any adverse event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Adverse events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

[00193] A subject experiencing 1 or more SAEs was to receive treatment and follow-up evaluations by the investigator or was to be referred to another appropriate physician for

treatment and follow-up. SAEs were to be monitored from the time of consent and for up to 28 days after the subject has discontinued study drug.

[00194] All adverse events, whether serious or non-serious, were to be followed to resolution (or stabilization, if applicable) or until the adverse event was determined by the investigator to be no longer clinically significant.

5.1.1.5. **Laboratory Outcomes of Interest**

[00195] A laboratory outcome of interest was one that met any one of the following criteria:

Ferritin $\geq$ 800 ng/ml

TSAT $\geq$ 50%

Liver enzyme elevations $\geq$ 3X the upper limit of normal (ULN)

5.1.1.6. **Analysis Population**

[00196] Efficacy

[00197] 26 subjects completed the 8-week treatment period on study drug. The efficacy analyses were based on data from the 26 subjects.

[00198] Safety

[00199] The safety analyses were based on the safety population that consisted of all subjects who take at least one dose of study drug.

5.1.2. **Results**

[00200] Fifty eight subjects were screened and 32 subjects were enrolled. All 32 subjects received at least 1 dose of Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) and were included in the Safety Population. Twenty six subjects (81.3%) completed the study and were included in the Analysis Population. Six subjects (18.8%) early terminated, 3 subjects (9.4%) due to an adverse event, 1 (3.1%) due the investigator judgment, and 2 (6.3%) due to other reasons. The majority of subjects in this trial were White/Caucasian (96.9%), Male (53.1%), aged 65 years or older and had Stage 3 CKD (43.8%).

[00201] Twenty six subjects completed the 8-week treatment period (81.3%) and were included in the analysis population. The mean and median duration of exposure in this trial were

40.2 and 42.0 days, respectively. The mean and median dose of Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) was 1.2 g per day. Overall, laboratory values for non-iron related parameters were similar to those at baseline throughout the study.

[00202] Treatment with Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) for 8 weeks resulted in a statistically significant increase in hemoglobin, from 10.8±0.7 g/dl at baseline to 11.2±0.9 g/dl at Week 8 (P=0.0212). *See* Table 6, *infra*. The mean change in hemoglobin from baseline to the highest value was 0.6 g/dl (P<0.0001). Six subjects (23.1%) had an increase in hemoglobin of at least 1.0 g/dl compared to baseline at any time during the study and 7 subjects (26.9%) achieved a Hemoglobin ≥12.0 g/dl at least once during the study. *See* Table 7, *infra*.

[00203] In addition, treatment with Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) for 8 weeks resulted in increases in iron storage parameters, serum ferritin and TSAT values, compared to baseline. Serum ferritin levels increased by an average of 35 ng/ml, from 84.9±64.7 ng/ml at baseline to 120.1±82.5 ng/ml at Week 8, p-value 0.001, in subjects taking Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.). *See* Table 8, *infra*. TSAT values increased an average of 5.7%, from 19.2±6.5% to 24.9±8.5%, p-value 0.003, in subject taking Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.).

[00204] Thus, administration of Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) without food was generally safe and well tolerated in this study. Treatment with Auryxia™ (Ferric Citrate; Keryx Biopharmaceuticals, Inc.) for 8 weeks resulted in a significant increase in hemoglobin as well as in serum ferritin levels and TSAT values.

Table 6. Hemoglobin Concentrations

	N	Mean (SD)	P-Value
Baseline	26	10.8 (0.7)	-
Week 8	26	11.2 (0.9)	0.0212
Highest Value	26	11.4 (0.7)	<0.0001

Table 7. Patients with >=1.0 g/dl Increase in Hemoglobin Concentrations and Patients with >= 12.0 g/dl Hemoglobin Concentrations

Item	Stat	KRX-0502 (N= 26)
Change >= 1.0 g/dl at any visit	n (%)	6 (23.1)

Item	Stat	KRX-0502 (N= 26)
Value >= 12.0 g/dl at any visit	n (%)	7 (26.9)

Table 8. Serum Ferritin Levels

		Summary Statistics (N= 26)								
Parameter	**Visit**	**n**	**Mean**	**SD**	**Median**	**P(25)**	**P(75)**	**Min**	**Max**	**P-value**
Ferritin (ng/ml)	Baseline	26	84.9	64.66	72.0	31.0	121.0	8	275	.
	Visit 3	26	91.6	64.58	77.5	43.0	125.0	13	310	.
	Visit 4	26	91.7	63.68	71.5	51.0	131.0	19	303	.
	Visit 5	26	92.2	62.02	89.0	45.0	117.0	21	261	.
	Visit 6	26	99.7	61.99	85.5	64.0	132.0	17	260	.
	Visit 7	26	120.1	82.53	85.5	63.0	163.0	23	340	.
Ferritin (ng/ml) Change from Baseline	Visit 3	26	6.7	22.90	2.5	-3.0	12.0	-41	65	0.1465
	Visit 4	26	6.8	25.72	11.5	-10.0	20.0	-60	60	0.1916
	Visit 5	26	7.3	20.60	7.5	-4.0	16.0	-30	54	0.0811
	Visit 6	26	14.8	24.03	16.5	-8.0	31.0	-36	55	0.0043
	Visit 7	26	35.2	48.38	30.5	15.0	43.0	-64	188	0.0010

5.2. Example 2: Animal Models For Colitis

[00205] To evaluate the ability of ferric citrate to treat IDA in subjects with an inflammatory bowel condition, animal models of colitis are administered ferric citrate and the effect of the ferric citrate on iron storage parameters, such as hemoglobin concentration and TSAT values, are determined.

[00206] **T-cell Transfer Model of Chronic Colitis**

[00207] Chronic colonic inflammation is induced in mice by the adoptive transfer of IL-102/2 $CD4^+$ T-cells into RAG2/2 recipients. Briefly, RAG2/2 recipient mice at an age of 2–3 months are injected with 10^6 $CD4^+$ T-cells obtained from IL-102/2 donor mice, with the T cells enriched (90%; from single-cell suspensions of splenocytes) by negative selection using a commercially available kit. Additional age-matched RAG2/2 mice and C57BL/6 mice are treated identically except for the injection of vehicle alone (phosphate-buffered saline [PBS])

instead of the T cells. At 8-week post-injection, the mice are used for treatment with ferric citrate or control.

[00208] DSS Model of Acute/Self-limiting Colitis

[00209] Acute colonic inflammation is induced in 2-month to 3-month C57BL/6 mice via administration of 5% dextran sulphate sodium (DSS) in drinking water for 6 days. The DSS is added to water that is filter purified. Filtered water (without DSS) is administered for 6 days to age matched C57BL/6 mice as a control group. At the end of the DSS administration, the mice are used for treatment with ferric citrate or control.

[00210] Both the T- cell transfer model of colitis and the DSS model of Colitis are known to induce significant decreases in hematocrit, blood hemoglobin, and TSAT, with the spleen and liver showing a decrease in iron content in the T-cell transfer model of colitis. In addition, both models of colitis have demonstrated significant increases in plasma erythropoietin and plasma iron-binding capacities.

[00211] Treatment Group

[00212] After colitis has been induced, a certain number of mice are administered ferric citrate via oral gavage or dietary administration at doses corresponding to the human effective doses. As a control, a certain number of mice are administered ferrous sulfate via oral gavage or dietary administration. Prior to administration of ferric citrate and a certain number of days (*e.g.*, 1, 2, 3, 4, 5,6 or more days) or weeks (*e.g.*, 1, 2, 3, 4, 5 or more weeks) after administration of ferric citrate or control, iron and hematology analysis is conducted.

[00213] Iron and Hematology Analysis

[00214] The mice are anesthetized with an intraperitoneal injection of 150 mg/kg ketamine and 10 mg/kg xylazine. A blood sample is withdrawn from the cannulated right carotid artery with a portion mixed with the anticoagulant EDTA for measures of hematocrit, hemoglobin concentration, and hemoglobin per RBC, and the remaining untreated blood processed for measures of serum iron, unsaturated iron-binding capacity, total iron-binding capacity (TIBC), transferrin saturation, serum ferritin, and plasma erythropoietin (all measures obtained with an Hematology Analyzer). After euthanasia, tissue sections (or entire organs in some cases) are dissected for iron measurements.

[00215] 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.

[00216] All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

What is claimed is:

1. A method for treating iron deficiency anemia in a human patient, wherein the patient has not been diagnosed with chronic kidney disease, the method comprising orally administering a ferric citrate tablet containing approximately 210 mg of ferric iron to the patient, wherein the ferric citrate in the tablet is a complex of iron (+3), 0.70 – 0.87 (1, 2, 3-propanetricarboxylic acid, 2-hydroxy-), 1.9 – 3 (H_2O).

2. The method of claim 1, wherein the patient has a serum ferritin level of between 5 ng/ml to 300 ng/ml.

3. The method of claim 1 or 2, wherein the ferric citrate is not administered with food.

4. A method for treating iron deficiency anemia in a human patient, wherein the patient has not been diagnosed with chronic kidney disease and the patient has a serum ferritin level of between 5 ng/ml to 300 ng/ml, the method comprising orally administering a ferric citrate tablet containing approximately 210 mg of ferric iron to the patient, wherein the ferric citrate in the tablet is a complex of iron (+3), 0.70 – 0.87 (1, 2, 3-propanetricarboxylic acid, 2-hydroxy-), 1.9 – 3 (H_2O).

5. A method for treating iron deficiency anemia in a human patient, wherein the patient has not been diagnosed with chronic kidney disease and the patient has a serum ferritin level of between 5 ng/ml to 300 ng/ml, the method comprising orally administering a ferric citrate tablet containing approximately 210 mg of ferric iron to the patient, wherein the ferric citrate is not administered within 2 hours of food being ingested by the patient, and wherein the ferric citrate in the tablet is a complex of iron (+3), 0.70 – 0.87 (1, 2, 3-propanetricarboxylic acid, 2-hydroxy-), 1.9 – 3 (H_2O).

6. The method of any of claims 1-5, wherein the patient has a serum ferritin level of between 5 ng/ml to 250 ng/ml.

7. The method of any of claims 1-5, wherein the patient has a serum ferritin level of between 5 ng/ml to 150 ng/ml.

8. The method of any of claims 1-5, wherein the patient has a serum ferritin level of between 5 ng/ml to 100 ng/ml.

9. The method of any of claims 1-5, wherein the patient has a serum ferritin level of between 5 ng/ml to 75 ng/ml.

10. The method of any of claims 1-5, wherein the patient has a serum ferritin level of between 5 ng/ml to 50 ng/ml.

11. The method of any of claims 1-5, wherein the patient has a serum ferritin level of between 5 ng/ml to 25 ng/ml.

12. The method of any of claims 1-5, wherein the patient has a serum ferritin level of between 5 ng/ml to 15 ng/ml.

13. The method of any of claims 1-5, wherein the patient has a serum ferritin level of between 5 ng/ml to 10 ng/ml.

14. A method for treating iron deficiency anemia in a human patient that has not been diagnosed with chronic kidney disease, the method comprising:

(a) orally administering to the patient one ferric citrate tablet containing approximately 210 mg of ferric iron per day, wherein the ferric citrate is not administered within 2 hours of food being ingested by the patient, and wherein the ferric citrate in the tablet is a complex of iron (+3), 0.70 – 0.87 (1, 2, 3-propanetricarboxylic acid, 2-hydroxy-), 1.9 – 3 (H_2O); and

(b) decreasing the dose of ferric citrate after 4 weeks if the hemoglobin concentration of the subject has increased by more than 5 g/dl and increasing the dose of ferric citrate after 4 weeks if the hemoglobin concentration of the subject has increased by less than 1 g/dl.

15. The method of any one of claims 1-14, wherein the patient has a gastrointestinal disorder.

16. The method of claim 15, wherein the gastrointestinal disorder is inflammatory bowel disease, inflammatory bowel syndrome, Crohn's disease, ulcerative colitis, microscopic colitis, or chemically-induced colitis.

17. The method of claim 16, wherein the microscopic colitis is collagenous colitis or lymphocytic colitis.

18. The method of claim 16, wherein the chemically-induced colitis is NSAID (nonsteroidal anti-inflammatory drug)-induced colitis.

19. The method of any one of claims 1-14, wherein the patient has blood loss.

20. The method of claim 19, wherein the blood loss is associated with childbirth or menstruation.

21. The method of claim 19, wherein the blood loss is associated with an infection.

22. The method of any one of claims 1-14, wherein the patient has insufficient dietary intake of iron.

23. The method of any one of claims 1-14, wherein the patient has insufficient absorption of iron.

24. The method of any one of claims 1-23, wherein the patient is monitored for one or more iron storage parameters.

25. The method of claim 24, wherein the one or more iron storage parameters is selected from the group consisting of hemoglobin concentration, serum ferritin level, TSAT value, serum iron level, hematocrit level, TIBC value, plasma erythropoietin level, and FEP level.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/20575

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/295, 33/26; C07F 15/02 (2016.01)
CPC - A61K 31/295, 33/26; C07F 15/02
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)
IPC(8): A61K 31/295, 33/26; C07F 15/02 (2016.01)
CPC: A61K 31/295, 33/26; C07F 15/02

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)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, Other Countries (INPADOC), RU, AT, CH, TH, BR, PH); EBSCO; Google/Google Scholar, IP.com: iron, deficient, anemia, ferric, citrate, ferritin, serum, kidney, complex, propanetricarboxylic, hemoglobin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2013/192565 A1 (KERYX BIOPHARMACEUTICALS, INC.) 27 December 2013; page 4, lines 20-29; page 5, lines 20-26; page 9, lines 29-34; page 10, lines 1-8; page 15, lines 32-34; page 16, lines 18-20; page 27, lines 21-30; page 46, lines 26-31	1-2, 3/1-2, 4-5, 14
Y	(KERYX BIOPHARMACEUTICALS) Highlights of Prescribing Information for Auryxia. Datasheet [online] November 2014 [Retrieved on 19 April 2016]. Retrieved from the Internet: <URL: https://auryxia.com/wp-content/uploads/Auryxia_PI_Keryx_112014.pdf>; page 6, paragraphs [1]-[2]	1-2, 3/1-2, 4-5, 14
Y	US 2012/0288531 A1 (TUVIA, S et al.) 15 November 2012; paragraphs [0160]-[0161]	5, 14
A	US 8,338,642 B2 (KWOK, DWK et al.) 25 December 2012; entire document	1-2, 3/1-2, 4-5, 14
A	US 8,299,298 B2 (CHAN, K et al.) 30 October 2012; entire document	1-2, 3/1-2, 4-5, 14

☐ Further documents are listed in the continuation of Box C. ☐ 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
29 April 2016 (29.04.2016)	23 MAY 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/20575

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.: 6-13, 15-25
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:

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 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.:

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.

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(54)发明名称

柠檬酸铁在治疗缺铁性贫血中的用途

(57)摘要

本文描述的是治疗缺铁性贫血(IDA)患者的方法,包括向这样的患者施用柠檬酸铁。在某些方面,被治疗缺铁性贫血的患者患有胃肠失调,例如,炎症性肠病、炎症性肠综合征、克罗恩病、显微镜下结肠炎(例如,胶原性或淋巴细胞性结肠炎),或化学诱导的结肠炎(例如,NSAID(非甾体抗炎药)诱导的结肠炎)。在某些方面,被治疗缺铁性贫血的患者患有与分娩、月经或感染相关的失血。在某些方面,被治疗缺铁性贫血的患者患有铁饮食摄入不足和/或铁吸收不足。

CN 107530310 A

1.一种治疗人类患者的缺铁性贫血的方法,其中所述患者没有被诊断患有慢性肾病,所述方法包括向所述患者口服施用含有大约210mg三价铁的柠檬酸铁片剂,其中所述片剂中的柠檬酸铁是铁(+3),0.70-0.87(1,2,3-丙烷三羧酸,2-羟基-),1.9-3(H_2O)的复合物。

2.权利要求1的方法,其中所述患者的血清铁蛋白水平在5ng/ml到300ng/ml之间。

3.权利要求1或2的方法,其中所述柠檬酸铁不与食物一起施用。

4.一种治疗人类患者的缺铁性贫血的方法,其中所述患者没有被诊断患有慢性肾病,以及所述患者的血清铁蛋白水平在5ng/ml到300ng/ml之间,所述方法包括向所述患者口服施用含有大约210mg三价铁的柠檬酸铁片剂,其中所述片剂中的柠檬酸铁是铁(+3),0.70-0.87(1,2,3-丙烷三羧酸,2-羟基-),1.9-3(H_2O)的复合物。

5.一种治疗人类患者的缺铁性贫血的方法,其中所述患者没有被诊断患有慢性肾病,以及所述患者的血清铁蛋白水平在5ng/ml到300ng/ml之间,所述方法包括向所述患者口服施用含有大约210mg三价铁的柠檬酸铁片剂,其中所述柠檬酸铁不在所述患者摄入食物的2小时之内施用,和其中所述片剂中的柠檬酸铁是铁(+3),0.70-0.87(1,2,3-丙烷三羧酸,2-羟基-),1.9-3(H_2O)的复合物。

6.权利要求1-5的任一项的方法,其中所述患者的血清铁蛋白水平在5ng/ml到250ng/ml之间。

7.权利要求1-5的任一项的方法,其中所述患者的血清铁蛋白水平在5ng/ml到150ng/ml之间。

8.权利要求1-5的任一项的方法,其中所述患者的血清铁蛋白水平在5ng/ml到100ng/ml之间。

9.权利要求1-5的任一项的方法,其中所述患者的血清铁蛋白水平在5ng/ml到75ng/ml之间。

10.权利要求1-5的任一项的方法,其中所述患者的血清铁蛋白水平在5ng/ml到50ng/ml之间。

11.权利要求1-5的任一项的方法,其中所述患者的血清铁蛋白水平在5ng/ml到25ng/ml之间。

12.权利要求1-5的任一项的方法,其中所述患者的血清铁蛋白水平在5ng/ml到15ng/ml之间。

13.权利要求1-5的任一项的方法,其中所述患者的血清铁蛋白水平在5ng/ml到10ng/ml之间。

14.一种治疗未被诊断患有慢性肾病的人类患者的缺铁性贫血的方法,所述方法包括:

(a)每天向所述患者口服施用含有大约210mg三价铁的一个柠檬酸铁片剂,其中所述柠檬酸铁不在所述患者摄入食物的2小时之内施用,以及其中所述片剂中的柠檬酸铁是铁(+3),0.70-0.87(1,2,3-丙烷三羧酸,2-羟基-),1.9-3(H_2O)的复合物;和

(b)如果4周后所述对象的血红蛋白浓度提高超过5g/dl,降低所述柠檬酸铁的剂量,以及如果4周后所述对象的血红蛋白浓度提高小于1g/dl,提高所述柠檬酸铁的剂量。

15.权利要求1-14的任一项的方法,其中所述患者患有胃肠失调。

16.权利要求15的方法,其中所述胃肠失调是炎症性肠病、炎症性肠综合征、克罗恩病、溃疡性结肠炎、显微镜下结肠炎或化学诱导的结肠炎。

17.权利要求16的方法,其中所述显微镜下结肠炎是胶原性结肠炎或淋巴细胞性结肠炎。

18.权利要求16的方法,其中所述化学诱导的结肠炎是NSAID(非甾体抗炎药)诱导的结肠炎。

19.权利要求1-14的任一项的方法,其中所述患者患有失血。

20.权利要求19的方法,其中所述失血与分娩或月经相关。

21.权利要求19的方法,其中所述失血与感染相关。

22.权利要求1-14的任一项的方法,其中所述患者患有铁饮食摄入不足。

23.权利要求1-14的任一项的方法,其中所述患者患有铁吸收不足。

24.权利要求1-23的任一项的方法,其中监测所述患者的一种或更多种铁储存参数。

25.权利要求24的方法,其中所述一种或更多种铁储存参数选自:血红蛋白浓度、血清铁蛋白水平、TSAT值、血清铁水平、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和FEP水平。

柠檬酸铁在治疗缺铁性贫血中的用途

[0001] 相关申请的交叉引用

[0002] 本申请要求2015年3月4日提交的美国临时专利申请No.62/127,963的权益，通过引用将其全部合并在本文中。

[0003] 1.领域

[0004] 本文描述的是治疗缺铁性贫血(IDA)患者的方法，包括向这样的患者施用柠檬酸铁。在某些方面，被治疗缺铁性贫血的患者患有胃肠失调，例如，炎症性肠病、炎症性肠综合征、克罗恩病、显微镜下结肠炎(例如，胶原性或淋巴细胞性结肠炎)，或化学诱导的结肠炎(例如，NSAID(非甾体抗炎药)诱导的结肠炎)。在某些方面，被治疗缺铁性贫血的患者患有与分娩、月经或感染相关的失血。在某些方面，被治疗缺铁性贫血的患者患有铁饮食摄入不足和/或铁吸收不足。

[0005] 2.背景

[0006] 全世界约二十亿人患有贫血，缺铁是贫血的最普遍的原因，在发达国家和欠发达国家影响了数百万儿童、妇女和男性(Baltussen et al.,Journal of Nutrition(2004)134,2678-2684;McLean et al.,Public Health Nutr.(2009)12,444-454)。虽然缺铁性贫血(IDA)对人体健康的影响是显著的，它常常被忽视或没有被充分治疗(Miller et al.,Cold Spring Harb.Perspect.Med.(2013)3,a011866)。

[0007] 生活在工业化国家的大多数营养良好、不缺铁的人在他们体内以某种方式(例如，作为循环铁或储存铁或这两者)储存着大约4到5克铁。这一数量的降低表示缺铁，这在IDA患者中是常见的。缺铁的症状可能在病症进展到IDA之前在患者中出现，可包括，例如，疲劳、昏眩、苍白、脱发、烦躁、虚弱、异食癖、脆性或凹槽的指甲、普鲁默-文森综合征(覆盖舌、咽部和食道的粘膜的痛苦的萎缩)、免疫功能受损、食冰癖和不宁腿综合征，等。

[0008] IDA的一般特征在于苍白(由皮肤和粘膜中氧合血红蛋白降低引起的苍白颜色)、疲劳、头昏和虚弱。然而，IDA的病征在患者之间可能不同。由于IDA患者的缺铁倾向于缓慢发展，可能发生对疾病的适应，它可能很长时间、甚至数年不被发现。在某些情况下，IDA患者可能发生呼吸困难(呼吸问题)、异食癖(不寻常的强迫性食物渴求)、常引起强迫-强制性失调(OCD)型强迫症和痴迷的焦虑、烦躁或忧虑、绞痛、便秘、嗜睡、耳鸣、口腔溃疡、心悸、脱发、昏晕或感觉模糊、抑郁症、运动时气喘、肌肉抽搐、皮肤苍黄、麻刺(麻痹)或烧灼感、月经周期错过、重月经期、社会发展缓慢、舌炎(舌头的炎症或感染)、口角炎(口角的炎性病变)、凹甲(匙形指甲)或脆弱或易碎的指甲、食欲不振、瘙痒(广义的发痒)、普鲁默-文森综合征(覆盖舌、咽部和食道的粘膜的痛苦的萎缩)、失眠、不宁腿综合征，等。

