2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24 and 2.25 mg/dl when administered for a period of 24 weeks; a mean reduction in serum phosphorus selected from 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19 and 2.20 mg/dl when administered for a period of 36 weeks; a mean reduction in serum phosphorus selected from 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 2.11, 2.12, 2.13, 2.14 and 2.15 mg/dl when administered for a period of 48 weeks; and a mean reduction in serum phosphorus selected from 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24, 2.25, 2.26, 2.27, 2.28, 2.29 and 2.30 mg/dl when administered for a period of 52 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.00 mg/dl when administered for a period of 12 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.20 mg/dl when administered for a period of 24 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.20 mg/dl when administered for a period of 36 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.10 mg/dl when administered for a period of 48 weeks. In some embodiments, the ferric citrate provides a mean reduction in serum phosphorus of 2.10 mg/dl when administered for a period of 52 weeks.

In another aspect, the present disclosure provides a method for controlling serum phosphorus levels in a patient with chronic kidney disease receiving intravenous iron, comprising (a) orally administering ferric citrate to the patient; (b) assessing the patient for changes in serum phosphorus levels and changes in one or more iron storage parameters, such as serum ferritin levels, TSAT values and hemoglobin concentration; and (c) reducing the intravenous iron the patient is receiving by 1-100%, 10-50%, 10-25%, 30-60%, 25-50%, 50-75%, 75-100%, 80-95%, or 90-95% based on the one or more iron storage parameters in the patient. In a specific embodiment, the intravenous iron the patient is receiving is reduced if one or more iron storage parameters in the patient exceeds levels found in non-CKD patients (*e.g.*, healthy humans). For example, if the TSAT values are 50% or higher and/or the serum ferritin levels are approximately 1000 micrograms/L or higher, approximately 1200 micrograms/L or higher, approximately 1500 micrograms/L or higher, approximately 1800 or higher, or 2000 micrograms/L or higher, then the amount of ferric citrate the patient is receiving might be reduced. In certain embodiments, one or more iron storage parameters are assessed in the patient

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

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

In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 60%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 70%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 80%. In some embodiments, the ferric citrate provides a mean reduction in average cumulative IV iron intake that is greater than 90 %. The above boundaries are disclosed in this format for purposes of efficiency, and any of the above boundaries can be combined with any method, formulation, lower boundary as disclosed below, or combination thereof.

serum phosphate found in non-CKD patients (*e.g.*, healthy humans). In specific embodiments, the CKD patient treated in accordance with the methods described herein for one or more adverse cardiac events has elevated FGF-23 levels. In some embodiments, the CKD patient treated in accordance with the methods described herein for one or more adverse cardiac events has serum phosphate levels within the normal range for non-CKD patients (*e.g.*, healthy humans) and elevated FGF-23 levels (*e.g.*, intact FGF-23 levels and/or C-terminal FGF-23 fragment levels). The normal level of intact FGF-23 in the serum of healthy humans is approximately 26.1 pg/mL and the normal level of C-terminal FGF-23 fragments in the serum of healthy humans is approximately 49.0 RU/mL. In certain embodiments, the CKD patient's FGF-23 levels (*e.g.*, intact FGF-23 and/or C-terminal FGF-23 fragments) are elevated relative to the normal range in healthy humans. In some embodiments, the CKD patient's intact FGF-23 levels in serum are between 250 pg/mL and 350 pg/mL, 200 pg/mL and 300 pg/mL, 200 pg/mL and 350 pg/mL, 300 pg/mL and 350 pg/mL, 300 pg/mL and 400 pg/mL, or 250 pg/mL and 500 pg/mL. In certain embodiments, the CKD patient's intact FGF-23 levels in serum are above 200 pg/mL, 225 pg/mL, 250 pg/mL, 275 pg/mL, 300 pg/mL, 325 pg/mL, or 350 pg/mL. In some embodiments, the CKD patient's C-terminal FGF-23 fragment levels in serum are between 60 RU/mL and 100 RU/mL, 100 RU/mL and 200 RU/mL, 200 RU/mL and 300 RU/mL, or 250 RU/mL and 400 RU/mL. In certain embodiments, the CKD patient's C-terminal FGF-23 fragment levels in serum are above 60 RU/mL, 100 RU/mL, 125 RU/mL, 150 RU/mL, 175 RU/mL, 200 RU/mL, 225 RU/mL, 250 RU/mL, 275 RU/mL, or 300 RU/mL.

In some embodiments, the CKD patient treated in accordance with the methods described herein for one or more adverse cardiac events is not receiving intravenous iron. In other embodiments, the CKD patient treated in accordance with the methods described herein is receiving intravenous iron. In certain embodiments, the amount of intravenous iron a CKD patient is receiving is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more following administration of the ferric citrate. In some embodiments, the CKD patient treated in accordance with the methods described herein for one or more adverse cardiac events is not receiving EPO. In other embodiments, the CKD patient treated in accordance with the methods described herein for one or more adverse cardiac events is receiving EPO. In certain embodiments, the amount of EPO a CKD patient is receiving is reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%,

45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more following administration of the ferric citrate.