[0009] IDA可能由铁饮食摄入不足、铁吸收不足、铁储存不足和/或由于出血的铁损失引起，出血可能来源于如胃肠、子宫或尿路的多种来源。因而，它通常与例如急性失血、慢性失血、分娩、月经、胃肠失调(例如，炎症性肠病(IBD))、慢性肾病(CKD)、寄生虫感染、铁饮食摄入不足和铁吸收不足的状况和失调相关。

[0010] 治疗IDA一般有三种方法。第一种方法是食用高铁的食物。如果这不足够，则临床医师可以开具口服补铁剂的处方。然而，许多口服补铁剂导致患者的许多不良副作用，这导

致患者的不顺应。在IDA患者不能服用口服补铁剂的情况下,它们可能不得不进行静脉内的补铁。

[0011] 静脉内(IV)补铁是一种通过用针头注射到肌肉或静脉中的释放铁的方法。接受IV铁的IDA患者通常这样做,因为他们不能耐受口服的铁。通过附着于含有铁溶液的IV袋子的针头,静脉内铁被递送入IDA患者的静脉。该过程在医生办公室或门诊进行,取决于医师开具处方的治疗可能花费数小时。患者通常在几次就诊的过程中接受铁注射直到他或她的铁水平正确。在某些情况下,IDA患者可能需要长期的IV铁补充。

[0012] 然而,IV铁还与短期的副作用相关,例如胃肠疼痛(例如,恶心和痉挛)、呼吸问题、皮肤问题(例如,皮疹)、胸痛、低血压、过敏症和死亡,以及长期毒性,包括动脉粥样硬化发展、感染和提高的死亡率(Quinibi,Arzneimittelforschung(2010)60,399-412)。此外,许多门诊,特别是社区位置,都缺乏施用静脉内铁的装备。这使得大部分IDA患者没有进行静脉内铁治疗。

[0013] IDA患者还可能服用一种或更多种红细胞生成刺激剂(ESA)以控制贫血。然而,使用ESA可能产生副作用。最常见的副作用包括:高血压;肿胀;发烧;昏眩;恶心;以及注射部位的疼痛,等。除了这些副作用之外,使用ESA产生几种安全问题。ESA提高了静脉血栓栓塞(静脉中的血凝块)的风险。ESA还可能导致血红蛋白过高,这使得患者有更高风险发生心脏病发作、中风、心力衰竭和死亡。另外,在某些情况下ESA可能使得铁减少恶化,并引起血小板增多症的提高。

[0014] 因而,需要开发用于IDA患者的口服铁治疗的改进的方法。

[0015] 3.概述

[0016] 在一个方面,本文提供的是治疗缺铁性贫血(IDA)的方法,包括向有需要的对象施用柠檬酸铁或其药物组合物。参见,例如,下文的章节4.2,关于治疗的患者群体,下文的章节4.3,关于柠檬酸铁或其药物组合物的给药和施用,以及下文的章节4.5,关于柠檬酸铁和其药物组合物的形式。在一个实施方式中,本文提供的是治疗缺铁性贫血的方法,包括向有需要的对象以一定频率(例如,每天、每隔一天、每2天、每3天、每4天、每5天等,持续一段时间)口服施用低剂量的柠檬酸铁或其药物组合物。在特定的实施方式中,所述低剂量每天一次、每隔一天或每两天施用持续一段时间,例如,1个月、2个月、3个月、4个月、5个月、6个月、9个月、12个月或更久。在某些实施方式中,柠檬酸铁或其药物组合物被施用给在一定时间段内没有摄入食物的对象。对于没有摄入食物的这种时间段的例子,参见,例如,下文的章节4.3。在某些实施方式中,监测对象的一种或更多种铁储存参数,例如,血红蛋白浓度、转铁蛋白饱和度(TSAT)值、血清铁蛋白水平、血清铁水平、血细胞比容水平、总铁结合力(TIBC)值、血浆促红细胞生成素水平和/或游离红细胞性原卟啉(FEP)水平(例如,每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数),在某些实施方式中,根据所述一种或更多种铁储存参数来改变施用柠檬酸铁或其药物组合物的频率和/或对象接受的柠檬酸铁或其药物组合物的数量(例如,如果在一段时间后血红蛋白浓度提高小于1g/dl,提高柠檬酸铁或其药物组合物的数量,以及如果血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl,降低柠檬酸铁或其药物组合物的数量)。在某些实施方式中,施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。在某些实施方式中,所述患者患有胃肠失调,例如,炎症性肠病、炎症性肠综合

征、克罗恩病、显微镜下结肠炎(例如,胶原性或淋巴细胞性结肠炎)和/或化学诱导的结肠炎(例如,NSAID(非甾体抗炎药)诱导的结肠炎)。在某些实施方式中,治疗缺铁性贫血的患者患有失血(例如,与分娩或月经相关的失血,或与感染相关的失血)。在某些实施方式中,治疗缺铁性贫血的患者患有铁饮食摄入不足。在某些实施方式中,治疗缺铁性贫血的患者患有铁吸收不足。

[0017] 在具体的实施方式中,本文提供的是治疗患者(例如,人类患者)的缺铁性贫血的方法,其中所述患者未被诊断患有慢性肾病,所述方法包括向所述患者口服施用含有大约210mg三价铁的柠檬酸铁片剂,其中所述片剂中的柠檬酸铁是铁(+3),0.70-0.87(1,2,3-丙烷三羧酸,2-羟基-),1.9-3(H_2O)的复合物。在某些实施方式中,所述患者的血清铁蛋白水平在5ng/ml到300ng/ml之间(例如,5ng/ml到250ng/ml之间,5ng/ml到150ng/ml之间,5ng/ml到100ng/ml之间,5ng/ml到75ng/ml之间,5ng/ml到50ng/ml之间,5ng/ml到25ng/ml之间,5ng/ml到15ng/ml之间,或5ng/ml到10ng/ml之间)。在某些实施方式中,所述柠檬酸铁不与食物一起施用。在某些实施方式中,监测所述对象的一种或更多种铁储存参数,例如,血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如,每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数),在某些实施方式中,根据所述一种或更多种铁储存参数来改变施用柠檬酸铁或其药物组合物的频率和/或对象接受的柠檬酸铁或其药物组合物的数量(例如,如果在一段时间后血红蛋白浓度提高小于1g/dl,提高柠檬酸铁或其药物组合物的数量,以及如果血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl,降低柠檬酸铁或其药物组合物的数量)。在某些实施方式中,所述患者患有胃肠失调,例如,炎症性肠病、炎症性肠综合征、克罗恩病、溃疡性结肠炎、显微镜下结肠炎(例如,胶原性或淋巴细胞性结肠炎)和/或化学诱导的结肠炎(例如,NSAID-诱导的结肠炎)。在某些实施方式中,治疗缺铁性贫血的患者患有失血(例如,与分娩或月经相关的失血,或与感染相关的失血)。在某些实施方式中,治疗缺铁性贫血的患者患有铁饮食摄入不足。在某些实施方式中,治疗缺铁性贫血的患者患有铁吸收不足。

[0018] 在另一个具体的实施方式中,本文提供的是治疗患者(例如,人类患者)的缺铁性贫血的方法,其中所述患者未被诊断患有慢性肾病,以及所述患者的血清铁蛋白水平在5ng/ml到300ng/ml之间(例如,5ng/ml到250ng/ml之间,5ng/ml到150ng/ml之间,5ng/ml到100ng/ml之间,5ng/ml到75ng/ml之间,5ng/ml到50ng/ml之间,5ng/ml到25ng/ml之间,5ng/ml到15ng/ml之间,或5ng/ml到10ng/ml之间),所述方法包括向所述患者口服施用含有大约210mg三价铁的柠檬酸铁片剂,其中所述柠檬酸铁不在所述患者摄入食物的2小时之内施用,以及其中所述片剂中的柠檬酸铁是铁(+3),0.70-0.87(1,2,3-丙烷三羧酸,2-羟基-),1.9-3(H_2O)的复合物。在某些实施方式中,监测所述对象的一种或更多种铁储存参数,例如,血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如,每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数),在某些实施方式中,根据所述一种或更多种铁储存参数来改变施用柠檬酸铁或其药物组合物的频率和/或对象接受的柠檬酸铁或其药物组合物的数量(例如,如果在一段时间后血红蛋白浓度提高小于1g/dl,提高柠檬酸铁或其药物组合物的数量,以及如果血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl,降低

柠檬酸铁或其药物组合物的数量)。在某些实施方式中,所述患者患有胃肠失调,例如,炎症性肠病、炎症性肠综合征、克罗恩病、溃疡性结肠炎、显微镜下结肠炎(例如,胶原性或淋巴细胞性结肠炎)和/或化学诱导的结肠炎(例如,NSAID-诱导的结肠炎)。在某些实施方式中,治疗缺铁性贫血的患者患有失血(例如,与分娩或月经相关的失血,或与感染相关的失血)。在某些实施方式中,治疗缺铁性贫血的患者患有铁饮食摄入不足。在某些实施方式中,治疗缺铁性贫血的患者患有铁吸收不足。

[0019] 在另一个具体的实施方式中,本文提供的是治疗未被诊断患有慢性肾病的人类患者的缺铁性贫血的方法,所述方法包括:(a)每天向所述患者口服施用含有大约210mg三价铁的一个柠檬酸铁片剂,其中所述柠檬酸铁不在所述患者摄入食物的2小时之内施用,以及其中所述片剂中的柠檬酸铁是铁(+3),0.70-0.87(1,2,3-丙烷三羧酸,2-羟基-),1.9-3(H_2O)的复合物;和(b)如果4周后所述对象的血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl或2g/dl,降低柠檬酸铁的剂量,以及如果4周后所述对象的血红蛋白浓度提高小于1g/dl,提高柠檬酸铁的剂量。在某些实施方式中,监测所述对象的一种或更多种铁储存参数,例如,血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如,每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中,所述患者患有胃肠失调,例如,炎症性肠病、炎症性肠综合征、克罗恩病、溃疡性结肠炎、显微镜下结肠炎(例如,胶原性或淋巴细胞性结肠炎)和/或化学诱导的结肠炎(例如,NSAID-诱导的结肠炎)。在某些实施方式中,治疗缺铁性贫血的患者患有失血(例如,与分娩或月经相关的失血,或与感染相关的失血)。在某些实施方式中,治疗缺铁性贫血的患者患有铁饮食摄入不足。在某些实施方式中,治疗缺铁性贫血的患者患有铁吸收不足。

[0020] 在任一上述实施方式的具体的实施方式中,监测治疗缺铁性贫血的患者的一种或更多种铁储存参数。所述一种或更多种铁储存参数可以选自血红蛋白浓度、血清铁蛋白水平、TSAT值、血清铁水平、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和FEP水平。

[0021] 4.详细说明

[0022] 当前的公开提供了使用柠檬酸铁来治疗患有缺铁性贫血(IDA)的患者的方法。当前的公开还提供了药物组合物,其可以施用给缺铁患者。还提供了在施用柠檬酸铁之前和/或之后评估患者的方法。

[0023] 4.1.治疗IDA的方法

[0024] 在一个方面,本文提供的是治疗IDA的方法,包括向有需要的对象施用柠檬酸铁或其药物组合物。在一个实施方式中,本文提供的是治疗IDA的方法,包括向有需要的对象施用有效量的柠檬酸铁或其药物组合物。参见,例如,下文的章节4.2,关于治疗的患者群体,下文的章节4.3,关于柠檬酸铁或其药物组合物的给药和施用,以及下文的章节4.5,关于柠檬酸铁和其药物组合物的形式。在另一个实施方式中,本文提供的是治疗IDA的方法,包括向有需要的对象口服施用有效量的柠檬酸铁或其药物组合物。参见,例如,下文的章节4.2,关于治疗的患者群体,下文的章节4.3,关于柠檬酸铁或其药物组合物的给药和施用,以及下文的章节4.5,关于柠檬酸铁和其药物组合物的形式。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的一种或更多种铁储存参数,例如,血红蛋白浓度、TSAT(转铁蛋白饱和度)值、血清铁蛋白水平、血清铁水平、组织铁水平(例如,可

持续组织铁水平)、血细胞比容水平、总铁结合力(TIBC)值、血浆促红细胞生成素水平和/或游离红细胞性原卟啉(FEP)水平。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种铁储存参数,例如,血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如,可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如,每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中,施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0025] 在具体的实施方式中,本文提供的是治疗IDA的方法,包括向有需要的对象以一定频率(例如,每天、每隔一天、每2天、每3天、每4天、每5天等,持续一段时间)口服施用低剂量的柠檬酸铁或其药物组合物。在特定的实施方式中,所述低剂量一天一次、每隔一天或每两天施用持续一段时间,例如,1个月、2个月、3个月、4个月、5个月、6个月、9个月、12个月或更久。在某些实施方式中,柠檬酸铁或其药物组合物被施用给在一定时间内没有摄入食物的对象。对于没有摄入食物的这种时间段的例子,参见,例如,下文的章节4.3。在某些实施方式中,监测所述对象的一种或更多种铁储存参数,例如,血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如,可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如,每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数),以及在某些实施方式中,根据所述一种或更多种铁储存参数改变柠檬酸铁或其药物组合物的施用频率和/或所述对象接受的柠檬酸铁或其药物组合物的数量(例如,如果在一段时间后血红蛋白浓度提高小于1g/dl,提高柠檬酸铁或其药物组合物的数量,以及如果血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl,降低柠檬酸铁或其药物组合物的数量)。在某些实施方式中,施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0026] 如本文使用的,在柠檬酸铁或其药物组合物的上下文中术语“低剂量”等价于1100mg三价铁的剂量或更低,但高于50mg三价铁(在某些实施方式中,高于100mg或200mg三价铁)。在一个实施方式中,低剂量的柠檬酸铁或其药物组合物等价于1050mg、840mg、630mg、420mg或210mg三价铁的剂量。在另一个实施方式中,低剂量的柠檬酸铁或其药物组合物等价于1050mg到1100mg、840mg到1050mg、840mg到1100mg、630mg到840mg、630mg到1050mg、630mg到1100mg、420mg到630mg、420mg到840mg、420mg到1050mg、210mg到420mg、210mg到630mg、210mg到840mg、或210mg到1050mg三价铁的剂量。在具体的实施方式中,低剂量的柠檬酸铁或其药物组合物等价于每天或每隔一天1、2、3、4或5片Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)。

[0027] 在具体的实施方式中,本文提供的是治疗IDA的方法,包括向没有食物的有需要的对象以一定频率(例如,每天、每隔一天、每2天、每3天、每4天、每5天等,持续一段时间)口服施用低剂量的柠檬酸铁或其药物组合物。在另一个具体的实施方式中,本文提供的是治疗IDA的方法,包括向有需要的对象以一定频率(例如,每天、每隔一天、每2天、每3天、每4天、每5天等,持续一段时间)口服施用低剂量的柠檬酸铁或其药物组合物,所述对象在摄入所述柠檬酸铁或其药物组合物的3小时、2小时或1小时内没有摄入食物。在特定的实施方式中,所述低剂量一天一次、每隔一天或每两天施用持续一段时间,例如,1个月、2个月、3个月、4个月、5个月、6个月、9个月、12个月或更久。在某些实施方式中,在向所述对象施用柠檬

酸铁或其药物组合物之前评估一种或更多种铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平。在某些实施方式中，监测所述对象的一种或更多种铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)，以及在某些实施方式中，根据所述一种或更多种铁储存参数改变柠檬酸铁或其药物组合物的施用频率和/或所述对象接受的柠檬酸铁或其药物组合物的数量(例如，如果在一段时间后血红蛋白浓度提高小于1g/dl，提高柠檬酸铁或其药物组合物的数量，以及如果血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl，降低柠檬酸铁或其药物组合物的数量)。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0028] 在另一个实施方式中，本文提供的是治疗对象的IDA的方法，包括：(a)评估对象的一种或更多种以下铁储存参数：(i)血红蛋白浓度，(ii)TSAT值，(iii)血清铁蛋白水平，(iv)血清铁水平，(v)组织铁水平(例如，可持续组织铁水平)，(vi)血细胞比容水平，(vii)TIBC值，(viii)血浆促红细胞生成素水平，和/或(ix)FEP水平；和(b)向具有一定血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平的对象施用(例如，口服施用)柠檬酸铁或其药物组合物。参见，例如下文的章节4.2，关于根据本文描述的方法可以施用柠檬酸铁或药物组合物的对象的血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平。在某些实施方式中，根据本文公开的方法治疗的对象在施用柠檬酸铁或药物组合物之前具有以下的一项、两项或所有的：(i)大约6克/dl到大约8克/dl、大约6克/dl到大约10克/dl、大约6克/dl到大约12克/dl、大约7克/dl到大约9克/dl、大约7克/dl到大约11克/dl、大约7克/dl到大约13克/dl、大约8克/dl到大约10克/dl、大约8克/dl到大约12克/dl、大约9克/dl到大约11克/dl、大约9克/dl到大约12克/dl、大约9克/dl到大约13克/dl、大约10克/dl到大约11克/dl、大约10克/dl到大约12克/dl、大约10克/dl到大约13克/dl、大约11克/dl到大约12克/dl、大约11克/dl到大约13克/dl、或大约12克/dl到大约13克/dl的血红蛋白浓度；(ii)10％到45％、12％到45％、20％到45％、20％到40％、10％到35％、20％到25％、15％到50％、10％到30％、或10％到25％的TSAT值；(iii)大约5ng/ml到大约25ng/ml、大约25ng/ml到大约50ng/ml、大约50ng/ml到大约100ng/ml、大约100ng/ml到大约150ng/ml、大约150ng/ml到大约200ng/ml、大约150ng/ml到大约250ng/ml、大约100ng/ml到大约300ng/ml、大约200ng/ml到大约300ng/ml、或大约250ng/ml到大约300ng/ml的血清铁蛋白水平；(iv)大约10μg/dl到大约20μg/dl、大约10μg/dl到大约30μg/dl、大约10μg/dl到大约40μg/dl、大约10μg/dl到大约50μg/dl、大约10μg/dl到大约60μg/dl、大约20μg/dl到大约30μg/dl、大约20μg/dl到大约40μg/dl、大约20μg/dl到大约50μg/dl、大约20μg/dl到大约60μg/dl、大约30μg/dl到大约40μg/dl、大约30μg/dl到大约50μg/dl、大约30μg/dl到大约60μg/dl、大约40μg/dl到大约50μg/dl、或大约40μg/dl到大约60μg/dl的血清铁水平；(v)2级、1级或0级的组织铁水平(例如，可持续组织铁水平)；(vi)10％到15％、10％到20％、10％到

25％、10％到30％、10％到35％、10％到40％、10％到45％、15％到20％、15％到25％、15％到30％、15％到35％、15％到40％、15％到45％、20％到25％、20％到30％、20％到35％、20％到40％、25％到45％、25％到30％、25％到35％、25％到40％、25％到45％、30％到35％、30％到40％、30％到45％、35％到40％、35％到45％、或40％到45％的血细胞比容水平；(vii)大约390μg/dl到大约600μg/dl、大约390μg/dl到大约800μg/dl、大约390μg/dl到大约1000μg/dl、大约390μg/dl到大约1200μg/dl、大约500μg/dl到大约700μg/dl、大约500μg/dl到大约900μg/dl、大约500μg/dl到大约1100μg/dl、大约600μg/dl到大约800μg/dl、大约600μg/dl到大约1000μg/dl、大约600μg/dl到大约1200μg/dl、大约700μg/dl到大约900μg/dl、大约700μg/dl到大约1100μg/dl、大约800μg/dl到大约1000μg/dl、大约800μg/dl到大约1200μg/dl、大约900μg/dl到大约1100μg/dl、大约1000μg/dl到大约1200μg/dl的TIBC值；(viii)大约20mU/ml到大约30mU/ml、大约20mU/ml到大约40mU/ml、大约20mU/ml到大约50mU/ml、大约20mU/ml到大约60mU/ml、大约30mU/ml到大约40mU/ml、大约30mU/ml到大约50mU/ml、大约30mU/ml到大约60mU/ml、大约40mU/ml到大约50mU/ml、大约40mU/ml到大约60mU/ml、或大约50mU/ml到大约60mU/ml的血浆促红细胞生成素水平；和/或(ix)大约50μg/dl到大约60μg/dl、大约50μg/dl到大约70μg/dl、大约50μg/dl到大约80μg/dl、大约50μg/dl到大约90μg/dl、大约50μg/dl到大约100μg/dl、大约60μg/dl到大约70μg/dl、大约60μg/dl到大约80μg/dl、大约60μg/dl到大约90μg/dl、大约60μg/dl到大约100μg/dl、大约70μg/dl到大约80μg/dl、大约70μg/dl到大约90μg/dl、大约70μg/dl到大约100μg/dl、大约80μg/dl到大约90μg/dl、大约80μg/dl到大约100μg/dl、或大约90μg/dl到大约100μg/dl的FEP水平。在某些实施方式中，其中根据本文公开的方法治疗的对象是女性，所述对象在施用柠檬酸铁或其药物组合物之前具有5％到45％、5％到35％、5％到25％、5％到15％、5％到12％、5％到10％、10％到45％、10％到35％、10％到25％、10％到15％、10％到12％、12％到45％、12％到35％、12％到25％、12％到15％、20％到45％、20％到35％、20％到25％、30％到45％、30％到35％、或40％到45％的TSAT值。在某些实施方式中，其中根据本文公开的方法治疗的对象是男性，所述对象在施用柠檬酸铁或其药物组合物之前具有5％到50％、5％到40％、5％到30％、5％到20％、5％到15％、5％到10％、10％到50％、10％到40％、10％到30％、10％到20％、10％到15％、15％到50％、15％到40％、15％到30％、15％到25％、15％到20％、20％到50％、20％到40％、20％到30％、20％到25％、30％到50％、30％到40％、30％到35％、40％到50％、40％到45％、或45％到50％的TSAT值。在具体的实施方式中，所述对象以一定频率(例如，每天、每隔一天、每两天、每三天、每四天、或每五天)施用低剂量的柠檬酸铁或其药物组合物。在另一个具体的实施方式中，所述柠檬酸铁或其药物组合物口服施用给没有食物、或数小时内，例如，小于3小时内没有摄入食物的对象。在某些实施方式中，根据所述一种或更多种铁储存参数改变柠檬酸铁或其药物组合物的施用频率和/或所述对象接受的柠檬酸铁或其药物组合物的数量(例如，如果在一段时间后血红蛋白浓度提高小于1g/dl，提高柠檬酸铁或其药物组合物的数量，以及如果血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl，降低柠檬酸铁或其药物组合物的数量)。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0029] 在另一个实施方式中，本文提供的是治疗对象的IDA的方法，包括：(a)每天或每隔一天以等价于210mg到1100mg三价铁的剂量向对象口服施用柠檬酸铁或其药物组合物；和

(b)一定时间段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后如果所述对象的血红蛋白浓度提高小于1g/dl,提高柠檬酸铁或其药物组合物的剂量。在某些实施方式中,柠檬酸铁或其药物组合物的剂量以增加量,例如210mg三价铁的增加量滴定提高。在另一个实施方式中,本文提供的是治疗对象的IDA的方法,包括:(a)每天或每隔一天以等价于210mg三价铁的剂量向对象口服施用柠檬酸铁或其药物组合物;和(b)一定时间段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后如果所述对象的血红蛋白浓度提高小于1g/dl,提高柠檬酸铁或其药物组合物的剂量。在某些实施方式中,所述剂量提高到每天或每隔一天420mg三价铁。在其他实施方式中,所述剂量从每隔一天210mg三价铁提高到每天210mg三价铁。在具体的实施方式中,所述柠檬酸铁或其药物组合物口服施用给没有食物、或数小时内,例如,小于3小时内没有摄入食物的对象。在某些实施方式中,施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0030] 在另一个实施方式中,本文提供的是治疗对象的IDA的方法,包括:(a)每天或每隔一天以等价于210mg到1100mg三价铁的剂量向对象口服施用柠檬酸铁或其药物组合物;和(b)一定时间段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后监测所述对象;和(c)如果一定时间段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后所述对象的血红蛋白浓度提高小于1g/dl,提高柠檬酸铁或其药物组合物的剂量。在某些实施方式中,柠檬酸铁或其药物组合物的剂量以增加量,例如210mg三价铁的增加量滴定提高。在另一个实施方式中,本文提供的是治疗对象的IDA的方法,包括:(a)每天或每隔一天以等价于210mg三价铁的剂量向对象口服施用柠檬酸铁或其药物组合物;和(b)一定时间段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后监测所述对象;和(c)如果一定时间段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后所述对象的血红蛋白浓度提高小于1g/dl,提高柠檬酸铁或其药物组合物的剂量。在某些实施方式中,所述剂量提高到每天或每隔一天420mg三价铁。在其他实施方式中,所述剂量从每隔一天210mg三价铁提高到每天210mg三价铁。在具体的实施方式中,所述柠檬酸铁或其药物组合物口服施用给没有食物、或数小时内,例如,小于3小时内没有摄入食物的对象。在某些实施方式中,施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0031] 在另一个实施方式中,本文提供的是治疗对象的IDA的方法,包括:(a)每天或每隔一天以等价于210mg到1100mg三价铁的剂量向对象口服施用柠檬酸铁或其药物组合物;和(b)一定时间段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后如果所述对象的血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl,降低柠檬酸铁或其药物组合物的剂量。在某些实施方式中,柠檬酸铁或其药物组合物的剂量以增加量,例如210mg三价铁的增加量滴定降低。在另一个实施方式中,本文提供的是治疗对象的IDA的方法,包括:(a)每天或每隔一天以等价于210mg三价铁的剂量向对象口服施用柠檬酸铁或其药物组合物;和(b)一定时间段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后如果所述对象的血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl,降低柠檬酸铁或其药物组合物的剂量。在某些实施方式中,所述剂量从每天210mg三价铁降低到每隔一天210mg三价铁。在具体的实施方式中,所述柠檬酸铁或其药物组合物口服

施用给没有食物、或数小时内，例如，小于3小时内没有摄入食物的对象。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0032] 在另一个实施方式中，本文提供的是治疗对象的IDA的方法，包括：(a)每天或每隔一天以等价于210mg到1100mg三价铁的剂量向对象口服施用柠檬酸铁或其药物组合物；和(b)一定时间段(例如，2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后监测所述对象；和(c)如果一定时间段(例如，2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后所述对象的血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl，降低柠檬酸铁或其药物组合物的剂量。在某些实施方式中，柠檬酸铁或其药物组合物的剂量以增加量，例如210mg三价铁的增加量滴定降低。在另一个实施方式中，本文提供的是治疗对象的IDA的方法，包括：(a)每天或每隔一天以等价于210mg三价铁的剂量向对象口服施用柠檬酸铁或其药物组合物；和(b)一定时间段(例如，2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后监测所述对象；和(c)如果一定时间段(例如，2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后所述对象的血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl，降低柠檬酸铁或其药物组合物的剂量。在某些实施方式中，所述剂量从每天210mg三价铁降低到每隔一天210mg三价铁。在具体的实施方式中，所述柠檬酸铁或其药物组合物口服施用给没有食物、或数小时内，例如，小于3小时内没有摄入食物的对象。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0033] 在另一个实施方式中，本文提供的是治疗对象的IDA的方法，包括：(a)每天或每隔一天以等价于210mg到1100mg三价铁的剂量向对象口服施用柠檬酸铁或其药物组合物；和(b)如果一定时间段(例如，2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后所述对象的血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl，降低柠檬酸铁或其药物组合物的剂量，以及如果一定时间段(例如，2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后所述对象的血红蛋白浓度提高小于1g/dl，提高柠檬酸铁或其药物组合物的剂量。在某些实施方式中，柠檬酸铁或其药物组合物的剂量以增加量，例如210mg三价铁的增加量滴定降低或提高。在另一个实施方式中，本文提供的是治疗对象的IDA的方法，包括：(a)每天或每隔一天以等价于210mg三价铁的剂量向对象口服施用柠檬酸铁或其药物组合物；和(b)如果一定时间段(例如，2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后所述对象的血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl，降低柠檬酸铁或其药物组合物的剂量，以及如果一定时间段(例如，2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后所述对象的血红蛋白浓度提高小于1g/dl，提高柠檬酸铁或其药物组合物的剂量。在某些实施方式中，所述剂量从每天210mg三价铁降低到每隔一天210mg三价铁。在其他实施方式中，所述剂量提高到每天或每隔一天420mg三价铁。在具体的实施方式中，所述柠檬酸铁或其药物组合物口服施用给没有食物、或数小时内，例如，小于3小时内没有摄入食物的对象。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0034] 在另一个实施方式中，本文提供的是治疗对象的IDA的方法，包括：(a)每天以等价于210mg到1100mg三价铁的剂量向对象口服施用柠檬酸铁或其药物组合物；和(b)一定时间

段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后监测所述对象;和(c)如果一定时间段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后所述对象的血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl,降低柠檬酸铁或其药物组合物的剂量,以及如果一定时间段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后所述对象的血红蛋白浓度提高小于1g/dl,提高柠檬酸铁或其药物组合物的剂量。在某些实施方式中,柠檬酸铁或其药物组合物的剂量以增加量,例如210mg三价铁的增加量滴定降低或提高。在另一个实施方式中,本文提供的是治疗对象的IDA的方法,包括:(a)每天以等价于210mg三价铁的剂量向对象口服施用柠檬酸铁或其药物组合物;和(b)一定时间段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后监测所述对象;和(c)如果一定时间段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后所述对象的血红蛋白浓度提高超过5g/dl、4g/dl、3g/dl、2g/dl或1.5g/dl,降低柠檬酸铁或其药物组合物的剂量,以及如果一定时间段(例如,2周、4周、5周、6周、7周、8周、3个月、4个月、5个月、6个月或更久)后所述对象的血红蛋白浓度提高小于1g/dl,提高柠檬酸铁或其药物组合物的剂量。在某些实施方式中,所述剂量从每天210mg三价铁降低到每隔一天210mg三价铁。在其他实施方式中,所述剂量提高到每天或每隔一天420mg三价铁。在具体的实施方式中,所述柠檬酸铁或其药物组合物口服施用给没有食物、或数小时内,例如,小于3小时内没有摄入食物的对象。在某些实施方式中,施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0035] 在某些实施方式中,根据本文描述的方法治疗IDA的对象经历治疗效益。在具体的实施方式中,根据本文描述的方法治疗IDA的对象经历一种、两种、三种或更多种、或所有的以下效果:(i)一种或更多种IDA症状的改善;(ii)与IDA相关的症状数量的降低;(iii)一种或更多种症状的持续时间的降低;(iv)一种或更多种铁储存参数,例如,血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如,可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平方面的改善(例如,提高);(v)静脉内铁和/或红细胞生成刺激剂的施用的降低;(vi)缺铁的降低;和/或(vii)一种、两种、三种、四种或更多种IDA症状的降低或消除。IDA的症状包括,但不限于,疲劳、昏眩、头昏眼花、皮肤苍白、毛发脱失、烦躁、虚弱、异食癖、易碎或凹槽的甲沟、呼吸困难、焦虑、忧愁、绞痛、便秘、嗜睡、耳鸣、口溃疡、普鲁默-文森综合征(覆盖舌、咽部和食道的粘膜的痛苦的萎缩)、心悸、毛发脱失、昏晕或感觉昏晕、抑郁症、肌肉抽搐、皮肤苍黄、麻刺感(麻痹)或烧灼感、月经周期错过、重月经期、社会发展缓慢、舌炎、口角炎、凹甲、食欲不振、瘙痒、失眠、昏眩、对非食物物品(例如,污物、冰和粘土)的怪异渴求、快速或不规则的心跳、头痛、呼吸急促、手足冰冷、免疫功能受损、食冰癖、不宁腿综合征以及上述的组合。在某些实施方式中,在通过施用柠檬酸铁或其药物组合物提高IDA患者体内铁总量时,发生铁缺乏的减少。

[0036] 在具体的方面,本文提供的是提高患有IDA和/或被诊断患有IDA的对象中的铁吸收的方法,包括向所述对象口服施用柠檬酸铁或其药物组合物。参见,例如,下文的章节4.2,关于治疗的患者群体,下文的章节4.3,关于柠檬酸铁或其药物组合物的给药和施用,以及下文的章节4.5,关于柠檬酸铁和其药物组合物的形式。在具体的实施方式中,所述对象以一定频率(例如,每天、每隔一天、每2天、每3天、每4天、或每5天)施用低剂量的柠檬酸铁。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的

一种或更多种铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0037] 在具体的方面，本文提供的是维持或提高患有IDA和/或被诊断患有IDA的对象中的铁储存的方法，包括向所述对象口服施用柠檬酸铁或其药物组合物。参见，例如，下文的章节4.2，关于治疗的患者群体，下文的章节4.3，关于柠檬酸铁或其药物组合物的给药和施用，以及下文的章节4.5，关于柠檬酸铁和其药物组合物的形式。在具体的实施方式中，所述对象以一定频率(例如，每天、每隔一天、每2天、每3天、每4天、或每5天)施用低剂量的柠檬酸铁。有几种可被测量的全身性铁状态的标志物，来确定IDA患者是否具有足够的铁储存来维持足够的健康。这些标志物可以是循环铁储存、储存在铁结合复合物中的铁、或这两者，一般也被称为铁储存参数。铁储存参数可以包括，例如，血细胞比容、血红蛋白浓度(Hb)、总铁结合力(TIBC)、TSAT、血清铁水平、作为可持续组织铁水平或组织铁浓度来测量的组织铁水平(例如，肝脏铁水平、脾脏铁水平)、血清铁蛋白水平、血浆促红细胞生成素水平和FEP水平。在这些之中，血细胞比容、血红蛋白浓度(Hb)、总铁结合力(TIBC)、TSAT和血清铁水平通常被称为循环铁储存。肝脏铁水平、脾脏铁水平和血清铁蛋白水平通常被称为储存的铁或铁结合复合物中储存的铁。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的一种或更多种铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0038] 在具体的方面，本文提供的是改善患有IDA和/或被诊断患有IDA的对象中的一种或更多种铁储存参数的方法，包括向所述对象口服施用柠檬酸铁或其药物组合物。参见，例如，下文的章节4.2，关于治疗的患者群体，下文的章节4.3，关于柠檬酸铁或其药物组合物的给药和施用，以及下文的章节4.5，关于柠檬酸铁和其药物组合物的形式。在某些实施方式中，所述一种或更多种铁储存参数选自血细胞比容、血红蛋白浓度(Hb)、总铁结合力(TIBC)、TSAT、血清铁水平、作为可持续组织铁水平或组织铁浓度来测量的组织铁水平(例如，肝脏铁水平、脾脏铁水平)、血清铁蛋白水平、血浆促红细胞生成素水平和FEP水平。在具体的实施方式中，所述对象以一定频率(例如，每天、每隔一天、每2天、每3天、每4天、或每5天)施用低剂量的柠檬酸铁。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的一种或更多种铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋

白水平、血清铁水平、组织铁水平(例如,可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种铁储存参数,例如,血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如,可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如,每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中,施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0039] 在具体的方面,本文提供的是提高或维持患有IDA和/或被诊断患有IDA的对象中的血清铁蛋白水平的方法,包括向所述对象口服施用柠檬酸铁或其药物组合物。参见,例如,下文的章节4.2,关于治疗的患者群体,下文的章节4.3,关于柠檬酸铁或其药物组合物的给药和施用,以及下文的章节4.5,关于柠檬酸铁和其药物组合物的形式。在具体的实施方式中,所述对象以一定频率(例如,每天、每隔一天、每2天、每3天、每4天、或每5天)施用低剂量的柠檬酸铁。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的血清铁蛋白水平。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的血清铁蛋白水平(例如,每1个月、2个月、3个月、4个月、5个月、6个月或更久监测)。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的一种或更多种其他铁储存参数,例如,血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如,可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种其他铁储存参数,例如,血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如,可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如,每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中,施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0040] 肝脏的铁蛋白储存是身体内储存铁的主要来源。铁蛋白是一种细胞内蛋白质,其以受控的方式储存铁和释放铁。医学上,血液样品中和/或肝脏组织的样品中存在的铁蛋白数量反映了保存在肝脏中的铁的数量(虽然铁蛋白是遍在性的,可以在肝脏之外的体内许多其他组织中存在)。铁蛋白充当了肝脏中无毒形式的储备铁,并将其转运到需要铁的区域。正常的铁蛋白血清水平,有时称为参考区间,通常是男性30-300ng/ml,女性15-200ng/ml。然而在IDA患者中,随着可用于铁蛋白结合的和保存在肝脏中的铁的数量降低,血清铁蛋白水平一般显著降低,其在身体丧失了吸收和/或储存铁的能力时出现。

[0041] 在某些实施方式中,根据本文描述的方法治疗IDA的对象经历5-15ng/ml、5-25ng/ml、5-50ng/ml、5-100ng/ml、5-200ng/ml、5-300ng/ml、5-400ng/ml、25-50ng/ml、25-100ng/ml、25-200ng/ml、25-300ng/ml、25-400ng/ml、50-100ng/ml、50-200ng/ml、50-300ng/ml、50-400ng/ml、100-200ng/ml、100-300ng/ml、100-400ng/ml、200-300ng/ml、或200-400ng/ml的血清铁蛋白水平的平均提高。在某些实施方式中,根据本文描述的方法治疗IDA的对象经历约5ng/ml或更多、约10ng/ml或更多、约25ng/ml或更多、约50ng/ml或更多、约100ng/ml或更多、约110ng/ml或更多、约120ng/ml或更多、约130ng/ml或更多、约140ng/ml或更多、约150ng/ml或更多、约160ng/ml或更多、约170ng/ml或更多、约180ng/ml或更多、约190ng/ml

或更多、约200ng/ml或更多、约210ng/ml或更多、约220ng/ml或更多、约230ng/ml或更多、约240ng/ml或更多、约250ng/ml或更多、约260ng/ml或更多、约270ng/ml或更多、约280ng/ml或更多、约290ng/ml或更多、约300ng/ml或更多、约310ng/ml或更多、约320ng/ml或更多、约330ng/ml或更多、约340ng/ml或更多、约350ng/ml或更多、约360ng/ml或更多、约370ng/ml或更多、约380ng/ml或更多、或约390ng/ml或更多的血清铁蛋白水平的平均提高。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历约1-100％、1-95％、10-95％、10-90％、10-85％、10-80％、10-75％、10-70％、10-65％、10-60％、10-50％、10-45％、10-40％、10-35％、10-30％、10-25％、10-20％、20-30％、20-40％、20-50％、20-60％、20-70％、20-80％、20-90％、30-90％、30-80％、30-70％、30-60％、30-50％、30-40％、40-90％、40-80％、40-70％、40-60％、40-50％、50-90％、50-80％、50-70％、50-65％、50-60％、60-90％、60-80％、60-75％、60-70％、70-90％、70％-80％、或80-90％的血清铁蛋白水平的平均提高。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历10％、15％、20％、25％、30％、35％、40％、45％、50％、55％、60％、65％、70％、75％、80％、85％、90％、95％或更多的血清铁蛋白水平的平均提高。在某些实施方式中，在所述柠檬酸铁或其药物组合物被施用给所述对象一段时间(例如，1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更久)之后，产生血清铁蛋白水平的平均提高。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历他们的血清铁蛋白水平的维持，从而他们的血清铁蛋白水平在施用柠檬酸铁或药物组合物期间保持基本上不变。

[0042] 如本文使用的，在铁储存参数的水平的上下文中，术语“基本上不变”是指所述铁储存参数的水平改变小于5％。

[0043] 在具体的方面，本文提供的是提高或维持患有IDA和/或被诊断患有IDA的对象中作为可持续组织铁水平或组织铁浓度测量的组织铁水平(例如，肝脏铁水平、脾脏铁水平)的方法，包括向所述对象口服施用柠檬酸铁或其药物组合物。在具体的实施方式中，所述组织铁水平作为可持续组织铁水平测量。参见，例如，下文的章节4.2，关于治疗的患者群体，下文的章节4.3，关于柠檬酸铁或其药物组合物的给药和施用，以及下文的章节4.5，关于柠檬酸铁和其药物组合物的形式。在具体的实施方式中，所述对象以一定频率(例如，每天、每隔一天、每2天、每3天、每4天、或每5天)施用低剂量的柠檬酸铁。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的组织铁水平(例如，可持续组织铁水平)。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的组织铁水平(例如，可持续组织铁水平)(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测)。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的一种或更多种其他铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种其他铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0044] 组织铁水平反映了组织(例如，肝脏、脾脏)中的铁含量，可以作为可持续组织铁水

平或组织铁浓度来测量。可持续组织铁水平和血清铁蛋白水平是中度缺铁的最敏感的实验室指标，在区分来自慢性失调的贫血的铁缺乏方面是特别有用的。可持续组织铁水平通过可持续铁的组织学分级来测定。正常的可持续肝脏铁水平通常大于3级。然而在IDA患者中，随着身体丧失吸收和/或储存铁的能力，可持续肝脏铁水平一般显著降低。

[0045] 在某些实施方式中，根据本文描述的方法治疗IDA的对象经历约1-100％、1-95％、10-95％、10-90％、10-85％、10-80％、10-75％、10-70％、10-65％、10-60％、10-50％、10-45％、10-40％、10-35％、10-30％、10-25％、10-20％、20-30％、20-40％、20-50％、20-60％、20-70％、20-80％、20-90％、30-90％、30-80％、30-70％、30-60％、30-50％、30-40％、40-90％、40-80％、40-70％、40-60％、40-50％、50-90％、50-80％、50-70％、50-65％、50-60％、60-90％、60-80％、60-75％、60-70％、70-90％、70％-80％、或80-90％的组织铁水平(例如，可持续组织铁水平)的平均提高。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历10％、15％、20％、25％、30％、35％、40％、45％、50％、55％、60％、65％、70％、75％、80％、85％、90％、95％或更多的组织铁水平(例如，可持续组织铁水平)的平均提高。在某些实施方式中，在所述柠檬酸铁或其药物组合物被施用给所述对象一段时间(例如，1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更久)之后，产生组织铁水平(例如，可持续组织铁水平)的平均提高。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历他们的组织铁水平(例如，可持续组织铁水平)的维持，从而他们的组织铁水平(例如，可持续组织铁水平)在施用柠檬酸铁或药物组合物期间保持基本上不变。

[0046] 在具体的方面，本文提供的是提高或维持患有IDA和/或被诊断患有IDA的对象中的TSAT值的方法，包括向所述对象口服施用柠檬酸铁或其药物组合物。参见，例如，下文的章节4.2，关于治疗的患者群体，下文的章节4.3，关于柠檬酸铁或其药物组合物的给药和施用，以及下文的章节4.5，关于柠檬酸铁和其药物组合物的形式。在具体的实施方式中，所述对象以一定频率(例如，每天、每隔一天、每2天、每3天、每4天、或每5天)施用低剂量的柠檬酸铁。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的TSAT值。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的TSAT值(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测)。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的一种或更多种其他铁储存参数，例如，血红蛋白浓度、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种其他铁储存参数，例如，血红蛋白浓度、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0047] 除了储存的铁之外，少量的铁，一般约3到4mg，与称为转铁蛋白的蛋白质结合在血浆中循环。因而，血清铁水平可以由血液中循环的、与蛋白质转铁蛋白结合的铁的数量来代表。转铁蛋白是肝脏产生的一种糖蛋白，其可以结合一个或两个三价铁(铁(III)或Fe3+)离

子。它是血液中最普遍的和动态性的铁携带者，因而是身体转运储存的铁用于全身的能力的主要部分。转铁蛋白饱和度(或TSAT)作为百分比来测量，按照血清铁和总铁结合力的比值乘以100来计算。这个数值告诉临床医师有多少血清铁实际地结合到可以结合铁的转铁蛋白总量。例如，35％的TSAT值意味着血液样品中转铁蛋白的可用的铁结合位点的35％被铁占据。在非IDA患者中，典型的TSAT值大约是男性15-50％，女性12-45％。然而在IDA患者中，随着可用于转铁蛋白结合的铁的数量降低，TSAT值一般显著降低，其在身体丧失了吸收和/或储存铁的能力时出现。

[0048] 在某些实施方式中，根据本文描述的方法治疗IDA的对象经历约1-10％、1-15％、1-20％、1-25％、1-50％、1-75％、1-100％、5-15％、5-20％、5-25％、5-50％、5-75％、5-100％、10-15％、10-20％、10-25％、10-50％、10-75％、10-100％、15-20％、15-25％、15-50％、15-75％、15-100％、20-25％、20-50％、20-75％、20-100％、25-50％、25-75％、25-100％、50-75％、或50-100％的TSAT值的平均提高。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历1％、2％、3％、4％、5％、6％、7％、8％、9％、10％、11％、12％、13％、14％、15％、16％、17％、18％、19％、20％、21％、22％、23％、24％、25％、50％、75％、100％或更多的TSAT值的平均提高。在某些实施方式中，在所述柠檬酸铁或其药物组合物被施用给所述对象一段时间(例如，1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更久)之后，产生TSAT值的平均提高。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历他们的TSAT值的维持，从而他们的TSAT值在施用柠檬酸铁或药物组合物期间保持基本上不变。

[0049] 在具体的方面，本文提供的是提高或维持患有IDA和/或被诊断患有IDA的对象中的血红蛋白浓度的方法，包括向所述对象口服施用柠檬酸铁或其药物组合物。参见，例如，下文的章节4.2，关于治疗的患者群体，下文的章节4.3，关于柠檬酸铁或其药物组合物的给药和施用，以及下文的章节4.5，关于柠檬酸铁和其药物组合物的形式。在具体的实施方式中，所述对象以一定频率(例如，每天、每隔一天、每2天、每3天、每4天、或每5天)施用低剂量的柠檬酸铁。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的血红蛋白浓度。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的血红蛋白浓度(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测)。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的一种或更多种其他铁储存参数，例如，TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种其他铁储存参数，例如，TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0050] 血红蛋白浓度是每体积(分升)全血的血红蛋白(克)浓度的度量。血红蛋白浓度还可以作为质量或重量分数来测量，表示为百分比(％)。对于非IDA患者，典型的血红蛋白浓度对于男性为13.8-18.0g/dl(即，8.56-11.17mmol/L)，对于女性为12.1-15.1g/dl(即，

7.51-9.37mmol/L)，对于而为11.0-16.0g/dl(即，6.83-9.93mmol/L)，对于怀孕女性为11.0-14.0g/dl(即，6.83-8.69mmol/L)。然而在IDA患者中，随着身体丧失吸收和/或储存铁的能力，血红蛋白浓度可能降低到低于正常范围。