In some embodiments, CKD patients treated according to the methods disclosed herein experience an increase in hemoglobin concentration and/or a decrease in FGF23. In specific embodiments, CKD patients treated according to the methods disclosed herein experience an increase in the hemoglobin level of the subject to a level above 10 g/dL, above 11 g/dL, above 12 g/dL, above 13 g/dL, or above 15 g/dL. In certain embodiments, CKD patients treated according to the methods disclosed herein experience an increase in the hemoglobin level of the subject to a level between 10 g/dL to 11 g/dL, 11g/dL to 12 g/dL, 10 g/dL to 13 g/dL, 11 g/dL to 13 g/dL, 11 g/dL to 15 g/dL, or 12 g/dL to 15 g/dL. In some embodiments, CKD patients treated according to the methods disclosed herein experience a decrease of at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, or 60% of intact FGF-23 levels in serum or plasma. In certain embodiments, CKD patients treated according to the methods disclosed herein experience a decrease of 15% to 30%, 20% to 30%, 25% to 50%, 30% to 60% or 15% to 60% of intact FGF-23 levels in serum or plasma. In some embodiments, CKD patients treated according to the methods disclosed herein experience a decrease of at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, or 60% of C-terminal FGF-23 fragment levels in serum or plasma. In some embodiments, CKD patients treated according to the methods disclosed herein experience a decrease of 15% to 30%, 20% to 30%, 25% to 50%, 30% to 60% or 15% to 60% of C-terminal FGF-23 fragment levels in serum or plasma.

In certain embodiments, the CKD patients treated according to the methods disclosed herein experience a decrease in serum phosphorus levels. In some embodiments, CKD patients treated according to the methods disclosed herein experience a decrease of at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, or 60% in serum phosphorus levels. In some embodiments, CKD patients treated according to the methods disclosed herein experience a decrease of 15% to 30%, 20% to 30%, 25% to 50%, 30% to 60% or 15% to 60% in serum phosphorus levels. In certain embodiments, CKD patients treated according the methods disclosed herein experience an increase in one or more iron storage parameters, such as serum ferritin levels, TSAT values and/or hemoglobin concentration. In some embodiments, CKD patients treated according to the methods disclosed herein experience an increase of at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, or 60% in one or more iron storage parameters,

CLAIMS

1. Use of ferric citrate in the manufacture of a medicament for reducing mortality and morbidity related to adverse cardiac events in a human patient with chronic kidney disease, wherein said medicament is to be administered orally to said patient as a tablet, and the ferric citrate is administered in an amount ranging from 1 g to 18 g, wherein the adverse cardiac event is selected from the group consisting of: heart failure, ventricular arrhythmias, myocardial infarction, decreased left ventricular (LV) ejection fraction, sudden cardiac death, aortic root dilation, and a cerebrovascular event, wherein each tablet comprises approximately 80% to approximately 92% by weight of ferric citrate, approximately 5% to approximately 15% by weight of pregelatinized starch, and approximately 0.5% to approximately 2% by weight of a lubricant; and wherein at least 80% of the ferric citrate in the tablet is dissolved in less than or equal to 60 minutes as measured by test method USP <711>, and the water content of the tablet is less than 11% by loss on drying (LOD).

2. The use of claim 1, wherein the ferric citrate raises the hemoglobin level of the patient to a level above 10 g/dL.

3. The use of claim 1, wherein the ferric citrate reduces FGF-23 levels of the patient by at least 30% compared to baseline.

4. Use of ferric citrate in the manufacture of a medicament for reducing incidence or risk of adverse cardiac events in a human patient with chronic kidney disease, wherein said medicament is to be administered orally to said patient as a tablet, and the ferric citrate is administered in an amount ranging from 1 g to 18 g, and wherein the adverse cardiac event is selected from the group consisting of: heart failure, ventricular arrhythmias, myocardial infarction, decreased left ventricular (LV) ejection fraction, sudden cardiac death, aortic root dilation, and a cerebrovascular event, wherein each tablet comprises approximately 80% to approximately 92% by weight of ferric citrate, approximately 5% to approximately 15% by weight of pregelatinized starch, and approximately 0.5% to approximately 2% by weight of a lubricant; and wherein at least 80% of the ferric citrate in the tablet is dissolved in less than or equal to 60 minutes as measured by test method USP <711>, and the water content of the tablet is less than 11% by loss on drying (LOD).