[0051] 在某些实施方式中，根据本文描述的方法治疗IDA的对象经历0.1-0.5g/dl、0.1-1g/dl、0.1-1.5g/dl、0.1-2g/dl、0.1-2.5g/dl、0.1-3g/dl、0.1-3.5g/dl、0.1-4g/dl、0.1-4.5g/dl、0.1-5g/dl、0.4-0.8g/dl、0.4-1g/dl、0.4-1.5g/dl、0.4-2g/dl、0.4-2.5g/dl、0.4-3g/dl、0.4-3.5g/dl、0.4-4g/dl、0.4-4.5g/dl、0.4-5g/dl、0.5-0.8g/dl、0.5-1g/dl、0.5-1.5g/dl、0.5-2g/dl、0.5-2.5g/dl、0.5-3g/dl、0.5-3.5g/dl、0.5-4g/dl、0.5-4.5g/dl、0.5-5g/分升1-1.5g/dl、1-2g/dl、1-2.5g/dl、1-3g/dl、1-3.5g/dl、1-4g/dl、1-4.5g/dl、1-5g/dl、1.5-2g/dl、1.5-2.5g/dl、1.5-3g/dl、1.5-3.5g/dl、1.5-4g/dl、1.5-4.5g/dl、1.5-5g/dl、2-2.5g/dl、2-3g/dl、2-3.5g/dl、2-4g/dl、2-4.5g/dl或2-5g/dl的血红蛋白浓度的平均提高。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历约0.1g/dl或更多、约0.2g/dl或更多、约0.3g/dl或更多、约0.4g/dl或更多、约0.5g/dl或更多、约1g/dl或更多、约1.5g/dl或更多、约2g/dl或更多、约2.5g/dl或更多、约3g/dl或更多、约3.5g/dl或更多、约4g/dl或更多、约4.5g/dl或更多、或约5g/dl或更多的血红蛋白浓度的平均提高。在某些实施方式中，血红蛋白浓度的提高不超过2g/dl、3g/dl、4g/dl或5g/dl。在某些实施方式中，在所述柠檬酸铁或其药物组合物被施用给所述对象一段时间(例如，1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更久)之后，产生血红蛋白浓度的平均提高。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历他们的血红蛋白浓度的维持，从而他们的血红蛋白浓度在施用柠檬酸铁或药物组合物期间保持基本上不变。

[0052] 在具体的方面，本文提供的是提高或维持患有IDA和/或被诊断患有IDA的对象中的血细胞比容水平的方法，包括向所述对象口服施用柠檬酸铁或其药物组合物。参见，例如，下文的章节4.2，关于治疗的患者群体，下文的章节4.3，关于柠檬酸铁或其药物组合物的给药和施用，以及下文的章节4.5，关于柠檬酸铁和其药物组合物的形式。在具体的实施方式中，所述对象以一定频率(例如，每天、每隔一天、每2天、每3天、每4天、或每5天)施用低剂量的柠檬酸铁。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的血细胞比容水平。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的血细胞比容水平(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测)。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的一种或更多种其他铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、TIBC值、血浆促红细胞生成素水平和/或FEP水平。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种其他铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0053] 血细胞比容也称为红细胞压积或红血球体积分数，是血液中红血细胞的体积百分

比。对于非IDA患者，血细胞比容一般是男性约45％的血容量，女性约40％的血容量。然而在IDA患者中，由于不良的铁吸收和/或不良的铁储存能力，血细胞比容常常显著地耗尽。

[0054] 在某些实施方式中，根据本文描述的方法治疗IDA的对象经历约1-25％、1-20％、1-15％、1-10％、5-15％、5-20％、5-25％、10-15％、10-20％、10-25％、15-20％、15-25％、或20-25％的血细胞比容水平的提高。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历1％、2％、3％、4％、5％、6％、7％、8％、9％、10％、11％、12％、13％、14％、15％、16％、17％、18％、19％、20％、21％、22％、23％、24％、25％或更多的血细胞比容水平的提高。在某些实施方式中，在所述柠檬酸铁或其药物组合物被施用给所述对象一段时间(例如，1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更久)之后，产生血细胞比容水平的提高。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历他们的血细胞比容水平的维持，从而他们的血细胞比容水平在施用柠檬酸铁或药物组合物期间保持基本上不变。

[0055] 在具体的方面，本文提供的是降低或维持患有IDA和/或被诊断患有IDA的对象中的总铁结合力(TIBC)值的方法，包括向所述对象口服施用柠檬酸铁或其药物组合物。参见，例如，下文的章节4.2，关于治疗的患者群体，下文的章节4.3，关于柠檬酸铁或其药物组合物的给药和施用，以及下文的章节4.5，关于柠檬酸铁和其药物组合物的形式。在具体的实施方式中，所述对象以一定频率(例如，每天、每隔一天、每2天、每3天、每4天、或每5天)施用低剂量的柠檬酸铁。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的TIBC值。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的TIBC值(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测)。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的一种或更多种其他铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、血浆促红细胞生成素水平和/或FEP水平。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种其他铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、血浆促红细胞生成素水平和/或FEP水平(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0056] 总铁结合力(TIBC)是血液用蛋白质转铁蛋白结合铁的能力的度量。TIBC一般通过抽取血液样品，测量样品可以携带的铁的最大数量来测量。因而，TIBC间接地度量转铁蛋白，其是血液中转运铁的蛋白质。对于非IDA患者，TIBC的典型的质量或摩尔度量分别在250-370μg/dl或45-66μmol/L的范围内。然而在IDA患者中，随着身体必需产生更多的转铁蛋白以图释放铁给红血球前体细胞来产生血红蛋白，TIBC一般提高到高于这些水平。

[0057] 在某些实施方式中，根据本文描述的方法治疗IDA的对象经历约1-25％、1-20％、1-15％、1-10％、5-15％、5-20％、5-25％、10-15％、10-20％、10-25％、15-20％、15-25％、或20-25％的TIBC值的降低。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历1％、2％、3％、4％、5％、6％、7％、8％、9％、10％、11％、12％、13％、14％、15％、16％、17％、18％、19％、20％、21％、22％、23％、24％、25％或更多的TIBC值的降低。在某些实施方式中，

在所述柠檬酸铁或其药物组合物被施用给所述对象一段时间(例如,1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更久)之后,产生TIBC值的降低。在某些实施方式中,根据本文描述的方法治疗IDA的对象经历他们的TIBC值的维持,从而他们的TIBC值在施用柠檬酸铁或药物组合物期间保持基本上不变。

[0058] 在具体的方面,本文提供的是提高或维持患有IDA和/或被诊断患有IDA的对象中的血清铁水平的方法,包括向所述对象口服施用柠檬酸铁或其药物组合物。参见,例如,下文的章节4.2,关于治疗的患者群体,下文的章节4.3,关于柠檬酸铁或其药物组合物的给药和施用,以及下文的章节4.5,关于柠檬酸铁和其药物组合物的形式。在具体的实施方式中,所述对象以一定频率(例如,每天、每隔一天、每2天、每3天、每4天、或每5天)施用低剂量的柠檬酸铁。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之前评估血清铁水平。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的血清铁水平(例如,每1个月、2个月、3个月、4个月、5个月、6个月或更久监测)。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的一种或更多种其他铁储存参数,例如,血红蛋白浓度、TSAT值、血清铁蛋白水平、组织铁水平(例如,可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种其他铁储存参数,例如,血红蛋白浓度、TSAT值、血清铁蛋白水平、组织铁水平(例如,可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如,每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中,施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0059] 铁的血清池是身体中所有铁的部分,其在血液中循环,主要与转铁蛋白结合。这个池中的铁非常快速地周转,代表了从一个位置到另一个位置转运中的铁。血清铁水平是血液中的循环铁的池的数量的度量。正常的血清铁水平通常是男性65-176μg/dl,女性50-170μg/dl,儿童50-120μg/dl。然而在IDA患者中,随着身体丧失吸收和/或储存铁的能力,血清铁水平一般降低到低于正常范围。

[0060] 在某些实施方式中,根据本文描述的方法治疗IDA的对象经历约1-100%、1-95%、10-95%、10-90%、10-85%、10-80%、10-75%、10-70%、10-65%、10-60%、10-50%、10-45%、10-40%、10-35%、10-30%、10-25%、10-20%、20-30%、20-40%、20-50%、20-60%、20-70%、20-80%、20-90%、30-90%、30-80%、30-70%、30-60%、30-50%、30-40%、40-90%、40-80%、40-70%、40-60%、40-50%、50-90%、50-80%、50-70%、50-65%、50-60%、60-90%、60-80%、60-75%、60-70%、70-90%、70%-80%、或80-90%的血清铁水平的平均提高。在某些实施方式中,根据本文描述的方法治疗IDA的对象经历10%、15%、20%、25%、30%、35%、40%、45%、50%、55%、60%、65%、70%、75%、80%、85%、90%、95%或更多的血清铁水平的平均提高。在某些实施方式中,在所述柠檬酸铁或其药物组合物被施用给所述对象一段时间(例如,1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更久)之后,产生血清铁水平的平均提高。在某些实施方式中,根据本文描述的方法治疗IDA的对象经历他们的血清铁水平的维持,从而他们的血清铁水平在施用柠檬酸铁或药物组合物期间保持基本上不变。

[0061] 在具体的方面，本文提供的是降低或维持患有IDA和/或被诊断患有IDA的对象中的血浆促红细胞生成素水平的方法，包括向所述对象口服施用柠檬酸铁或其药物组合物。参见，例如，下文的章节4.2，关于治疗的患者群体，下文的章节4.3，关于柠檬酸铁或其药物组合物的给药和施用，以及下文的章节4.5，关于柠檬酸铁和其药物组合物的形式。在具体的实施方式中，所述对象以一定频率(例如，每天、每隔一天、每2天、每3天、每4天、或每5天)施用低剂量的柠檬酸铁。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的血浆促红细胞生成素水平。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的血浆促红细胞生成素水平(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测)。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的一种或更多种其他铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值和/或FEP水平。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种其他铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值和/或FEP水平(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0062] 促红细胞生成素是一种肾脏的糖蛋白激素，其是定向的红细胞祖细胞的增殖和分化的专性的生长因子。血浆促红细胞生成素水平通常随着血细胞比容水平降低而提高。正常的血浆促红细胞生成素水平通常是成年人4.1-19.5mU/ml，儿童9-28mU/ml。然而在IDA患者中，随着身体丧失吸收和/或储存铁的能力，血浆促红细胞生成素水平一般提高到高于正常范围。

[0063] 在某些实施方式中，根据本文描述的方法治疗IDA的对象经历约1-100％、1-95％、10-95％、10-90％、10-85％、10-80％、10-75％、10-70％、10-65％、10-60％、10-50％、10-45％、10-40％、10-35％、10-30％、10-25％、10-20％、20-30％、20-40％、20-50％、20-60％、20-70％、20-80％、20-90％、30-90％、30-80％、30-70％、30-60％、30-50％、30-40％、40-90％、40-80％、40-70％、40-60％、40-50％、50-90％、50-80％、50-70％、50-65％、50-60％、60-90％、60-80％、60-75％、60-70％、70-90％、70％-80％、或80-90％的血浆促红细胞生成素水平的平均降低。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历10％、15％、20％、25％、30％、35％、40％、45％、50％、55％、60％、65％、70％、75％、80％、85％、90％、95％或更多的血浆促红细胞生成素水平的平均降低。在某些实施方式中，在所述柠檬酸铁或其药物组合物被施用给所述对象一段时间(例如，1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更久)之后，产生血浆促红细胞生成素水平的平均提高。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历他们的血浆促红细胞生成素水平的维持，从而他们的血浆促红细胞生成素水平在施用柠檬酸铁或药物组合物期间保持基本上不变。

[0064] 在具体的方面，本文提供的是降低或维持患有IDA和/或被诊断患有IDA的对象中的游离红细胞性原卟啉(FEP)水平的方法，包括向所述对象口服施用柠檬酸铁或其药物组合物。参见，例如，下文的章节4.2，关于治疗的患者群体，下文的章节4.3，关于柠檬酸铁或

其药物组合物的给药和施用，以及下文的章节4.5，关于柠檬酸铁和其药物组合物的形式。在具体的实施方式中，所述对象以一定频率(例如，每天、每隔一天、每2天、每3天、每4天、或每5天)施用低剂量的柠檬酸铁。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的FEP水平。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的FEP水平(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测)。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的一种或更多种其他铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值和/或血浆促红细胞生成素水平。在某些实施方式中，在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种其他铁储存参数，例如，血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如，可持续组织铁水平)、血细胞比容水平、TIBC值和/或血浆促红细胞生成素水平(例如，每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中，施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0065] 在血红蛋白合成期间骨髓中缺少铁用于掺入血红素基团时，锌作为替代被掺入，形成称为锌卟啉(ZPP)的化合物。游离红细胞性原卟啉(FEP)是在提取和化学测量过程期间除去锌离子之后留下的复合物。FEP水平的提高是骨髓中铁不足的第一指标之一。正常的FEP水平通常是30-40μg/dl红血细胞。然而在IDA患者中，随着身体丧失吸收和/或储存铁的能力，血清铁水平一般提高到高于正常范围。

[0066] 在某些实施方式中，根据本文描述的方法治疗IDA的对象经历约1-100％、1-95％、10-95％、10-90％、10-85％、10-80％、10-75％、10-70％、10-65％、10-60％、10-50％、10-45％、10-40％、10-35％、10-30％、10-25％、10-20％、20-30％、20-40％、20-50％、20-60％、20-70％、20-80％、20-90％、30-90％、30-80％、30-70％、30-60％、30-50％、30-40％、40-90％、40-80％、40-70％、40-60％、40-50％、50-90％、50-80％、50-70％、50-65％、50-60％、60-90％、60-80％、60-75％、60-70％、70-90％、70％-80％、或80-90％的FEP水平的平均降低。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历10％、15％、20％、25％、30％、35％、40％、45％、50％、55％、60％、65％、70％、75％、80％、85％、90％、95％或更多的FEP水平的平均降低。在某些实施方式中，在所述柠檬酸铁或其药物组合物被施用给所述对象一段时间(例如，1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更久)之后，产生FEP水平的平均提高。在某些实施方式中，根据本文描述的方法治疗IDA的对象经历他们的FEP水平的维持，从而他们的FEP水平在施用柠檬酸铁或药物组合物期间保持基本上不变。

[0067] 治疗IDA一般有三种方法。第一种方法是食用高铁的食物。如果这不足够，则临床医师可以开具口服的或静脉内的(IV)补铁剂的处方。静脉内(IV)补铁是一种通过用针头注射到肌肉或静脉中的释放铁的方法。接受IV铁的IDA患者通常这样做，因为他们不能耐受口服的铁。通过附着于含有铁溶液的IV袋子的针头，静脉内铁被递送入IDA患者的静脉。该过程在医生办公室或门诊进行，取决于医师开具处方的治疗可能花费数小时。患者通常在几次就诊的过程中接受铁注射直到他或她的铁水平正确。在某些情况下，IDA患者可能需要永久性IV铁补充。IV铁与短期的副作用相关，例如胃肠疼痛(例如，恶心和痉挛)、呼吸问题、皮

肤问题(例如,皮疹)、胸痛、低血压、过敏症和死亡,以及长期毒性,包括动脉粥样硬化发展、感染和提高的死亡率(Quinibi,Arzneimittelforschung(2010)60,399-412)。此外,许多门诊,特别是社区位置,都缺乏施用静脉内铁的装备。这使得大部分IDA患者没有进行静脉内铁治疗。

[0068] 此外,IDA患者还可能服用一种或更多种红细胞生成刺激剂(ESA)以控制贫血。ESA通过帮助身体产生红血细胞来起作用。这些红血细胞然后从骨髓释放到血流中,在此它们帮助维持血液铁水平。红细胞生成刺激剂,通常缩写为ESA,是与细胞因子促红细胞生成素在结构和/或功能上类似的试剂,其刺激身体的红血细胞产生(红血细胞生成)。典型的ESA在结构上和生物学上类似于天然发生的蛋白质促红细胞生成素。商业上可获得的ESA的实例包括促红细胞生成素(Epo)、阿法依伯汀(Procrit/Epogen)、倍他依泊汀(NeoRecormon)、阿法达贝泊汀(Aranesp)和甲氧基聚乙二醇-倍他依泊汀(Mircera)。当前被批准在美国上市的两种ESA是阿法依伯汀(Procrit,Epogen)和阿法达贝泊汀(Aranesp)。

[0069] 使用ESA最常发生的副作用包括:高血压;肿胀;发烧;昏眩;恶心;以及注射部位的疼痛,等。除了这些副作用之外,使用ESA产生了几种安全问题。ESA提高了静脉血栓栓塞(静脉中的血凝块)的风险。ESA还可能导致血红蛋白过高,这使得患者有更高风险发生心脏病发作、中风、心力衰竭和死亡。另外,在某些情况下ESA可能使得铁减少恶化,并引起血小板增多症的提高。

[0070] 在具体的方面,本文提供的是降低或维持患有IDA和/或被诊断患有IDA的对象的静脉内铁和/或促红细胞生成刺激剂摄入的方法,包括向所述对象口服施用柠檬酸铁或其药物组合物。参见,例如,下文的章节4.2,关于治疗的患者群体,下文的章节4.3,关于柠檬酸铁或其药物组合物的给药和施用,以及下文的章节4.5,关于柠檬酸铁和其药物组合物的形式。在具体的实施方式中,所述对象以一定频率(例如,每天、每隔一天、每2天、每3天、每4天、或每5天)施用低剂量的柠檬酸铁。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之前评估所述对象的一种或更多种铁储存参数,例如,血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如,可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平。在某些实施方式中,在向所述对象施用柠檬酸铁或其药物组合物之后监测所述对象的一种或更多种其他铁储存参数,例如,血红蛋白浓度、TSAT值、血清铁蛋白水平、血清铁水平、组织铁水平(例如,可持续组织铁水平)、血细胞比容水平、TIBC值、血浆促红细胞生成素水平和/或FEP水平(例如,每1个月、2个月、3个月、4个月、5个月、6个月或更久监测所述一种或更多种铁储存参数)。在某些实施方式中,施用柠檬酸铁或其药物组合物的对象不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0071] 在某些实施方式中,根据本文描述的方法治疗IDA的对象经历约1-25%、1-20%、1-15%、1-10%、5-15%、5-20%、5-25%、10-15%、10-20%、10-25%、15-20%、15-25%、20-25%、1-100%、20-25%、20-30%、20-40%、20-50%、20-60%、20-70%、20-80%、20-90%、25-30%、25-45%、25-50%、25-75%、25-80%、25-85%、25-90%、25-95%、30-40%、30-60%、30-70%、30-80%、30-90%、40-50%、40-80%、40-95%、50-60%、50-75%、50-95%、60-70%、60-90%、60-95%、75-85%、75-95%、或75-100%的平均累积IV铁摄入的平均降低。在某些实施方式中,根据本文描述的方法治疗IDA的对象1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、11%、12%、13%、14%、15%、16%、17%、18%、19%、20%、21%、

22％、23％、24％、25％、30％、35％、40％、50％、55％、60％、65％、70％、75％、80％、85％、90％、95％或更多的平均累积IV铁摄入的平均降低。在某些实施方式中，在所述柠檬酸铁或其药物组合物被施用给所述对象一段时间(例如，1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更久)之后，产生平均累积IV铁摄入的平均降低。

[0072] 在某些实施方式中，根据本文描述的方法治疗IDA的对象经历约1-25％、1-20％、1-15％、1-10％、5-15％、5-20％、5-25％、10-15％、10-20％、10-25％、15-20％、15-25％、20-25％、1-100％、20-25％、20-30％、20-40％、20-50％、20-60％、20-70％、20-80％、20-90％、25-30％、25-45％、25-50％、25-75％、25-80％、25-85％、25-90％、25-95％、30-40％、30-60％、30-70％、30-80％、30-90％、40-50％、40-80％、40-95％、50-60％、50-75％、50-95％、60-70％、60-90％、60-95％、75-85％、75-95％、或75-100％的中值ESA摄入的降低。在某些实施方式中，根据本文描述的方法治疗IDA的对象1％、2％、3％、4％、5％、6％、7％、8％、9％、10％、11％、12％、13％、14％、15％、16％、17％、18％、19％、20％、21％、22％、23％、24％、25％、30％、35％、40％、50％、55％、60％、65％、70％、75％、80％、85％、90％、95％或更多的中值ESA摄入的降低。在某些实施方式中，在所述柠檬酸铁或其药物组合物被施用给所述对象一段时间(例如，1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月、9个月、10个月、11个月、12个月或更久)之后，产生中值ESA摄入的降低。

[0073] 4.2.患者群体

[0074] 术语“患者”和“对象”在此可互换地使用，是指动物。在某些实施方式中，根据本文公开的方法治疗的对象是哺乳动物，例如，人灵长类(例如，牛、猪、马、猫、狗、鼠，等)或灵长类(例如，猴或人类)。在优选的实施方式中，根据本文公开的方法治疗的患者是人类。

[0075] 在某些实施方式中，根据本文公开的方法治疗的对象是男性、或非怀孕的或非哺乳的女性。在某些实施方式中，根据本文公开的方法治疗的患者是18岁以上的人类。

[0076] 在某些实施方式中，根据本文公开的方法治疗的患者不患有高磷酸血症和/或未被诊断患有高磷酸血症。在其他实施方式中，根据本文公开的方法治疗的患者是高血糖的。

[0077] 在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有与慢性肾病(CKD)相关的IDA。CKD是一种特征在于肾脏功能随着时间逐渐损失的状况，IDA是CKD的常见并发症。肾小球过滤率(GFR)<60ml/分钟/1.73m^{2}持续3个月的所有个体被分类为患有CKD，不管是否存在肾脏损坏。根据严重程度，CKD可以分类为五期。1期是最轻微的，通常引起少数症状。2期的特征在于GFR的轻度降低(60-89ml/分钟/1.73m^2)，伴有肾脏损坏。3期的特征在于GFR的中度降低(30-59ml/分钟/1.73m^2)。4期的特征在于GFR的严重降低(15-29ml/分钟/1.73m^2)。5期的特征在于确定的肾衰竭(GFR<15ml/分钟/1.73m^2)。5期是严重的疾病，如果不治疗有不良的预期寿命。需要透析或肾脏移植的患有CKD的个体一般被称为晚期肾病(ESRD)患者。因此，当患者得到CKD的非透析依赖性早期阶段的结论时，患者传统上被归类为ESRD患者。在此之前，这些患者被称为非透析依赖性CKD(ND-CKD)患者。一般地，在药学上必需透析之前，患者从1期进展到4期。然而，还没有开始透析或没有被建议移植的5期患者也是非透析依赖性CKD患者。在各种实施方式中，IDA患者是3-5期CKD患者。

[0078] 在某些实施方式中，根据本文公开的方法治疗的患者不患有和/或未被诊断患有慢性肾病。在某些实施方式中，根据本文公开的方法治疗的患者不患有和/或未被诊断患有

1、2、3、4或5期慢性肾病。在某些实施方式中，根据本文公开的方法治疗的患者不患有和/或未被诊断患有末期慢性肾病。在某些实施方式中，根据本文公开的方法治疗的患者不患有和/或未被诊断患有慢性肾病和/或高磷酸血症。

[0079] 在某些其他实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有慢性肾病。在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有1、2、3、4或5期慢性肾病。在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有末期慢性肾病。在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有慢性肾病并在接受透析。在其他实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有慢性肾病并且没有接受透析。

[0080] 在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大约9克/dl或更高，例如，大约9.5克/dl、10克/dl、11克/dl、11.5克/dl或12克/dl的血红蛋白浓度。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大约9克/dl，以及小于或等于大约12.5克/dl、12克/dl或11.5克/dl的血红蛋白浓度。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大约6克/dl到大约8克/dl、大约6克/dl到大约10克/dl、大约6克/dl到大约12克/dl、大约7克/dl到大约9克/dl、大约7克/dl到大约11克/dl、大约7克/dl到大约13克/dl、大约8克/dl到大约10克/dl、大约8克/dl到大约12克/dl、大约9克/dl到大约11克/dl、大约9克/dl到大约12克/dl、大约9克/dl到大约13克/dl、大约10克/dl到大约11克/dl、大约10克/dl到大约12克/dl、大约10克/dl到大约13克/dl、大约11克/dl到大约12克/dl、大约11克/dl到大约13克/dl、或大约12克/dl到大约13克/dl的血红蛋白浓度。

[0081] 在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有小于50％、45％、40％、35％、30％、25％、20％、15％、12％或10％的TSAT值。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有5％到50％、5％到45％、5％到40％、5％到35％、5％到30％、5％到25％、5％到20％、5％到15％、5％到12％、5％到10％、10％到50％、10％到45％、10％到40％、10％到35％、10％到30％、10％到25％、10％到20％、10％到15％、10％到12％、12％到50％、12％到45％、12％到40％、12％到35％、12％到30％、12％到25％、12％到20％、12％到15％、15％到50％、15％到45％、15％到40％、15％到35％、15％到30％、15％到25％、15％到20％、20％到50％、20％到45％、20％到40％、20％到35％、20％到30％、20％到25％、30％到50％、30％到45％、30％到40％、30％到35％、40％到50％、40％到45％、或45％到50％的TSAT值。在某些实施方式中，其中根据本文公开的方法治疗的患者是女性，在施用柠檬酸铁或其药物组合物之前，所述患者具有5％到45％、5％到35％、5％到25％、5％到15％、5％到12％、5％到10％、10％到45％、10％到35％、10％到25％、10％到15％、10％到12％、12％到45％、12％到35％、12％到25％、12％到15％、20％到45％、20％到35％、20％到25％、30％到45％、30％到35％、或40％到45％的TSAT值。在某些实施方式中，其中根据本文公开的方法治疗的患者是男性，所述患者在施用柠檬酸铁或其药物组合物之前具有5％到50％、5％到40％、5％到30％、5％到20％、5％到15％、5％到10％、10％到50％、10％到40％、10％到30％、10％到20％、10％到15％、15％到50％、15％到40％、15％到30％、15％到25％、15％到20％、20％到50％、20％到40％、20％到30％、20％到25％、30％到50％、30％到40％、30％到35％、40％到50％、40％到

45％、或45％到50％的TSAT值。

[0082] 在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有小于300ng/ml(例如，小于或等于275ng/ml、小于或等于250ng/ml、小于或等于225ng/ml、小于或等于200ng/ml、小于或等于175ng/ml、小于或等于150ng/ml、小于或等于125ng/ml、小于或等于100ng/ml、小于或等于75ng/ml、小于或等于50ng/ml、小于或等于25ng/ml、小于或等于15ng/ml、小于或等于10ng/ml、或小于或等于5ng/ml)的血清铁蛋白水平。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大约5ng/ml、10ng/ml、15ng/ml、20ng/ml、25ng/ml、30ng/ml、35ng/ml、40ng/ml、45ng/ml、50ng/ml、55ng/ml、60ng/ml、65ng/ml、70ng/ml、75ng/ml、80ng/ml、85ng/ml、90ng/ml、95ng/ml、100ng/ml、125ng/ml、150ng/ml、175ng/ml、200ng/ml、225ng/ml、250ng/ml、275ng/ml、或300ng/ml的血清铁蛋白水平。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大约5ng/ml到大约15ng/ml、大约5ng/ml到大约25ng/ml、大约5ng/ml到大约50ng/ml、大约15ng/ml到大约25ng/ml、大约15ng/ml到大约50ng/ml、大约15ng/ml到大约75ng/ml、大约25ng/ml到大约50ng/ml、大约25ng/ml到大约75ng/ml、大约25ng/ml到大约100ng/ml、大约50ng/ml到大约75ng/ml、大约50ng/ml到大约100ng/ml、大约50ng/ml到大约150ng/ml、大约75ng/ml到大约100ng/ml、大约75ng/ml到大约150ng/ml、大约100ng/ml到大约150ng/ml、大约150ng/ml到大约200ng/ml、大约150ng/ml到大约250ng/ml、大约100ng/ml到大约300ng/ml、大约200ng/ml到大约300ng/ml、或大约250ng/ml到大约300ng/ml的血清铁蛋白水平。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有5ng/ml到300ng/ml之间(例如，5ng/ml到250ng/ml之间，5ng/ml到150ng/ml之间，5ng/ml到100ng/ml之间，5ng/ml到75ng/ml之间，5ng/ml到50ng/ml之间，5ng/ml到25ng/ml之间，5ng/ml到15ng/ml之间，或5ng/ml到10ng/ml之间)的血清铁蛋白水平。

[0083] 在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有小于45％、40％、35％、30％、25％、20％、15％或10％的血细胞比容水平。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有10％到15％、10％到20％、10％到25％、10％到30％、10％到35％、10％到40％、10％到45％、15％到20％、15％到25％、15％到30％、15％到35％、15％到40％、15％到45％、20％到25％、20％到30％、20％到35％、20％到40％、25％到45％、25％到30％、25％到35％、25％到40％、25％到45％、30％到35％、30％到40％、30％到45％、35％到40％、35％到45％、或40％到45％的血细胞比容水平。

[0084] 在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大于390μg/dl(例如，大于或等于390μg/dl、大于或等于400μg/dl、大于或等于450μg/dl、大于或等于450μg/dl、大于或等于500μg/dl、大于或等于550μg/dl、大于或等于600μg/dl、大于或等于650μg/dl、大于或等于700μg/dl、大于或等于800μg/dl、大于或等于900μg/dl、大于或等于1000μg/dl、大于或等于1100μg/dl、或大于或等于1200μg/dl)的TIBC值。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大约390μg/dl、400μg/dl、450μg/dl、500μg/dl、550μg/dl、600μg/dl、650μg/dl、700μg/dl、800μg/dl、900μg/dl、1000μg/dl、1100μg/dl、或1200μg/dl的TIBC值。在某些

实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大约390μg/dl到大约600μg/dl、大约390μg/dl到大约800μg/dl、大约390μg/dl到大约1000μg/dl、大约390μg/dl到大约1200μg/dl、大约500μg/dl到大约700μg/dl、大约500μg/dl到大约900μg/dl、大约500μg/dl到大约1100μg/dl、大约600μg/dl到大约800μg/dl、大约600μg/dl到大约1000μg/dl、大约600μg/dl到大约1200μg/dl、大约700μg/dl到大约900μg/dl、大约700μg/dl到大约1100μg/dl、大约800μg/dl到大约1000μg/dl、大约800μg/dl到大约1200μg/dl、大约900μg/dl到大约1100μg/dl、或大约1000μg/dl到大约1200μg/dl ml的TIBC值。

[0085] 在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有2级的组织铁水平(例如，可持续组织铁水平)。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有1级的组织铁水平(例如，可持续组织铁水平)。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有0级的组织铁水平(例如，可持续组织铁水平)。

[0086] 在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有小于60μg/dl(例如，小于或等于50μg/dl、小于或等于40μg/dl、小于或等于30μg/dl、小于或等于20μg/dl、或小于或等于10μg/dl)的血清铁水平。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大约5μg/dl、10μg/dl、15μg/dl、20μg/dl、25μg/dl、30μg/dl、40μg/dl、50μg/dl、或60μg/dl的血清铁水平。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大约10μg/dl到大约20μg/dl、大约10μg/dl到大约30μg/dl、大约10μg/dl到大约40μg/dl、大约10μg/dl到大约50μg/dl、大约10μg/dl到大约60μg/dl、大约20μg/dl到大约30μg/dl、大约20μg/dl到大约40μg/dl、大约20μg/dl到大约50μg/dl、大约20μg/dl到大约60μg/dl、大约30μg/dl到大约40μg/dl、大约30μg/dl到大约50μg/dl、大约30μg/dl到大约60μg/dl、大约40μg/dl到大约50μg/dl、或大约40μg/dl到大约60μg/dl的血清铁水平。

[0087] 在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大于20mU/ml(例如，大于或等于20mU/ml、大于或等于25mU/ml、大于或等于30mU/ml、大于或等于40mU/ml、大于或等于50mU/ml、或大于或等于60mU/ml)的血浆促红细胞生成素水平。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大约20mU/ml、25mU/ml、30mU/ml、35mU/ml、40mU/ml、45mU/ml、50mU/ml、55mU/ml、或60mU/ml的血浆促红细胞生成素水平。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大约20mU/ml到大约30mU/ml、大约20mU/ml到大约40mU/ml、大约20mU/ml到大约50mU/ml、大约20mU/ml到大约60mU/ml、大约30mU/ml到大约40mU/ml、大约30mU/ml到大约50mU/ml、大约30mU/ml到大约60mU/ml、大约40mU/ml到大约50mU/ml、大约40mU/ml到大约60mU/ml、或大约50mU/ml到大约60mU/ml的血浆促红细胞生成素水平。

[0088] 在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大于50μg/dl(例如，大于或等于50μg/dl、大于或等于60μg/dl、大于或等于70μg/dl、大于或等于80μg/dl、大于或等于90μg/dl、或大于或等于100μg/dl)的FEP。在某些实施方式中，在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有50μg/dl、60μg/dl、70μg/dl、80μg/dl、90μg/dl、或100μg/dl的FEP水平。在某些实施方式中，

在施用柠檬酸铁或其药物组合物之前，根据本文公开的方法治疗的患者具有大约50μg/dl到大约60μg/dl、大约50μg/dl到大约70μg/dl、大约50μg/dl到大约80μg/dl、大约50μg/dl到大约90μg/dl、大约50μg/dl到大约100μg/dl、大约60μg/dl到大约70μg/dl、大约60μg/dl到大约80μg/dl、大约60μg/dl到大约90μg/dl、大约60μg/dl到大约100μg/dl、大约70μg/dl到大约80μg/dl、大约70μg/dl到大约90μg/dl、大约70μg/dl到大约100μg/dl、大约80μg/dl到大约90μg/dl、大约80μg/dl到大约100μg/dl、或大约90μg/dl到大约100μg/dl的FEP水平。

[0089] 在某些实施方式中，在施用柠檬酸铁或药物组合物之前，根据本文公开的方法治疗的患者具有以下一项、两项、三项或更多项、或所有：(i)小于或等于大约12.5克/dl、12克/dl或11.5克/dl的血红蛋白浓度；(ii)小于50％、45％、40％、35％、30％、25％、20％、15％、12％或10％的TSAT值；(iii)小于300ng/ml(小于或等于275ng/ml、小于或等于250ng/ml、小于或等于225ng/ml、小于或等于200ng/ml、小于或等于175ng/ml、小于或等于150ng/ml、小于或等于125ng/ml、小于或等于100ng/ml、小于或等于75ng/ml、小于或等于50ng/ml、小于或等于25ng/ml、小于或等于15ng/ml、小于或等于10ng/ml、或小于或等于5ng/ml)的血清铁蛋白水平；(iv)小于60μg/dl(例如，小于或等于50μg/dl、小于或等于40μg/dl、小于或等于30μg/dl、小于或等于20μg/dl、或小于或等于10μg/dl)的血清铁水平；(v)2级、1级或0级的组织铁水平(例如，可持续组织铁水平)；(vi)小于45％、40％、35％、30％、25％、20％、15％或10％的血细胞比容水平；(vii)大于390μg/dl(例如，大于或等于390μg/dl、大于或等于400μg/dl、大于或等于450μg/dl、大于或等于450μg/dl、大于或等于500μg/dl、大于或等于550μg/dl、大于或等于600μg/dl、大于或等于650μg/dl、大于或等于700μg/dl、大于或等于800μg/dl、大于或等于900μg/dl、大于或等于1000μg/dl、大于或等于1100μg/dl、或大于或等于1200μg/dl)的TIBC值；(viii)大于20mU/ml(例如，大于或等于20mU/ml、大于或等于25mU/ml、大于或等于30mU/ml、大于或等于40mU/ml、大于或等于50mU/ml、或大于或等于60mU/ml)的血浆促红细胞生成素水平；和/或(ix)大于50μg/dl(例如，大于或等于50μg/dl、大于或等于60μg/dl、大于或等于70μg/dl、大于或等于80μg/dl、大于或等于90μg/dl、或大于或等于100μg/dl)的FEP。在某些实施方式中，其中根据本文公开的方法治疗的患者是女性，在施用柠檬酸铁或其药物组合物之前，所述患者具有小于45％、40％、35％、30％、25％、20％、15％或12％的TSAT值。在某些实施方式中，其中根据本文公开的方法治疗的患者是男性，在施用柠檬酸铁或其药物组合物之前，所述患者具有小于50％、45％、40％、35％、30％、25％、20％、15％或10％的TSAT值。

[0090] 在某些实施方式中，在施用柠檬酸铁或药物组合物之前，根据本文公开的方法治疗的患者具有以下一项、两项、三项或更多项、或所有：(i)大约6克/dl到大约8克/dl、大约6克/dl到大约10克/dl、大约6克/dl到大约12克/dl、大约7克/dl到大约9克/dl、大约7克/dl到大约11克/dl、大约7克/dl到大约13克/dl、大约8克/dl到大约10克/dl、大约8克/dl到大约12克/dl、大约9克/dl到大约11克/dl、大约9克/dl到大约12克/dl、大约9克/dl到大约13克/dl、大约10克/dl到大约11克/dl、大约10克/dl到大约12克/dl、大约10克/dl到大约13克/dl、大约11克/dl到大约12克/dl、大约11克/dl到大约13克/dl、或大约12克/dl到大约13克/dl的血红蛋白浓度；(ii)10％到45％、12％到45％、20％到45％、20％到40％、10％到35％、20％到25％、15％到50％、10％到30％、或10％到30％的TSAT值；(iii)大约5ng/ml到大约15ng/ml、大约5ng/ml到大约25ng/ml、大约5ng/ml到大约50ng/ml、大约15ng/ml到大约

25ng/ml、大约15ng/ml到大约50ng/ml、大约15ng/ml到大约75ng/ml、大约25ng/ml到大约50ng/ml、大约25ng/ml到大约75ng/ml、大约25ng/ml到大约100ng/ml、大约50ng/ml到大约75ng/ml、大约50ng/ml到大约100ng/ml、大约50ng/ml到大约150ng/ml、大约75ng/ml到大约100ng/ml、大约75ng/ml到大约150ng/ml、大约100ng/ml到大约150ng/ml、大约150ng/ml到大约200ng/ml、大约150ng/ml到大约250ng/ml、大约100ng/ml到大约300ng/ml、大约200ng/ml到大约300ng/ml、或大约250ng/ml到大约300ng/ml的血清铁蛋白水平；(iv)大约10μg/dl到大约20μg/dl、大约10μg/dl到大约30μg/dl、大约10μg/dl到大约40μg/dl、大约10μg/dl到大约50μg/dl、大约10μg/dl到大约60μg/dl、大约20μg/dl到大约30μg/dl、大约20μg/dl到大约40μg/dl、大约20μg/dl到大约50μg/dl、大约20μg/dl到大约60μg/dl、大约30μg/dl到大约40μg/dl、大约30μg/dl到大约50μg/dl、大约30μg/dl到大约60μg/dl、大约40μg/dl到大约50μg/dl、或大约40μg/dl到大约60μg/dl的血清铁水平；(v)2级、1级或0级的组织铁水平(例如，可持续组织铁水平)；(vi)10％到15％、10％到20％、10％到25％、10％到30％、10％到35％、10％到40％、10％到45％、15％到20％、15％到25％、15％到30％、15％到35％、15％到40％、15％到45％、20％到25％、20％到30％、20％到35％、20％到40％、25％到45％、25％到30％、25％到35％、25％到40％、25％到45％、30％到35％、30％到40％、30％到45％、35％到40％、35％到45％、或40％到45％的血细胞比容水平；(vii)大约大约390μg/dl到大约600μg/dl、大约390μg/dl到大约800μg/dl、大约390μg/dl到大约1000μg/dl、大约390μg/dl到大约1200μg/dl、大约500μg/dl到大约700μg/dl、大约500μg/dl到大约900μg/dl、大约500μg/dl到大约1100μg/dl、大约600μg/dl到大约800μg/dl、大约600μg/dl到大约1000μg/dl、大约600μg/dl到大约1200μg/dl、大约700μg/dl到大约900μg/dl、大约700μg/dl到大约1100μg/dl、大约800μg/dl到大约1000μg/dl、大约800μg/dl到大约1200μg/dl、大约900μg/dl到大约1100μg/dl、或大约1000μg/dl到大约1200μg/dl的TIBC值；(viii)大约20mU/ml到大约30mU/ml、大约20mU/ml到大约40mU/ml、大约20mU/ml到大约50mU/ml、大约20mU/ml到大约60mU/ml、大约30mU/ml到大约40mU/ml、大约30mU/ml到大约50mU/ml、大约30mU/ml到大约60mU/ml、大约40mU/ml到大约50mU/ml、大约40mU/ml到大约60mU/ml、或大约50mU/ml到大约60mU/ml的血浆促红细胞生成素水平；和/或(ix)大约50μg/dl到大约60μg/dl、大约50μg/dl到大约70μg/dl、大约50μg/dl到大约80μg/dl、大约50μg/dl到大约90μg/dl、大约50μg/dl到大约100μg/dl、大约60μg/dl到大约70μg/dl、大约60μg/dl到大约80μg/dl、大约60μg/dl到大约90μg/dl、大约60μg/dl到大约100μg/dl、大约70μg/dl到大约80μg/dl、大约70μg/dl到大约90μg/dl、大约70μg/dl到大约100μg/dl、大约80μg/dl到大约90μg/dl、大约80μg/dl到大约100μg/dl、或大约90μg/dl到大约100μg/dl的FEP水平。在某些实施方式中，其中根据本文公开的方法治疗的患者是女性，在施用柠檬酸铁或其药物组合物之前，所述患者具有5％到45％、5％到35％、5％到25％、5％到15％、5％到12％、5％到10％、10％到45％、10％到35％、10％到25％、10％到15％、10％到12％、12％到45％、12％到35％、12％到25％、12％到15％、20％到45％、20％到35％、20％到25％、30％到45％、30％到35％、或40％到45％的TSAT值。在某些实施方式中，其中根据本文公开的方法治疗的患者是男性，所述患者在施用柠檬酸铁或其药物组合物之前具有5％到50％、5％到40％、5％到30％、5％到20％、5％到15％、5％到10％、10％到50％、10％到40％、10％到30％、10％到20％、10％到15％、15％到50％、15％到40％、15％到30％、15％到25％、15％到20％、20％到50％、20％到40％、20％到30％、20％

到25％、30％到50％、30％到40％、30％到35％、40％到50％、40％到45％、或45％到50％的TSAT值。

[0091] 在某些实施方式中，在施用第一剂的柠檬酸铁或其药物组合物的2周、3周、4周、1个月、2个月、3个月、4个月、5个月、6个月或更久之内，根据本文公开的方法治疗的患者没有服用磷酸盐结合剂药物。在某些实施方式中，在施用第一剂的柠檬酸铁或其药物组合物的2周、3周、4周、1个月、2个月、3个月、4个月、5个月、6个月或更久之内，根据本文公开的方法治疗的患者没有经历急性肾脏损伤。在某些实施方式中，在施用第一剂的柠檬酸铁或其药物组合物的2周、3周、4周、1个月、2个月、3个月、4个月、5个月、6个月或更久之内，根据本文公开的方法治疗的患者没有透析或被要求透析。在某些实施方式中，在第一剂的柠檬酸铁或其药物组合物的2周、3周、4周、5周、6周、1个月、2个月、3个月、4个月、5个月、6个月、7个月、8个月或更久之内，根据本文公开的方法治疗的患者预期不需要肾脏移植或开始透析。

[0092] 在某些实施方式中，在施用第一剂的柠檬酸铁或其药物组合物的2周、3周、4周、1个月、2个月、3个月、4个月、5个月、6个月或更久之内，根据本文公开的方法治疗的患者没有接受静脉内的铁。在某些实施方式中，在施用第一剂的柠檬酸铁或其药物组合物的2周、3周、4周、1个月、2个月、3个月、4个月、5个月、6个月或更久之内，根据本文公开的方法治疗的患者没有接受红细胞生成刺激剂(ESA)。在某些实施方式中，在施用第一剂的柠檬酸铁或其药物组合物的2周、3周、4周、1个月、2个月、3个月、4个月、5个月、6个月或更久之内，根据本文公开的方法治疗的患者没有接受静脉内的铁和红细胞生成刺激剂(ESA)。在某些实施方式中，根据本文公开的方法治疗的患者没有正在接受静脉内铁和/或红细胞生成刺激剂(ESA)。

[0093] 在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有IDA相关的一种、两种或更多种以下状况：慢性的失血；急性的失血；分娩；月经；月经过多；透析；慢性肾病(CKD)；功能性月经失调；重的子宫出血；尿路出血；血红蛋白尿；长期的内部出血；胃肠出血；血管发育异常；自发性肺部含铁血黄素沉着病；来自损伤、手术、急性创伤或频繁抽血的失血；出血性溃疡；胃溃疡；十二指肠溃疡；血管内溶血；长期的反复的咯血；结肠息肉；胃肠癌症(例如结肠癌、胃癌和肠癌)；胃肠失调(例如，炎症性肠病(IBD)和克罗恩病)；乳糜泻；外科的肠切除术后；肠切除术或旁路；惠普耳氏病；慢性心力衰竭；全身性炎症；寄生虫感染(例如疟疾和钩虫、带虫、吸虫、鞭虫、蛔虫、毛首鞭形线虫、或幽门螺杆菌的感染)；和/或妊娠。在某些实施方式中，根据本文公开的方法治疗的患者具有与IDA相关的质子泵抑制物使用；抗酸剂使用；非甾体抗炎药物(NSAID)(例如，阿司匹林、抗凝血剂，如氯吡格雷和华法林))使用；长期摄入醇类；长期摄入水杨酸盐；长期摄入类固醇；长期摄入非载体抗炎试剂；长期摄入红细胞生成刺激剂；铁饮食摄入不足和/或铁吸收不足；血红蛋白水平缺陷；儿童发育；儿童的精神运动性和认知发育；和/或屏气发作。

[0094] 铁饮食摄入不足、女性的失血以及传染性疾病也是IDA的主要原因。在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有与铁饮食摄入不足相关的IDA。在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有与铁吸收不足相关的IDA。在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有与铁饮食摄入不足和/或铁吸收不足相关的IDA。在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有与月经相关的IDA。在某些实施方式中，根据本文公开

的方法治疗的患者患有和/或被诊断患有与儿童出生相关的IDA。在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有与钩虫感染相关的IDA。在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有与疟疾相关的IDA。

[0095] 在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有与一种、两种或更多种以下状况相关的IDA：胃肠出血；血管发育异常；胃溃疡；十二指肠溃疡；结肠息肉；胃肠癌症(例如，结肠癌、胃癌和肠癌)；胃肠失调(例如，炎症性肠病(IBD)和克罗恩病)；乳糜泻；外科肠切除术后；肠切除术或旁路；和惠普耳氏病。在具体的实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有与胃肠癌症(例如，结肠癌、胃癌和肠癌)相关的IDA。