5. Use of ferric citrate in the manufacture of a medicament for reducing incidence or risk of hospitalizations related to adverse cardiac events in a human patient with chronic kidney disease, wherein said medicament is to be administered orally to said patient as a tablet, and the ferric citrate is administered in an amount ranging from 1 g to 18 g, wherein each tablet comprises approximately 80% to approximately 92% by weight of ferric citrate, approximately 5% to approximately 15% by weight of pregelatinized starch, and approximately 0.5% to approximately 2% by weight of a lubricant; and wherein at least 80% of the ferric citrate in the tablet is dissolved in less than or equal to 60 minutes as measured by test method USP <711>, and the water content of the tablet is less than 11% by loss on drying (LOD).

6. Use of ferric citrate in the manufacture of a medicament for reducing incidence or risk of sudden cardiac death in a human patient with chronic kidney disease, wherein said medicament is to be administered orally to said patient as a tablet, and the ferric citrate is administered in an amount ranging from 1 g to 18 g, wherein each tablet comprises approximately 80% to approximately 92% by weight of ferric citrate, approximately 5% to approximately 15% by weight of pregelatinized starch, and approximately 0.5% to approximately 2% by weight of a lubricant; and wherein at least 80% of the ferric citrate in the tablet is dissolved in less than or equal to 60 minutes as measured by test method USP <711>, and the water content of the tablet is less than 11% by loss on drying (LOD).

7. Use of ferric citrate in the manufacture of a medicament for treating left ventricular hypertrophy (LVH) in a human patient with chronic kidney disease, wherein said medicament is to be administered orally to a said patient as a tablet, and the ferric citrate is administered in an amount ranging from 1 g to 18 g, wherein each tablet comprises approximately 80% to approximately 92% by weight of ferric citrate, approximately 5% to approximately 15% by weight of pregelatinized starch, and approximately 0.5% to approximately 2% by weight of a lubricant; and wherein at least 80% of the ferric citrate in the tablet is dissolved in less than or equal to 60 minutes as measured by test method USP <711>, and the water content of the tablet is less than 11% by loss on drying (LOD).

8. The use of claim 5, wherein the adverse cardiac event is selected from the group consisting of: heart failure, ventricular arrhythmias, myocardial infarction, decreased left

ventricular (LV) ejection fraction, sudden cardiac death, aortic root dilation, and a cerebrovascular event.

9. The use of any one of claims 1-8, wherein the ferric citrate is a complex comprising iron(III) and citric acid with a molar ratio of 1:0.69 to 1:0.87.

10. The use of any one of claims 1-9, wherein the lubricant is calcium stearate.

11. The use of any one of claims 1-10, wherein the tablet is coated.

12. The use of any one of claims 1-11, wherein the water content of the tablet is between 5% and 10% by loss on drying (LOD).

13. The use of any one of claims 1-12, wherein the chronic kidney disease patient is an end stage renal disease patient.

14. The use of any one of claims 1-12, wherein the chronic kidney disease patient is a non-dialysis chronic kidney disease patient.

15. The use of any one of claims 1-12, wherein the patient has serum phosphate levels within the normal range for non-chronic kidney disease patients.

16. The use of any one of claim 1-15, wherein the patient has FGF-23 levels that are elevated relative to the normal range in healthy humans.

17. The use of claim 16, wherein the FGF-23 levels measured are intact FGF-23 and C-terminal FGF-23 fragments.

18. The use of claim 17, wherein the patients's intact FGF-23 levels in serum are between 250 pg/mL and 350 pg/mL or 250 pg/mL and 500 pg/mL prior to administration of said medicament.

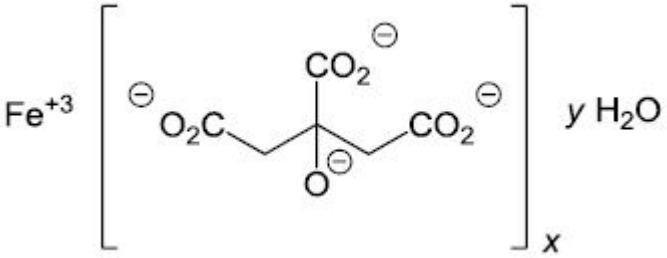
19. The use of claim 17 or 18, wherein the patients C-terminal FGF-23 levels in serum are between 60 RU/mL and 100 RU/mL or 100 RU/mL and 200 RU/mL.

20. The use of any one of claims 1-19, wherein the method further comprises monitoring the patient for (i) hemoglobin concentration; (ii) FGF-23 levels; and (iii) phosphate levels.

21. The use of any one of claims 1-20, wherein the patient is not receiving IV iron.

22. The use of any one of claims 1-20, wherein the patient is not receiving EPO.

23. The use of any one of claims 1-22, wherein the ferric citrate is iron (+3), *x* (1, 2, 3-propanetricarboxylic acid, 2-hydroxy-), *y* (H_2O)



x=0.70 – 0.87, y = 1.9 – 3.3.