[0096] 在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有胃肠病症。在某些实施方式中，根据本文公开的方法治疗的患者患有和/或被诊断患有炎症性肠病、炎症性肠综合征、溃疡性结肠炎、克罗恩病、显微镜下结肠炎(例如，胶原性或淋巴细胞性结肠炎)和/或化学诱导的结肠炎(例如，NSAID(非甾体抗炎药)诱导的结肠炎)。在某些实施方式中，根据本文公开的方法治疗的患者患有胃肠出血。在具体的实施方式中，根据本文公开的方法治疗的患者患有与胃肠状况相关的胃肠出血，所述胃肠状况例如炎症性肠病、炎症性肠综合征、溃疡性结肠炎、克罗恩病、显微镜下结肠炎(例如，胶原性或淋巴细胞性结肠炎)或化学诱导的结肠炎(例如，NSAID(非甾体抗炎药)诱导的结肠炎)。

[0097] 在某些实施方式中，根据本文公开的方法治疗的患者在开始施用柠檬酸铁的2周、3周、4周、5周、6周或更久之内没有接受输血。在其他实施方式中，根据本文公开的方法治疗的患者在开始施用柠檬酸铁的2周、3周、4周、5周、6周或更久之内接受了输血。

[0098] 在某些实施方式中，根据本文公开的方法治疗的患者在开始施用柠檬酸铁的1个月、3个月、6个月、1年、2年、3年、4年、5年或6年之内未被诊断患有恶性肿瘤。在其他实施方式中，根据本文公开的方法治疗的患者被诊断患有恶性肿瘤。在某些实施方式中，根据本文公开的方法治疗的患者未被诊断患有血色沉着病。在其他实施方式中，根据本文公开的方法治疗的患者被诊断患有血色沉着病。在具体的实施方式中，根据本文公开的方法治疗的患者没有对铁产品的已知的变态反应，和/或没有对口服柠檬酸铁的早先的不耐受。

[0099] 在具体的实施方式中，根据本文公开的方法治疗的患者满足下文的章节5中的一个、两个、三个或更多个入选标准，和/或不满足下文的章节5中的一个、两个、三个或更多个排除标准。

[0100] 4.3.给药和施用

[0101] 在一个方面，根据本文公开的方法，柠檬酸铁或其药物组合物按照必需的和/或希望治疗IDA的频率被施用给对象。在根据本文公开的方法的某些实施方式中，柠檬酸铁或其药物组合物每天一次施用给对象。在根据本文公开的方法的某些实施方式中，柠檬酸铁或其药物组合物每天两次施用给对象。在根据本文公开的方法的某些实施方式中，柠檬酸铁或其药物组合物每天三次施用给对象。在根据本文公开的方法的具体实施方式中，柠檬酸铁或其药物组合物口服施用给对象。

[0102] 在各种方面中，施用给对象的柠檬酸铁或其药物组合物的日剂量在一天内分开。举例来说，柠檬酸铁的单日剂量可以是6克，这6克可以分布在一天中，从而2克在早上服用，2克在下午服用，最后2克在晚上服用，一天内总共6克。

[0103] 可以制备本文公开的药物组合物，例如，片剂和其他口服剂型以容纳一定数量的柠檬酸铁剂量。可以施用给对象的包含柠檬酸铁的药物组合物在下文的章节4.5中描述。在某些实施方式中，单个片剂或其他口服剂型的重量取决于要生产的最终剂量：例如，每片剂125mg、250mg、500mg、667mg、750mg和1,000mg柠檬酸铁。在具体的实施方式中，在包含等价于大约210mg三价铁的大约1克柠檬酸铁的片剂剂型中提供柠檬酸铁。施用给对象的片剂或其他口服剂型的数量可以调节，以符合要施用的期望的柠檬酸铁数量。例如，如果对象被指导以单次剂量每天服用4克柠檬酸铁，对象可以服用4个片剂或其他口服剂型，每个包含1克柠檬酸铁，或可以服用8个片剂或其他口服剂型，每个包含500mg柠檬酸铁。

[0104] 在某些实施方式中，根据本文公开的方法施用给对象的柠檬酸铁的日剂量是1克到12克，三价铁的剂量从210mg到2,520mg。在某些实施方式中，包含1克柠檬酸铁的一个或更多个片剂，每个片剂具有210mg的三价铁剂量，根据本文公开的方法施用给对象。

[0105] 在某些实施方式中，根据本文公开的方法以每天1个片剂的日剂量将柠檬酸铁施用给对象，所述片剂包含1克柠檬酸铁，含有210mg三价铁，总的日剂量1克柠檬酸铁和210mg三价铁。在某些实施方式中，根据本文公开的方法以每天2个片剂的日剂量将柠檬酸铁施用给对象，每个片剂包含1克柠檬酸铁，含有210mg三价铁，总的日剂量2克柠檬酸铁和420mg三价铁。在某些实施方式中，根据本文公开的方法以每天3个片剂的日剂量将柠檬酸铁施用给对象，每个片剂包含1克柠檬酸铁，含有210mg三价铁，总的日剂量3克柠檬酸铁和630mg三价铁。在某些实施方式中，根据本文公开的方法以每天4个片剂的日剂量将柠檬酸铁施用给对象，每个片剂包含1克柠檬酸铁，含有210mg三价铁，总的日剂量4克柠檬酸铁和840mg三价铁。在某些实施方式中，根据本文公开的方法以每天5个片剂的日剂量将柠檬酸铁施用给对象，每个片剂包含1克柠檬酸铁，含有210mg三价铁，总的日剂量5克柠檬酸铁和1,050mg三价铁。在某些实施方式中，根据本文公开的方法以每天6个片剂的日剂量将柠檬酸铁施用给对象，每个片剂包含1克柠檬酸铁，含有210mg三价铁，总的日剂量6克柠檬酸铁和1,260mg三价铁。在某些实施方式中，根据本文公开的方法以每天7个片剂的日剂量将柠檬酸铁施用给对象，每个片剂包含1克柠檬酸铁，含有210mg三价铁，总的日剂量7克柠檬酸铁和1,470mg三价铁。在某些实施方式中，根据本文公开的方法以每天8个片剂的日剂量将柠檬酸铁施用给对象，每个片剂包含1克柠檬酸铁，含有210mg三价铁，总的日剂量8克柠檬酸铁和1,680mg三价铁。在某些实施方式中，根据本文公开的方法以每天9个片剂的日剂量将柠檬酸铁施用给对象，每个片剂包含1克柠檬酸铁，含有210mg三价铁，总的日剂量9克柠檬酸铁和1,890mg三价铁。在某些实施方式中，根据本文公开的方法以每天10个片剂的日剂量将柠檬酸铁施用给对象，每个片剂包含1克柠檬酸铁，含有210mg三价铁，总的日剂量10克柠檬酸铁和2,100mg三价铁。在某些实施方式中，根据本文公开的方法以每天11个片剂的日剂量将柠檬酸铁施用给对象，每个片剂包含1克柠檬酸铁，含有210mg三价铁，总的日剂量11克柠檬酸铁和2,310mg三价铁。在某些实施方式中，根据本文公开的方法以每天12个片剂的日剂量将柠檬酸铁施用给对象，每个片剂包含1克柠檬酸铁，含有210mg三价铁，总的日剂量12克柠檬酸铁和2,520mg三价铁。可以施用给对象的片剂在下文的章节4.5中描述。在具体的实施方式中，所述片剂是Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)。

[0106] 在具体的方面，根据所述方法施用给对象的柠檬酸铁的每个剂量不与食物一起。在根据本文公开的方法的某些实施方式中，在摄入食物之前大约1小时将每个剂量的柠檬

酸铁施用给对象。在根据本文公开的方法的某些实施方式中，在摄入食物之前大约2小时将每个剂量的柠檬酸铁施用给对象。在根据本文公开的方法的某些实施方式中，在摄入食物之前大约3小时将每个剂量的柠檬酸铁施用给对象。在根据本文公开的方法的某些实施方式中，在摄入食物之前大约4小时将每个剂量的柠檬酸铁施用给对象。在根据本文公开的方法的某些实施方式中，在摄入食物之前大约1-2、1-3、1-4、2-3、2-4或3-4小时将每个剂量的柠檬酸铁施用给对象。根据这些实施方式，所述柠檬酸铁可以作为药物组合物施用，例如，下文的章节4.5中描述的。

[0107] 在根据本文公开的方法的某些实施方式中，在摄入食物之后大约1小时将每个剂量的柠檬酸铁施用给对象。在根据本文公开的方法的某些实施方式中，在摄入食物之后大约2小时将每个剂量的柠檬酸铁施用给对象。在根据本文公开的方法的某些实施方式中，在摄入食物之后大约3小时将每个剂量的柠檬酸铁施用给对象。在根据本文公开的方法的某些实施方式中，在摄入食物之后大约4小时将每个剂量的柠檬酸铁施用给对象。在根据本文公开的方法的某些实施方式中，在摄入食物之后大约1-2、1-3、1-4、2-3、2-4或3-4小时将每个剂量的柠檬酸铁施用给对象。根据这些实施方式，所述柠檬酸铁可以作为药物组合物施用，例如，下文的章节4.5中描述的。

[0108] 在根据本文公开的方法的某些实施方式中，在施用每个剂量的柠檬酸铁的大约1小时之内对象不摄入食物。在根据本文公开的方法的某些实施方式中，在施用每个剂量的柠檬酸铁的大约2小时之内对象不摄入食物。在根据本文公开的方法的某些实施方式中，在施用每个剂量的柠檬酸铁的大约3小时之内对象不摄入食物。在根据本文公开的方法的某些实施方式中，在施用每个剂量的柠檬酸铁的大约4小时之内对象不摄入食物。在根据本文公开的方法的某些实施方式中，在施用每个剂量柠檬酸铁的大约1-2、1-3、1-4、2-3、2-4或3-4小时之内对象不摄入食物根据这些实施方式，所述柠檬酸铁可以作为药物组合物施用，例如，下文的章节4.5中描述的。

[0109] 在一个实施方式中，柠檬酸铁以下文章节5中的实施例中描述的剂量施用给对象。在具体的实施方式中，柠檬酸铁以下文章节5中的实施例中描述的剂量并以片剂形式施用给对象。在另一个具体的实施方式中，根据本文公开的方法施用给对象的柠檬酸铁的剂量不足以治疗高磷酸血症。

[0110] 所述柠檬酸铁或其药物组合物可以施用持续任何时间长度，例如，医学专家(例如，医生、护理师或医师助理)开具处方的持续时间。在任一本文描述的方法中，柠檬酸铁或其药学上可接受的组合物可以施用给患者持续长时间，例如，达到和包括52周，包括达到和包括56周。柠檬酸铁还可以施用给对象持续短的时间，例如，2周、4周、6周、8周、9周、10周或12周。

[0111] 4.4.组合治疗

[0112] 在某些实施方式中，本文描述的柠檬酸铁或其药物组合物可以单独地或与其他试剂组合地施用或应用。本文描述的柠檬酸铁或其药物组合物还可以单独地或与其他药学活性试剂组合地施用或应用，包括已知改善一种或更多种铁储存参数(例如，提高血清铁蛋白水平、提高转铁蛋白饱和度(TSAT)、提高血红蛋白浓度、提高血清铁水平、提高组织铁水平(例如，可持续组织铁水平)、提高TIBC值、提高血浆促红细胞生成素水平、提高FEP水平)、提高铁吸收、维持铁储存、治疗缺铁或治疗贫血的其他试剂。在具体的实施方式中，本文描述

的柠檬酸铁或其药物组合物不与其他药学活性试剂组合地施用，所述其他药学活性试剂已知改善一种或更多种铁储存参数(例如，提高血清铁蛋白水平、提高转铁蛋白饱和度(TSAT)、提高血红蛋白浓度、提高血清铁水平、提高组织铁水平(例如，可持续组织铁水平)、提高TIBC值、提高血浆促红细胞生成素水平、提高FEP水平)、提高铁吸收、维持铁储存、治疗缺铁或治疗贫血。例如，在具体的实施方式中，本文描述的柠檬酸铁或其药物组合物不与一种、两种或所有以下的组合施用：红细胞生成刺激剂、静脉内铁和/或输血。

[0113] 如本文使用的，在施用试剂或治疗的上下文中“组合”是指使用超过一种试剂或治疗。使用术语“组合”不限制施用给患病患者的试剂或治疗的顺序。在某些实施方式中，向患病的患者施用一种或更多种试剂或治疗包括，无限制地，在向患有疾病或对疾病敏感的患者施用第二试剂或治疗之前(例如，1分钟、5分钟、15分钟、30分钟、45分钟、1小时、2小时、4小时、6小时、12小时、24小时、48小时、72小时、96小时、1周、2周、3周、4周5周、6周、8周或12周以前)，相伴随地，或随后(例如，1分钟、5分钟、15分钟、30分钟、45分钟、1小时、2小时、4小时、6小时、12小时、24小时、48小时、72小时、96小时、1周、2周、3周、4周5周、6周、8周或12周之后)，可以施用第一试剂或治疗。

[0114] 在某些实施方式中，本文描述的柠檬酸铁或其药物组合物与已知治疗胃肠状况，例如，结肠炎或炎症性肠病的药学活性试剂或已知改善其一种或更多种症状的试剂组合地施用。例如，在某些实施方式中，本文描述的柠檬酸铁或其药物组合物与抗炎症药物(例如，氨基水杨酸盐或皮质类固醇)、免疫抑制剂(例如，硫唑嘌呤(Azasan，Imuran)、巯嘌呤、环孢霉素、英夫利昔单抗(Remicade®)、阿达木单抗(Humira®)、戈利木单抗(Simponi®)、维多珠单抗(Entyvio®))、抗生素、抗腹泻试剂和/或止痛药组合施用。柠檬酸铁和其他试剂可以以本领域已知的任何方式组合，例如，单元剂型。做为选择，柠檬酸铁和其他试剂可以在为了同时或连续施用给对象的独立的剂型中施用给对象。当连续施用时，组合可以在两次或更多次施用中施用。在某些实施方式中，本文描述的柠檬酸铁或其药物组合物与一种或更多种其他试剂通过不同的途径施用。在其他实施方式中，本文描述的柠檬酸铁或其药物组合物与一种或更多种其他试剂通过相同的途径施用。

[0115] 4.5.柠檬酸铁

[0116] 本文公开的柠檬酸铁的制品和包含柠檬酸铁的药物组合物，根据本文描述的方法使用。在各种实施方式中，所述柠檬酸铁制品和包含所述柠檬酸铁制品的药物组合物满足一定的溶解、制片和崩解标准。在各种方面，所述药物组合物可以包括作为活性成分的柠檬酸铁和结合剂。所述药物组合物还可以包括润滑剂和/或崩解剂(在某些实施方式中，其可以是与结合剂相同的)。

[0117] 在某些实施方式中，如本文描述使用的柠檬酸铁在美国专利No.7,767,851、8,093,423、8,299,298、8,338,642、8,754,258、8,846,976和/或8,754,257，和/或国际专利公开No.WO 2004/074444、WO 2007/022435、WO 2007/089571、WO 2007/089577和/或WO 2011/011541中公开。在某些实施方式中，如本文描述使用的柠檬酸铁具有美国专利No.7,767,851、8,093,423、8,299,298、8,338,642、8,754,258、8,846,976和/或8,754,257，和/或国际专利公开No.WO 2004/074444、WO 2007/022435、WO 2007/089571、WO 2007/089577和/或WO 2011/011541中公开的柠檬酸铁的某些特征或性质。

[0118] 在具体的方面，如本文描述使用的柠檬酸铁与商业上可获得的或化学级形式的柠

檬酸铁相比显示了增强的BET活性表面积。BET理论解释了气体分子在固体表面上的物理吸附。该理论充当了测量材料的比表面积的基础。这个理论容许以非常精确的方式计算材料的表面积，因而能够区分看起来是相同材料的独立制品之间的差异。例如，活性碳是一种碳形式，其被加工变得极其多孔，因而具有非常大的表面积。利用来自BET理论的算法，以及在实验上测定了活性碳，具有约3000m^2g^{-1}的表面积。这个表面积显著高于其他碳制品的活性表面积，虽然它们由相同的材料制成。

[0119] 在某些实施方式中，如本文描述使用的柠檬酸铁具有超过16m^2/g的BET活性表面积。在某些实施方式中，根据本文描述的方法使用的柠檬酸铁具有超过20m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁具有超过25m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁具有超过30m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁具有超过35m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁具有超过40m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁具有超过45m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁具有超过50m^2/g的BET活性表面积。

[0120] 在某些实施方式中，如本文描述使用的柠檬酸铁具有16.17m^2/g到19.85m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁具有选自16.17m^2/g和19.85m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁具有超过27m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁具有27.99m^2/g到32.34m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁具有28.5m^2/g到31.5m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁具有选自27.99m^2/g、28.87m^2/g和32.34m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁具有选自28.5m^2/g、29.1m^2/g、30.6m^2/g和31.5m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁制品具有30m^2/g到40m^2/g的BET活性表面积。在某些实施方式中，如本文描述使用的柠檬酸铁制品具有20m^2/g到35m^2/g的BET活性表面积。

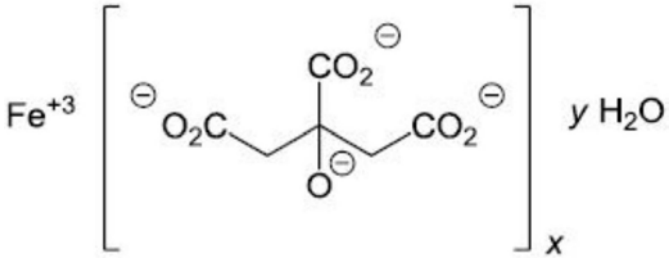
[0121] 在某些实施方式中，所述柠檬酸铁的三价铁含量大于或超过约19％w/w。在某些实施方式中，所述柠檬酸铁的三价铁含量是21.2％w/w、22.1％w/w或22.4％w/w。在某些实施方式中，所述柠檬酸铁的三价铁含量在19.5％w/w到22.5％之间。在某些实施方式中，所述柠檬酸铁的三价铁含量在21％w/w到23％w/w之间。本领域技术人员已知的技术可以用于测定柠檬酸铁的铁含量。在具体的实施方式中，三价铁含量如下测定：预先称重的柠檬酸铁与适量的水和适量的盐酸混合。加热混合物至沸腾，然后冷却。将固体碘化钾添加到混合物中，溶液变为暗红色和几乎褐色。从溶液中取出样品，用硫代硫酸钠滴定直到样品变为橄榄绿色，添加淀粉溶液时，样品则变为蓝黑色。继续用硫代硫酸钠滴定直到蓝黑色消失。然后使用柠檬酸铁的重量、硫代硫酸钠的预先测定的滴度和添加的硫代硫酸钠的总体积计算铁含量。

[0122] 在具体的实施方式中，如本文描述使用的柠檬酸铁是包含铁(III)和柠檬酸的复合物。在具体的方面，所述铁(III)和柠檬酸的复合物包含水。在某些实施方式中，铁(III)与柠檬酸的摩尔比是1:0.70到1:0.78。在一些方面，铁(III)与柠檬酸的摩尔比是1:0.69到1:0.87。在某些实施方式中，铁(III)与柠檬酸的摩尔比是1:0.75到1:1.10。在某些实施方式中，铁(III)与柠檬酸的摩尔比是1:0.78到1:0.95。在某些实施方式中，铁(III)与柠檬酸

的摩尔比是1:0.80到1:0.92。在某些实施方式中，铁(III)与柠檬酸的摩尔比是1:0.81到1:0.91。在某些实施方式中，铁(III)与柠檬酸的摩尔比是1:0.75到1:1.15。在某些实施方式中，铁(III)与柠檬酸的摩尔比是1:0.80到1:1.10。

[0123] 在某些实施方式中，铁(III)与水的摩尔比是1:0.32到1:0.42。在某些实施方式中，铁(III)与水的摩尔比是1:0.32到1:0.46。在一些方面，铁(III)与水的摩尔比是1:1.8到1:3.2。在某些实施方式中，铁(III)与水的摩尔比是1:1.8到1:3.2。在某些实施方式中，铁(III)与水的摩尔比是1:2.4到1:3.1。在某些实施方式中，铁(III)与水的摩尔比是1:2.7到1:3.1。

[0124] 在具体的实施方式中，如本文描述使用的柠檬酸铁化学上被称为铁(+3)，x(1,2,3-丙烷三羧酸，2-羟基-)，y(H_2O)

[0125] 

[0126] x＝0.70-0.87，y＝1.9-3.3

[0127] 在具体的实施方式中，如本文描述使用的柠檬酸铁是四铁三柠檬酸十水合物。

[0128] 在具体的实施方式中，如本文描述使用的柠檬酸铁基本上没有混杂物，例如，beta-氢氧化铁氧化物。在特定的实施方式中，如本文描述使用的柠檬酸铁含有小于6％的混杂物，例如，beta-氢氧化铁氧化物，按照根据柠檬酸铁的总重量的重量。在某些实施方式中，如本文描述使用的柠檬酸铁含有小于5％的混杂物，例如，beta-氢氧化铁氧化物，按照根据柠檬酸铁的总重量的重量。在某些实施方式中，如本文描述使用的柠檬酸铁含有小于4％的混杂物，例如，beta-氢氧化铁氧化物，按照根据柠檬酸铁的总重量的重量。在某些实施方式中，如本文描述使用的柠檬酸铁含有小于3％的混杂物，例如，beta-氢氧化铁氧化物，按照根据柠檬酸铁的总重量的重量。

[0129] 在具体的方面，如本文描述使用的柠檬酸铁与商业上可获得的或化学级形式的柠檬酸铁相比更为可溶。在具体的实施方式中，在溶解测试中，5分钟内溶解的柠檬酸铁的百分比是91％或更多，15分钟内是96％或更多，30分钟内是96％或更多，60分钟内是95％或更多，在使用Apparatus II在USP<711>容器中对柠檬酸铁制品进行的溶解测试中。用于溶解测试的特定标志物建立了100的基线，从而一定程度上批次可能具有大于100％的溶解度，大是相对于标志物的溶解速率。

[0130] 在某些实施方式中，在使用Apparatus II在USP<711>容器中进行的溶解度测试中，80％或更多的如本文描述使用的柠檬酸铁在15分钟内溶解。在某些实施方式中，在使用Apparatus II在USP<711>容器中进行的溶解度测试中，85％或更多的如本文描述使用的柠檬酸铁在15分钟内溶解。在某些实施方式中，在使用Apparatus II在USP<711>容器中进行的溶解度测试中，90％或更多的如本文描述使用的柠檬酸铁在15分钟内溶解。在某些实施方式中，在使用Apparatus II在USP<711>容器中进行的溶解度测试中，91％或更多的如本文描述使用的柠檬酸铁在15分钟内溶解。在某些实施方式中，在使用Apparatus II在USP<

711>容器中进行的溶解度测试中,95%或更多的如本文描述使用的柠檬酸铁在15分钟内溶解。在某些实施方式中,在使用Apparatus II在USP<711>容器中进行的溶解度测试中,96%或更多的如本文描述使用的柠檬酸铁在15分钟内溶解。在某些实施方式中,在使用Apparatus II在USP<711>容器中进行的溶解度测试中,97%或更多的如本文描述使用的柠檬酸铁在15分钟内溶解。在某些实施方式中,在使用Apparatus II在USP<711>容器中进行的溶解度测试中,100%的如本文描述使用的柠檬酸铁在15分钟内溶解。

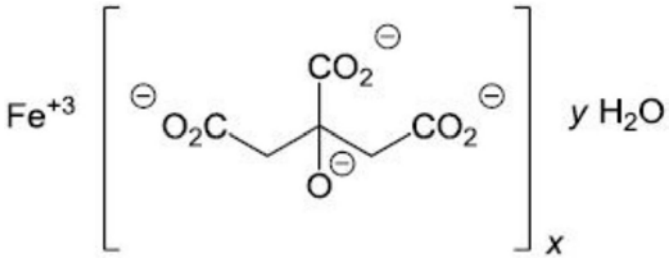
[0131] 不受任何理论的限制,柠檬酸铁的溶解度的提高被认为是所述柠檬酸铁的独特的、显著大的活性表面积的结果。固有溶解速率被定义为纯的物质在恒定表面积的条件下的溶解速率。药物物质的固有溶解速率和生物利用率受到它的固体性质的影响,包括:结晶性、无定形性、多态性、水化、溶剂化、颗粒大小和颗粒表面积。测得的固有溶解速率取决于这些固体性质,一般通过将恒定表面积的材料暴露于适当的溶解介质同时维持恒定温度、搅动速率和pH值来测定。

[0132] 在某些实施方式中,如本文描述使用的柠檬酸铁具有1.88mg/cm^2/分钟到4mg/cm^2/分钟的固有溶解速率。在某些实施方式中,如本文描述使用的柠檬酸铁具有大于2.28mg/cm^2/分钟的固有溶解速率。在某些实施方式中,如本文描述使用的柠檬酸铁具有超过2.28mg/cm^2/分钟的固有溶解速率。在某些实施方式中,如本文描述使用的柠檬酸铁具有2.99mg/cm^2/分钟的固有溶解速率。在某些实施方式中,如本文描述使用的柠檬酸铁具有2.28mg/cm^2/分钟到2.99mg/cm^2/分钟的固有溶解速率。在某些实施方式中,如本文描述使用的柠檬酸铁具有选自2.28mg/cm^2/分钟和2.99mg/cm^2/分钟的固有溶解速率。在具体的实施方式中,商品等级的柠檬酸铁制品具有的固有溶解速率实质上低于本文描述的柠檬酸铁。

[0133] 制造柠檬酸铁的制品的示范性的方法在美国专利No.7,767,851、8,093,423、8,299,298、8,338,642、8,754,258、8,846,976和8,754,257,美国公开No.2012/0238622,和国际公开No.WO 2004/074444、WO 2007/022435、WO 2007/089571、WO 2007/089577和/或WO 2011/011541中公开。

[0134] 4.5.1.柠檬酸铁的药物组合物

[0135] 在具体的实施方式中,所述柠檬酸铁被含在药物组合物。在一个实施方式中,药物组合物包含柠檬酸铁和药学上可接受的赋形剂或载运体。在特定的实施方式中,药物组合物包含柠檬酸铁和结合剂。在某些实施方式中,所述药物组合物进一步包含润滑剂和/或崩解剂(在某些实施方式中,其可以与结合剂相同)。在具体的实施方式中,所述药物组合物包括柠檬酸铁作为活性成分。在某些实施方式中,所述药物组合物是口服片剂剂型。在某些实施方式中,所述药物组合物是片剂之外的口服制剂,例如,胶囊剂、悬浮液、糖浆或小袋。在具体的实施方式中,所述药物组合物中使用的柠檬酸铁是下文章节4.5中描述的一种或更多种形式的柠檬酸铁。在具体的实施方式中,本文描述的药物组合物中使用的柠檬酸铁化学上被称为铁(+3),x(1,2,3-丙烷三羧酸,2-羟基-),y(H_2O)

[0136] 

[0137] x＝0.70-0.87,y＝1.9-3.3

[0138] 在具体的实施方式中,本文描述的药物组合物中使用的柠檬酸铁是四铁三柠檬酸十水合物。

[0139] 本文描述的药物组合物可以用于本文描述的方法中。

[0140] 在某些实施方式中,本公开内容提供的药物组合物和口服片剂剂型在国际公开No.WO 2011/011541和美国公开No.2012/0115945中公开。

[0141] 在具体的方面,所述药物组合物是片剂或其他包含柠檬酸铁和结合剂的口服制剂。在某些实施方式中,所述片剂或其他口服制剂可以包括柠檬酸铁、结合剂、润滑剂和崩解剂。在具体的实施方式中,单个片剂包含1克柠檬酸铁,具有210mg剂量的三价铁。

[0142] 在某些实施方式中,所述片剂或其他口服制剂的特征在于片剂中存在的柠檬酸铁的高度药物装载,数值大于按制剂重量计算大约65%、大于按制剂重量计算大约70%、大于按制剂重量计算大约75%、大于按制剂重量计算大约80%、大于按制剂重量计算大约85%、大于按制剂重量计算大约90%、以及高达大约92%或大约95%的制剂。中间值,例如,按柠檬酸铁重量计算大约80%、按柠檬酸铁重量计算大约85%、和按柠檬酸铁重量计算大约90%也可以用于所述柠檬酸铁片剂或其他口服制剂。在某些实施方式中,所述片剂或其他口服制剂的特征在于片剂中存在的柠檬酸铁的高度药物装载,数值大约80%到大约92%、大约85%到大约92%、大约80%到大约90%、大约85%到大约90%、大约90%到大约92%、大约80%到大约95%、大约85%到大约95%、或大约90%到大约95%。在这些高装载重量百分数下生产的片剂的特征可以通过变量来控制,例如,结合剂、结合剂数量、崩解剂、崩解剂数量、使用的制剂方法(例如,造粒、直接压缩)、压片参数,等。因而,如果制备片剂,通过改变一种或更多种上述变量,它可以有少量的分层或帽化,所述叠层或帽化可以被校正。

[0143] 在各种实施方式中,所述片剂或其他口服制剂包含铁以及选自一种或更多种结合剂、一种或更多种润滑剂和一种或更多种崩解剂的一种或更多种成分。在某些实施方式中,所述片剂或其他口服制剂包含柠檬酸铁和一种或更多种结合剂。在某些实施方式中,所述片剂或其他口服制剂包含柠檬酸铁、一种或更多种结合剂以及一种或更多种润滑剂。在某些实施方式中,所述片剂或其他口服制剂包含柠檬酸铁、一种或更多种结合剂、一种或更多种润滑剂和一种或更多种崩解剂。

[0144] 本领域技术人员已知的任何结合剂可以用于本文描述的片剂或其他口服制剂中。在某些实施方式中,所述结合剂是羟基丙基纤维素(HPC)、羟基丙基甲基纤维素(HPMC)、海藻酸钠、海藻酸、瓜耳豆胶、阿拉伯树胶、黄原胶、卡波姆、纤维素胶(羟甲基化纤维素)、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、或甲基纤维素。在某些实施方式中,所述片剂或其他口服制剂包含两种或更多种以下结合剂的组合:包括羟基丙基纤维素(HPC)、羟基丙基甲基纤维素(HPMC)、海藻酸钠、海藻酸、瓜耳豆胶、阿拉

伯树胶、黄原胶、卡波姆、纤维素胶(羟甲基化纤维素)、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、或甲基纤维素。当用于柠檬酸铁片剂或其他口服制剂时,麦芽糊精、PVP/VA和甲基纤维素作为立即释放结合剂起作用。在具体的实施方式中,片剂或其他口服制剂中使用的结合剂包含部分或完全预胶化的淀粉。

[0145] 还应该理解的是,结合剂的组合可以用于控制和改变结合剂的作用。例如,结合剂系统可以由有或者没有微晶纤维素的羟基丙基纤维素和聚乙烯基吡咯烷酮(聚维酮)制成。羟基丙基纤维素和聚维酮的一种或两者可以用预胶化淀粉替换。

[0146] 在各种方面,所述片剂或其他口服制剂可以包括润滑剂。本领域技术人员已知的任何润滑剂可以用于所述片剂或其他口服制剂中。在某些实施方式中,所述柠檬酸铁片剂或其他口服制剂中使用的润滑剂是硬脂酸镁、硬脂酸钙、硬脂酰延胡索酸钠。在某些实施方式中,所述柠檬酸铁片剂包含两种或更多种以下的组合:硬脂酸镁、硬脂酸钙、硬脂酰延胡索酸钠。可以用于柠檬酸铁片剂或其他口服制剂的其他适合的润滑剂包括聚乙二醇(分子量高于3350)、十二烷基硫酸钠、滑石粉、矿物油、亮氨酸和泊洛沙姆的一种或更多种。在具体的实施方式中,所述柠檬酸铁片剂或其他口服制剂中使用的润滑剂是硬脂酸钙。

[0147] 在各种方面,所述片剂或其他口服制剂可以包括崩解剂。所述崩解剂可以相同于或不同于结合剂。举例来说和非限制性的,微晶纤维素具有结合剂和崩解剂的性质,在所述片剂和/或口服补铁剂中微晶纤维素可以用作溶胶结合剂/崩解剂。其他适合的崩解剂的实例包括交联羧甲纤维素钠、交聚维酮、羟甲基淀粉钠和淀粉。

[0148] 结合剂可以以按重量计算大约4.5%到按重量计算大约30%的数量存在于片剂或其他口服制剂中。在某些实施方式中,所述结合剂可以以按重量计算大约5%到按重量计算大约15%的数量存在于片剂或其他口服制剂中。在某些实施方式中,所述结合剂可以以按重量计算大约10%到按重量计算大约15%的数量存在于片剂或其他口服制剂中。所述崩解剂可以可以以按重量计算大约1.5%到按重量计算大约15%的数量存在于片剂或其他口服制剂中。在各种实施方式中,某些非淀粉崩解剂经常以更低的重量百分比使用,例如,低至0.25%,因而,所述片剂或其他口服制剂中存在的崩解剂在某些条件下可以低至0.25%。

[0149] 所述润滑剂可以可以以按重量计算大约0.5%到按重量计算大约3%的数量存在于片剂或其他口服制剂中。在某些实施方式中,所述润滑剂可以可以以按重量计算大约0.5%到按重量计算2%的数量存在于片剂或其他口服制剂中。在某些实施方式中,所述润滑剂可以可以以按重量计算大约0.5%到按重量计算大约1%的数量存在于片剂或其他口服制剂中。要理解的是,某些成分,例如,微晶纤维素,可以以崩解剂和结合剂的性质起作用。

[0150] 单个片剂或其他口服制剂的重量取决于要生产的最终剂量;例如,125mg、250mg、500mg、667mg、750mg和1,000mg的柠檬酸铁。在某些实施方式中,所述片剂包含1克柠檬酸铁,因而包含210mg三价铁的剂量。

[0151] 在各种实施方式中,所述柠檬酸铁片剂或其他口服制剂可以被包被,重量增加大约2%到5%。在具体的实施方式中,所述柠檬酸铁片剂使用Opadry悬浮液或等价物在多孔盘包被机中包被。

[0152] 在具体的方面,所述片剂和/或口服补铁剂具有降低的水含量。在一个实施方式中,按照干燥失重(LOD)百分比测量的,所述片剂的水含量小于20%。在另一个实施方式中,

按照LOD％测量的，所述片剂的水含量小于19％。在另一个实施方式中，按照LOD％测量的，所述片剂的水含量小于18％。在另一个实施方式中，按照LOD％测量的，所述片剂的水含量小于17％。在另一个实施方式中，按照LOD％测量的，所述片剂的水含量小于16％。在另一个实施方式中，按照LOD％测量的，所述片剂的水含量小于15％。在另一个实施方式中，按照LOD％测量的，所述片剂的水含量小于14％。在另一个实施方式中，按照LOD％测量的，所述片剂的水含量小于13％。在另一个实施方式中，按照LOD％测量的，所述片剂的水含量小于12％。在另一个实施方式中，按照LOD％测量的所述水含量小于11％。在另一个实施方式中，按照LOD％测量的所述水含量小于10％。在另一个实施方式中，按照LOD％测量的，所述片剂的水含量小于9％。在另一个实施方式中，按照LOD％测量的，所述片剂的水含量小于8％。在另一个实施方式中，按照LOD％测量的，所述片剂的水含量小于7％。在另一个实施方式中，按照LOD％测量的，所述片剂的水含量小于6％。在另一个实施方式中，按照LOD％测量的，所述片剂的水含量小于5％。

[0153] 在某些实施方式中，按照LOD％测量的，所述片剂的水含量在10％到15％之间。在某些实施方式中，按照LOD％测量的，所述片剂的水含量在5％到10％之间。在某些实施方式中，按照LOD％测量的，所述片剂的水含量在5％到14％之间。在某些实施方式中，按照LOD％测量的，所述片剂的水含量在5％到12％之间。在某些实施方式中，按照LOD％测量的，所述片剂的水含量在10％到14％之间。在某些实施方式中，按照LOD％测量的，所述片剂的水含量在2％到14％之间。在某些实施方式中，按照LOD％测量的，所述片剂的水含量在2％到10％之间。在某些实施方式中，按照LOD％测量的，所述片剂的水含量在2％到12％之间。在某些实施方式中，按照LOD％测量的，所述片剂的水含量在8％到10％之间。在某些实施方式中，按照LOD％测量的，所述片剂的水含量在6％到9％之间。在某些实施方式中，按照LOD％测量的，所述片剂的水含量在7％到9％之间。

[0154] LOD(干燥失重)是热解重量水分测定的方法。在热解重量过程中，材料的水分包括在加热期间挥发的物质，因而增加了材料的质量损失。与水一起，这还可以包括醇或分解产物。当使用热解重量测量方法时(使用红外线、卤素、微波或烘箱干燥)，在水和其他挥发性组分之间不产生区别。本领域技术人员已知的技术可以用于测量LOD。在具体的实施方式中，所述片剂的LOD％通过Mettler-Toledo’s型号HB-43-S Moisture Balance，使用“标准”干燥程序来测量，温度设置在105℃，终点设置在50秒内平均重量损失小于1mg，使用0.9-1.1克的样品。

[0155] 在某些实施方式中，所述片剂或其他口服制剂包含选自大约1000mg、大约667mg、大约500mg、大约250mg和大约125mg的柠檬酸铁数量。在具体的实施方式中，所述片剂或其他口服制剂包含1克(1000mg)柠檬酸铁。在具体的实施方式中，所述片剂或口服制剂包含1克柠檬酸铁，含有大约210mg三价铁。

[0156] 在某些实施方式中，所述片剂或其他口服制剂包含1.1克柠檬酸铁。在某些实施方式中，所述片剂或其他口服制剂包含1.2克柠檬酸铁。在某些实施方式中，所述片剂或其他口服制剂包含1.3克柠檬酸铁。在某些实施方式中，所述片剂或其他口服制剂包含1.5克柠檬酸铁。在某些实施方式中，所述片剂或其他口服制剂包含1.6克柠檬酸铁。在某些实施方式中，所述片剂或其他口服制剂包含选自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的柠檬酸铁数量。在具体的实施方式中，所述片剂或其他口服制剂包含大约1g柠檬酸铁。在某些实施方式中，所述片剂或其他口服制剂包含大约1000mg到1050mg、975mg到1050mg、或950mg到1050mg的柠檬酸铁。

[0157] 在某些实施方式中，所述片剂或其他口服制剂包含大约65wt％到92wt％的柠檬酸铁；大约4.5wt％到30wt％的结合剂；和0.5wt％到3wt％的润滑剂。在某些实施方式中，所述片剂或其他口服制剂包含大约80wt％到92wt％的柠檬酸铁；大约5wt％到大约15wt％的结合剂；和大约0.5wt％到大约2wt％的润滑剂。在某些实施方式中，所述片剂或其他口服制剂包含大约85wt％到92wt％的柠檬酸铁；大约5wt％到大约15wt％的结合剂；和大约0.5wt％到大约1wt％的润滑剂。在某些实施方式中，所述润滑剂选自硬脂酸镁、硬脂酸钙和硬脂酰延胡索酸钠的一种或更多种。在具体的实施方式中，所述润滑剂是硬脂酸钙。在具体的实施方式中，所述结合剂是预胶化淀粉，以及所述润滑剂是硬脂酸钙。

[0158] 在某些实施方式中，所述片剂或其他口服制剂包含按重量计算65％到按重量计算92％的柠檬酸铁，和按重量计算4.5％到按重量计算30％的结合剂，其中所述片剂的平均表面积与质量比等于或大于1m^2每克，其中所述片剂的LOD％水小于20％水w/w。在某些实施方式中，所述片剂或其他口服制剂的所述平均表面积与质量比等于或大于5m^2每克。在某些实施方式中，所述片剂或其他口服制剂的所述平均表面积与质量比等于或大于10m^2每克。在某些实施方式中，所述片剂或其他口服制剂包含按重量计算70％到92％的柠檬酸铁。在某些实施方式中，所述片剂或其他口服制剂包含按重量计算80％到92％的柠檬酸铁。在某些实施方式中，所述片剂或其他口服制剂包含按重量计算90％到93％的柠檬酸铁。在某些实施方式中，所述片剂或其他口服制剂的LOD％小于15％但大于2％、3％、4％或5％的水w/w。在某些实施方式中，所述片剂或其他口服制剂的LOD％小于10％但大于2％、3％、4％或5％的水w/w。在某些实施方式中，所述片剂或其他口服制剂进一步包含选自硬脂酸镁、硬脂酸钙和硬脂酰延胡索酸钠的一种或更多种的润滑剂。在某些实施方式中，所述片剂或其他口服制剂包含0.5％到3％的润滑剂。在具体的实施方式中，所述结合剂包含预胶化淀粉，以及所述润滑剂是硬脂酸钙。在某些实施方式中，按照测试方法USP<711>测量的，所述片剂或其他口服制剂中至少80％的柠檬酸铁在小于或等于60分钟的时间内溶解。在某些实施方式中，按照测试方法USP<711>测量的，所述片剂或其他口服制剂中至少80％的柠檬酸铁在小于或等于45分钟的时间内溶解。在某些实施方式中，所述片剂或口服制剂包含大约1000mg柠檬酸铁。

[0159] 在某些实施方式中，所述片剂或其他口服制剂包含大约80wt％到大约92wt％的柠檬酸铁和大约5wt％到大约15wt％的结合剂，其中所述片剂的平均表面积与质量比等于或大于1m^2每克，以及其中所述片剂的LOD％水在5％到14％之间。在某些实施方式中，所述片剂或其他口服制剂包含大约85wt％到大约92wt％的柠檬酸铁和大约5wt％到大约15wt％的结合剂；其中所述片剂的平均表面积与质量比等于或大于1m^2每克；以及其中所述片剂的

LOD％水在5％到14％之间。在某些实施方式中，所述片剂或其他口服制剂的所述平均表面积与质量比等于或大于5m^{2}每克。在某些实施方式中，所述片剂或其他口服制剂的所述平均表面积与质量比等于或大于10m^{2}每克。在某些实施方式中，所述片剂或其他口服制剂包含大约0.5％到大约3％的润滑剂。在某些实施方式中，所述片剂或其他口服制剂包含大约0.5％到大约2％的润滑剂。在具体的实施方式中，所述结合剂包含预胶化淀粉。在另一个具体的实施方式中，所述润滑剂包含硬脂酸钙。在某些实施方式中，按照测试方法USP<711>测量的，所述片剂或其他口服制剂中至少80％的柠檬酸铁在小于或等于60分钟的时间内溶解。在某些实施方式中，按照测试方法USP<711>测量的，所述片剂或其他口服制剂中至少80％的柠檬酸铁在小于或等于45分钟的时间内溶解。在某些实施方式中，所述片剂或其他口服制剂包含大约1000mg柠檬酸铁。在具体的实施方式中，所述片剂或其他口服制剂包含包衣。

[0160] 在某些实施方式中，所述片剂或其他口服制剂包含大约80wt％到大约92wt％的柠檬酸铁；大约5wt％到大约15wt％的结合剂；以及大约0.5wt％到大约2wt％的润滑剂，其中按照测试方法USP<711>测量的，所述片剂或其他口服制剂中至少80％的柠檬酸铁在小于或等于45分钟的时间内溶解。在某些实施方式中，所述片剂或其他口服制剂包含大约85wt％到大约92wt％的柠檬酸铁；大约5wt％到大约15wt％的结合剂；以及大约0.5wt％到大约1wt％的润滑剂，其中按照测试方法USP<711>测量的，所述片剂或其他口服制剂中至少85％的柠檬酸铁在小于或等于45分钟的时间内溶解。在具体的实施方式中，所述结合剂是预胶化淀粉，以及所述润滑剂是硬脂酸钙。在另一个具体的实施方式中，所述片剂或其他口服制剂包含包衣。

[0161] 在某些实施方式中，所述片剂或其他口服制剂包含大约80wt％到大约92wt％的柠檬酸铁和大约5wt％到大约15wt％的结合剂，其中所述片剂的平均表面积与质量比等于或大于1m^{2}每克，以及其中所述片剂的LOD％水在5％到10％之间。在某些实施方式中，所述片剂或其他口服制剂包含大约85wt％到大约92wt％的柠檬酸铁和大约5wt％到大约15wt％的结合剂；其中所述片剂的平均表面积与质量比等于或大于1m^{2}每克；以及其中所述片剂的LOD％水在5％到10％之间。在某些实施方式中，所述片剂或其他口服制剂的所述平均表面积与质量比等于或大于5m^{2}每克。在某些实施方式中，所述片剂或其他口服制剂的所述平均表面积与质量比等于或大于10m^{2}每克。在某些实施方式中，所述片剂或其他口服制剂包含大约0.5％到大约3％的润滑剂。在某些实施方式中，所述片剂或其他口服制剂包含大约0.5％到大约2％的润滑剂。在具体的实施方式中，所述结合剂包含预胶化淀粉。在另一个具体的实施方式中，所述润滑剂包含硬脂酸钙。在某些实施方式中，按照测试方法USP<711>测量的，所述片剂或其他口服制剂中至少80％的柠檬酸铁在小于或等于60分钟的时间内溶解。在某些实施方式中，按照测试方法USP<711>测量的，所述片剂或其他口服制剂中至少80％的柠檬酸铁在小于或等于45分钟的时间内溶解。在某些实施方式中，所述片剂或其他口服制剂包含大约1000mg柠檬酸铁。在具体的实施方式中，所述片剂或其他口服制剂包含包衣。

[0162] 表1提供了根据当前的公开的一个实施方式的柠檬酸铁片剂的配方：

[0163] 表1.

[0164]

材料说明	理论 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
纯水	15.30*	N/A*
片芯总计	17.00	100.0
Opadry Purple 03K100000	0.51	15.0
纯水	2.89*	85.0*
包被的片剂总计	17.5	100.0

[0165] *-纯水在制造过程的干燥阶段期间被除去

[0166] 表2提供了根据当前的公开的一个实施方式的柠檬酸铁片剂的配方：

[0167] 表2.

[0168]

材料说明	目标 kg/批	理论 100 kg/Lot	% w/w 单独的	% w/w 包被的片剂
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 –富马酸硬脂酸钠 (1)	0.4	2.0 – 3.0	2.0 – 3.0	1.9 – 2.9
纯水	15.3*	72.0-135.0*	*	*
片芯总计	17. 0	100.0	100.0	N/A*
Opadry Purple	0.9	5.3	15.0	2.0 – 5.0
纯水	5.1*	30.0*	85.0*	N/A*
包被的片剂总计	17.5 to 17.9	35.3	100.0	100.0

[0169] (1)-使用硬脂酸钙或硬脂酰延胡索酸钠作为润滑剂

[0170] *-纯水被除去

[0171] 表3提供了根据当前的公开的一个实施方式的柠檬酸铁片剂的配方：

[0172] 表3.

[0173]

材料说明	目标kg/批	%w/w单独的
柠檬酸铁	14.89	87.6
预胶化淀粉	1.70	10.0
硬脂酸钙(1)	0.406	2.4
纯水	15.30	N/A
片芯总计	17.00	100.0
Opadry Purple	0.51	15.0
纯水	2.89	85.0
包被的片剂总计	17.5	100.0

[0174] 表4提供了根据当前的公开的一个实施方式的柠檬酸铁口服制剂的配方：

[0175] 表4.

[0176]

材料/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
硬脂酰延胡索酸钠	0.0到3.0
纯水	N/A*
片芯总计	100.0
薄膜包被	0.0到5.0
纯水	N/A*
包被的片剂总计	100.0

[0177] *纯水被除去。

[0178] 表5提供了根据当前的公开的一个实施方式的柠檬酸铁口服制剂的配方：

[0179] 表5.

[0180]

材料	重量mg+10%
柠檬酸铁	1,500
淀粉	150
微晶纤维素	0
聚乙烯吡咯烷酮	0
硬脂酸钙	16
硬脂酰延胡索酸钠	0
纯水	N/A*
片芯总计-mg	1,666
薄膜包被	50
纯水	N/A*
包被的片剂总计-mg	1,766

[0181] *纯水被除去。

[0182] 在具体的实施方式中,所述柠檬酸铁片剂是称为JTT-751(Japan Tobacco Inc.和Torii Pharmaceutical Co.,Ltd.)的柠檬酸铁片剂。在另一个具体的实施方式中,所述柠檬酸铁片剂是Keryx Biopharmaceuticals,Inc.销售的Auryxia™片剂。

[0183] 4.6.评估铁储存参数的方法

[0184] 如上所述,可以测量铁储存参数来确定IDA患者是否有足够的铁储存以维持足够的健康。在评估IDA患者是否可以用柠檬酸铁适当地治疗以及柠檬酸铁治疗的效力,以指导健康处理人员确定和/或调整患者的给药方案方面,这些铁储存参数是有用的。为了评估一

种或更多种铁储存参数，可以用针头从手臂的静脉中抽取血液样品，进行铁测试(即，铁研究)以及全血计数测试，来确定血液中循环铁的数量、血液转运铁的能力以及组织中储备的铁的数量。在某些实施方式中，所述一种或更多种铁储存参数选自血细胞比容、血红蛋白(Hb)浓度、总铁结合力(TIBC)、TSAT、血清铁水平、肝脏铁水平、脾脏铁水平核血清铁蛋白水平。在具体的实施方式中，所述一种或更多种铁储存参数是血红蛋白浓度、TSAT或血清铁蛋白水平。

5.实施例

[0185] 这个章节(即，章节5)中的以下实施例描述了使用柠檬酸铁治疗IDA。特别地，实施例1展现了在没有红细胞生成刺激剂和静脉内铁的情况下，使用柠檬酸铁实现了IDA患者中血红蛋白浓度的临床上显著的提高。令人惊讶的是，不与食物一起服用的低剂量柠檬酸铁是良好耐受的，在IDA患者中产生了血红蛋白浓度的临床上显著的提高。

[0186] 提供以下实施例的目的在于阐述，而非限制本发明。

[0187] 5.1.实施例1:在患有3-5期非透析依赖性慢性肾病(NDD-CKD)的患者中KRX-0502(柠檬酸铁配位复合物)治疗IDA的2期试点研究

[0188] 5.1.1.方案

[0189] 研究的目标是评估Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)在患有3-5期非透析依赖性慢性肾病(NDD-CKD)的对象中治疗IDA的效力和安全性，通过8周治疗期内血红蛋白的改变来测量。研究的主要终点是到8周治疗期(第8周)的结束时血红蛋白浓度距基线(第0天)的改变。研究的第二终点包括最高血红蛋白值距离基线的平均改变;在研究期间任一次就诊时实现≥1.0g/dl的血红蛋白改变的对象的百分比;和研究期间任一次就诊时实现血红蛋白≥12.0g/dl血红蛋白的患者的百分比。

[0190] 5.1.1.1.总体设计

[0191] 这是一个2期、单臂、多中心、开放标签的临床试验。

[0192] 在筛查就诊之后，合格的对象被加入，接受不与食物一起的固定的起始剂量的Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)，1片/天。所有对象在他们的筛查就诊时必需是血红蛋白≥9.0g/dl并且≤11.5g/dl，以进入8周治疗期。

[0193] 在第0天以1片/天的起始剂量开始用Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)治疗之后，在每次研究就诊时测量血红蛋白。在前4周之后与基线(第0天)相比血红蛋白提高<1.0g/dl的对象在剩余试验中滴定增加到2片/天。在前4周之后与基线(第0天)相比血红蛋白提高>1.5g/dl的对象在剩余试验中滴定降低到每隔一天1片的剂量(一名对象在前4周后与基线(第0天)相比血红蛋白提高>1.5g/dl，然而由于主要研究者(PI)背离方案的请求，该对象在剩余试验中保持1片/天的剂量)。除此之外，对象在剩余试验中保持1片/天的剂量(在前4周之后与基线(第0天)相比，两名对象血红蛋白提高≥1.0g/dl并≤1.5g/dl;两名对象的一人在剩余试验中保持1片/天的剂量，另一名对象在剩余试验中滴定增加到2片/天)。

[0194] 在试验期间任何时候不允许使用磷酸盐结合剂。在试验期间任何适合不允许使用口服或IV的铁核红细胞生成刺激剂(ESA)和接受输血。

[0195] 在筛查时，在第0天，以及在开始治疗后1、2、4、6和8周，采集血液样品用于完整化

学分布(CCP)、铁研究和全血计数(CBC)。

[0196] 5.1.1.2.患者群体/入选和排除标准

[0197] 筛选人类对象,32名人类对象加入该项研究。合格的对象接受不与食物一起的起始固定剂量的1片/天的Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)。在前4周之后与基线(第0天)相比血红蛋白提高<1.0g/dl的对象在剩余试验中滴定增加到2片/天。在前4周之后与基线(第0天)相比血红蛋白提高≥1.0g/dl并≤1.5g/dl的一名对象在剩余试验中也滴定增加到2片/天。在前4周之后与基线(第0天)相比血红蛋白提高≥1.0g/dl并≤1.5g/dl的另一名对象在剩余试验中保持1片/天的剂量。由于PI背离方案的请求,在前4周后与基线(第0天)相比血红蛋白提高>1.5g/dl的一名对象在剩余试验中保持1片/天的剂量。

[0198] 在筛查就诊之后,合格的对象进入8周治疗期。进入研究(第0天)一般在筛查就诊的一周之内。

[0199] 入选标准

[0200] 加入该项研究的对象满足以下入选标准:

[0201] 1.男性,以及在筛查就诊时血清妊娠试验阴性(女性怀孕的可能性)的非哺乳女性

[0202] 2.年龄>18岁

[0203] 3.筛查就诊时血清铁蛋白<300ng/ml以及TSAT<25%

[0204] 4.筛查就诊时血红蛋白≥9.0g/dl并且≤11.5g/dl

[0205] 5.利用肾病(MDRD)公式中4-变量膳食修饰,筛查就诊时eGFR<60ml/分钟

[0206] 排除标准

[0207] 满足任一下述排除标准的对象不加入这项研究:

[0208] 1.筛查之时、或筛查之前4周内接受磷酸盐结合剂药物的对象

[0209] 2.筛查就诊之前24周内有胃肠出血、炎症性肠病、炎症性肠综合征和/或克罗恩病的症状

[0210] 3.筛查就诊之前8周内急性肾脏损伤的证据或需要透析

[0211] 4.筛查就诊16周内预期的肾脏移植或预计开始透析

[0212] 5.筛查就诊之前4周内施用了静脉内铁

[0213] 6.筛查就诊之前4周内施用了红细胞生成刺激剂(ESA)

[0214] 7.筛查就诊之前4周内有输血

[0215] 8.筛查就诊之前4周内接受任何研究性药物

[0216] 9.铁缺乏或慢性肾病之外的贫血原因

[0217] 10.最近五年的恶性肿瘤病史(如果由Keryx批准,治疗的子宫颈癌或皮肤癌可以被允许)

[0218] 11.血色沉着病的病史

[0219] 12.筛查就诊之前12个月内主动的药物或酒精依赖性或滥用(排除吸食烟草)或这种滥用的证据

[0220] 13.对铁产品的任何已知变态反应的对象

[0221] 14.对口服柠檬酸铁的早先的不耐受

[0222] 15.干扰患者遵守研究方案的能力的精神失调

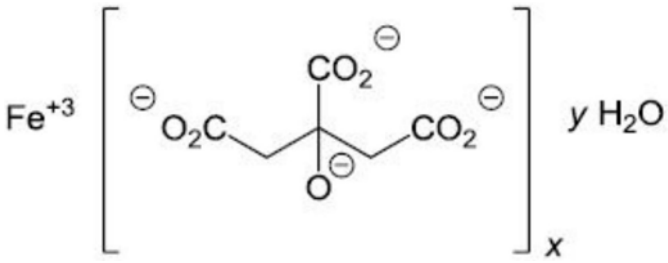
[0223] 16.试验期间有计划的手术或住院

[0224] 17.任何其他医学状况,就PI的观点而言,将使得对象不能或不大可能完成试验,或影响试验的最佳参与性,或产生对对象的显著风险。

[0225] 18.不能与研究人员协作或由不顺应史

[0226] 5.1.1.3.药物施用和滴定

[0227] Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)片剂中的活性成分在化学上称为铁(+3),x(1,2,3-丙烷三羧酸,2-羟基-),y(H_2O)

[0228] 

[0229] x=0.70-0.87,y=1.9-3.3

[0230] Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)是含有210mg三价铁、相当于1克柠檬酸铁的片剂。

[0231] 在前4周之后与第0天相比血红蛋白提高<1.0g/dl的对象在剩余的研究中滴定增加到2片/天。在前4周之后与第0天相比血红蛋白提高≥1.0g/dl并且≤1.5g/dl的一名对象在剩余试验中也滴定增加到2片/天。在前4周之后与第0天相比血红蛋白提高≥1.0g/dl并且≤1.5g/dl的另一名对象在剩余试验中保持1片/天的剂量。一名对象在前4周之后与第0天相比血红蛋白提高>1.5g/dl,由于主要研究者(PI)背离方案的请求,在剩余的研究中保持1片/天的剂量。

[0232] 每天允许的Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)的最大数量是2片,或2g/天。与Keryx Biopharmaceuticals,Inc商议,主要研究者(PI)允许因有害事件降低研究药物的剂量。

[0233] 对象没有进食地口服服用Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)。如果对象摄入食物或零食后不到2小时,对象被指示不服用Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)。对象被提议尽量在每天的大约相同时间服用它们的日剂量。每日的水溶性多种维生素(即,Centrum,Nephrocaps,Renaphro等)在研究期间是容许的。对象被提议与Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)独立地服用多种维生素(至少2小时间隔)。鼓励对象在整个试验中保持多种维生素的稳定剂量和类型(如果有的话)。对象被提议与Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)独立地服用钙增补剂(至少2小时间隔)。

[0234] 5.1.1.4.研究药物停药

[0235] 允许对象因以下任一原因停止研究药物:

[0236] 1.需要停止研究药物的并发疾病、医学事件或住院需求

[0237] 2.为了对象的最佳利益的研究者的判断

[0238] 如果由于已解决的并发疾病或有害事件研究药物被停止,对象可以在他们剩余的试验参与中再次给予研究药物。

[0239] 5.1.1.4.1.早期终止

[0240] 允许对象因以下原因停止试验：

[0241] 1.对象请求

[0242] 2.跟踪丢失

[0243] 3.赞助者或研究者在任何时候判定终止试验

[0244] 4.开始透析

[0245] 5.怀孕

[0246] 6.肾脏移植

[0247] 7.满足预定的早期终止标准(见下文)

[0248] 8.安全性

[0249] 9.死亡

[0250] 10.其他

[0251] 如果在第0天后的8周治疗期内，对象的Hgb连续两次研究就诊(至少7天间隔)<9.0或>13.0g/dl，对象被指令停止药物研究并退出试验。

[0252] 如果对象因任何原因从试验中早期终止，应当鼓励对象完成最后的就诊评估。

[0253] 5.1.1.4.2.有害事件

[0254] 记录所有的有害事件。有害事件(AE)被定义为与在人类中的药物、生物产品或诊断试剂的使用关联发生的任何反应、副作用或其他意外事件，不论该事件是否被认为与药物相关。在这项试验中，这包括在临床试验的过程中出现或恶化的任何疾病、病征、症状或临床上显著的实验室试验异常，不考虑与在研药物的因果关系。在询问和检查对象之后，要求注明所有的AE。如果已知，要求记录基础性疾病或失调(即，诊断)的名称，而不是它的个体症状。

[0255] 经历了引起试验药物的中断或停止的AE的对象，或经历了在参与试验的末期出现的有害事件的对象应当视情况接受跟踪(为了分析或稳定化)。

[0256] AE的严重度被定义为AE的强度程度的定量评估，由研究者确定，或对象报告给研究者。不考虑药物关系或事件严重度地进行严重度评估，应当根据以下尺度来评估：

[0257] 1＝轻度(注意到不适，但是不破坏正常的日常活动。)

[0258] 2＝中度(足以降低或影响正常的日常活动的不适。)

[0259] 3＝严重(使得无法工作或进行正常的日常活动。)

[0260] 非严重有害事件

[0261] 要求记录如下文定义的未被指定为严重的任何有害事件。

[0262] 严重有害事件

[0263] 要求记录严重的事件并标记为“严重”。严重有害事件(SAE)是满足任一以下标准的事件：

[0264] 引起死亡

[0265] 是危及生命的体验，

[0266] 需要或延长住院病人住院，定义为>24小时住院

[0267] 引起持续性或显著的失能/无能力

[0268] 引起先天性异常

[0269] 是重要的医学事件,其可能危及对象并可能需要医学或外科介入来防止上文所列结果之一

[0270] 危及生命的体验:就研究者的观点而言,将对象置于因发生有害事件而死亡的即刻风险中的任何有害事件(即,不包括如果以更严重的形式发生可能导致死亡的有害事件)。

[0271] 持续性或显著的失能/无能力:可能引起进行正常生活功能的个人能力的实质破坏的任何有害事件。

[0272] 重要医学事件:可能危及对象并可能需要医学或外科介入来防止上文所列结果之一的任何有害事件。可能引起死亡的、危急生命的、或需要住院的有害事件可以被认为是SAE,在基于适当的医学判断时,它们可能危及对象,并可能需要医学或外科介入来防止上文所列结果之一。

[0273] 经历1个或更多个SAE的对象要接受治疗和研究者的跟踪评估,或要指引给其他适合的医师进行治疗和跟踪。从同意之时直到对象停止研究药物之后达28天监测SAE。

[0274] 无论是严重还是非严重的,所有的有害事件进行跟踪来分析(或稳定化,如果可用),或直到研究者确定该有害事件不再是临床上显著的。

[0275] 5.1.1.5.目标实验室结果

[0276] 目标实验室结果是满足任一以下标准的结果:

[0277] 铁蛋白≥800ng/ml

[0278] TSAT≥50%

[0279] 肝脏酶升高≥3X正常值上限(ULN)

[0280] 5.1.1.6.分析群体

[0281] 效力

[0282] 26名对象完成了研究药物的8周治疗期。效力分析基于26名对象的数据。

[0283] 安全性

[0284] 安全性分析基于由服用至少一剂研究药物的所有对象组成的安全性群体。

[0285] 5.1.2.结果

[0286] 筛查了58名对象,32名对象加入。所有32名对象接受至少1剂Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.),被包括在安全性群体中。26名对象(81.3%)完成了研究,被包括在分析群体中。六名对象(18.8%)早期终止,3名对象(9.4%)是由于有害事件,1人(3.1%)由于研究者判断,2人(6.3%)由于其他原因。这项试验中的大部分对象是白人/高加索人(96.9%),男性(53.1%),年龄65岁或以上,患有3期CKD(43.8%)。

[0287] 二十六名对象完成了8周治疗期(81.3%),被包括在分析群体中。这项试验的平均和中值暴露时间分别是40.2和42.0天。Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)的平均和中值剂量是1.2g每天。总体上,非铁相关参数的实验室值在整个研究中与基线的值相似。

[0288] 用Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)治疗8周引起了血红蛋白的统计学上显著的提高,从基线的10.8±0.7g/dl提高到第8周的11.2±0.9g/dl(P=0.0212)。参见下文表6。从基线到最高值的血红蛋白平均改变是0.6g/dl(P<0.0001)。在研究期间的任何时候与基线相比,六名对象(23.1%)的血红蛋白提高至少1.0g/dl,在研究期

间至少一次,7名对象(26.9%)达到了血红蛋白≥12.0g/dl。参见下文表7。

[0289] 此外,用Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)治疗8周引起了铁储存参数,血清铁蛋白和TSAT值相比基线的提高。在服用Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)的对象中,血清铁蛋白水平平均提高35ng/ml,从基线的84.9±64.7ng/ml提高到第8周的120.1±82.5ng/ml,p-值0.001。参见下文表8。在服用Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)的对象中,TSAT值平均提高5.7%,从19.2±6.5%到24.9±8.5%,p-值0.003。

[0290] 因而,在这项研究中,不与食物一起施用Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)一般是安全的和良好耐受的。用Auryxia™(柠檬酸铁;Keryx Biopharmaceuticals,Inc.)治疗8周引起了血红蛋白以及血清铁蛋白水平和TSAT值的显著提高。

[0291] 表6.血红蛋白浓度

[0292]

	N	平均(SD)	P-值
基线	26	10.8(0.7)	-
第8周	26	11.2(0.9)	0.0212
最高值	26	11.4(0.7)	<0.0001

[0293] 表7.血红蛋白浓度提高>=1.0g/dl的对象和血红蛋白浓度>=12.0g/dl的对象

[0294]

项目	Stat	KRX-0502 (N=26)
任何就诊时改变>=1.0 g/dl	n (%)	6 (23.1)
任何就诊时值>=12.0 g/dl	n (%)	7 (26.9)

[0295] 表8.血清铁蛋白水平

[0296]

		统计量概述 (N=26)								
参数	就诊	n	平均	SD	中值	P(25)	P(75)	最小	最大	P-值
铁蛋白 (ng/ml)	基线	26	84.9	64.66	72.0	31.0	121.0	8	275	.
	就诊3	26	91.6	64.58	77.5	43.0	125.0	13	310	.
	就诊4	26	91.7	63.68	71.5	51.0	131.0	19	303	.
	就诊5	26	92.2	62.02	89.0	45.0	117.0	21	261	.
	就诊6	26	99.7	61.99	85.5	64.0	132.0	17	260	.
	就诊7	26	120.1	82.53	85.5	63.0	163.0	23	340	.

[0297]

		统计量概述 (N=26)								
参数	就诊	n	平均	SD	中值	P(25)	P(75)	最小	最大	P-值
铁蛋白(ng/ml)距离基线的改变	就诊3	26	6.7	22.90	2.5	-3.0	12.0	-41	65	0.1465
	就诊4	26	6.8	25.72	11.5	-10.0	20.0	-60	60	0.1916
	就诊5	26	7.3	20.60	7.5	-4.0	16.0	-30	54	0.0811
	就诊6	26	14.8	24.03	16.5	-8.0	31.0	-36	55	0.0043
	就诊7	26	35.2	48.38	30.5	15.0	43.0	-64	188	0.0010

[0298] 5.2.实施例2:结肠炎的动物模型

[0299] 为了评估在患有炎症性肠病症的对象中柠檬酸铁治疗IDA的能力,结肠炎的动物模型施用柠檬酸铁,测定柠檬酸铁对铁储存参数例如血红蛋白浓度和TSAT值的影响。

[0300] 慢性结肠炎的T细胞转移模型

[0301] 通过将IL-102/2CD4$^+$T细胞继承转移到RAG2/2接受者中,在小鼠中诱导慢性结肠炎症。简要地说,年龄2-3个月的RAG2/2接受者小鼠用获自IL-102/2供体小鼠的10^6个CD4+T细胞注射,通过使用商业上可获得的试剂盒的负选择来富集T细胞(90%;来自脾细胞的单细胞悬液)。其他年龄匹配的RAG2/2小鼠和C57BL/6小鼠同样地处置,指示注射单独的载体(磷酸盐缓冲盐水[PBS])而不是T细胞。在注射后8周,小鼠用于柠檬酸铁治疗或对照。

[0302] 急性/自限性结肠炎的DSS模型

[0303] 通过在饮用水中施用5%葡聚糖硫酸钠(DSS)6天,在2个月至3个月的C57BL/6小鼠中诱导急性结肠炎症。将DSS加入过滤净化的水中。过滤的水(没有DSS)施用6天给年龄匹配的C57Bl/6小鼠作为对照组。在DSS施用的结束时,小鼠用于柠檬酸铁治疗或对照。

[0304] 已知结肠炎的T细胞转移模型和结肠炎的DSS模型都诱导血细胞比容、血红蛋白和TSAT的显著降低,在结肠炎的T细胞转移模型中,脾脏和肝脏显示铁含量的降低。另外,两种结肠炎模型都展现了血浆促红细胞生成素和血浆铁结合能力的显著提高。

[0305] 治疗组

[0306] 在诱导了结肠炎之后,以相应于人类有效剂量的剂量,一定数量的小鼠通过口服管饲法或饮食施用来施用柠檬酸铁。作为对照,一定数量的小鼠通过口服管饲法或饮食施用来施用硫酸亚铁。在施用柠檬酸铁之前,和施用柠檬酸铁或对照之后一定天数(例如,1、2、3、4、5、6或更多天)或周数(例如,1、2、3、4、5或更多周),进行铁和血液学分析。

[0307] 铁和血液学分析

[0308] 用150mg/kg氯胺酮和10mg/kg甲苯噻嗪的腹膜内注射来麻醉小鼠。从右侧颈动脉插入的导管抽取血液样品,一部分与抗凝血剂EDTA混合用于测量血细胞比容、血红蛋白浓度和每RBC的血红蛋白,其余未处理的血液用于测量血清铁、不饱和铁结合力、总铁结合力(TIBC)、转铁蛋白饱和度、血清铁蛋白和血浆促红细胞生成素(所有的测量用血液学分析仪获得)。在安乐死之后,对组织切片(或在某些情况下完整的器官)进行解剖用于铁测量。

[0309] 最后,应当注意到,存在着实施本文公开的实施方式的替换性方法。因此,当前的实施方式被认为是说明性的而不是限制性的。此外,权利要求不限于本文给出的细节,并且

其权利是其全部范围和等同物。

[0310] 在此引用的所有参考文献在此为了所有目的通过将它们完全引用来合并在此，其程度与具体的或单独的指示为了所有目的通过将其完全引用来合并每个单独的出版物或专利或专利申请相同。