CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205874Orig1s000

MEDICAL REVIEW(S)

DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS

Divisional Memo

NDA: 205874 Ferric citrate

Sponsor: Keryx Biopharmaceuticals

Review date: 11 August 2014

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 205874

The proposed claims relate to control of serum phosphorus and [redacted] (b) (4) in patients with chronic kidney disease on dialysis. This memo conveys the Division's decision to approve this application for the phosphorus claim, pending agreement on labeling.

This application has been the subject of reviews of CMC (Cooper & Wong; 31 March 2014; 29 July 2014), pharmacology/toxicology (Dwivedi; 16 January 2014), clinical pharmacology (Lai; 10 June 2014, 23 July 2014), clinical (Xu; 28 April 2014), statistics (Lawrence; 22 April 2014), and biopharmaceutics (Chikhale; 2 April 2014)). There is a consult to Division of Hematology Products (Dmytrijuk; 14 March 2014) addressing the claim for [redacted] (b) (4) There is a comprehensive CDTL memo (Thompson; 8 August 2014) with which I am in full agreement. I highlight a few matters here.

There are no CMC issues. Facility inspections are complete. The product will have a shelf-life of [redacted] (b) (4) 18 months requested. The sponsor addressed a plethora of CMC issues, mostly process control matters, between the first CMC review and the second.

The statistical review notes some problems with studies as planned and executed. The analyses were not intent-to-treat. The studies were open-label. One of the early dose-response studies did not effectively control overall alpha. Dr. Lawrence was sometimes unable to match the sponsor's findings. Nevertheless, he concludes that effectiveness was demonstrated, and I concur.

The safety database was adequate, but there was not much placebo-controlled experience, so the label will mostly focus on adverse events. Gastrointestinal events were probably adverse reactions.

There is little doubt that the program showed effects on serum iron parameters, [redacted] (b) (4) (b) (4)

There are no post-marketing commitments or requirements.

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/s/

NORMAN L STOCKBRIDGE
08/11/2014

CLINICAL REVIEW

Application Type	205874
Application Number(s)	000-000
Priority or Standard	Standard
Submit Date(s)	8/8/13
Received Date(s)	8/16/13
PDUFA Goal Date	6/7/14
Division / Office	Division of Cardiovascular and Renal Products/ ODE I/OND
Reviewer Name(s)	Nancy N. Xu M.D.
Review Completion Date	4/25/14
Established Name	Ferric citrate
(Proposed) Trade Name	Zerenex™
Therapeutic Class	Phosphate binder
Applicant	Keryx Biopharmaceuticals
Formulation(s)	Tablet 1 g
Dosing Regimen	Initial dose (b) (4) 2 g orally 3 times per day, adjust dose every 2 to 4 weeks as needed up to a maximum of 12 g daily
Indication(s)	1) control of serum phosphorus levels (b) (4)
Intended Population(s)	subjects with chronic kidney disease on dialysis

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, I recommend approval of Zenerex for control of serum phosphorus levels in subjects on dialysis with chronic kidney disease. This recommendation is contingent on the resolution of the outstanding chemistry manufacturing and controls issues. The Division of Hematology Products (DHP), which regulates the proposed indication- (b) (4) does not recommend approval of KRX-0502 for this indication.

1.2 Risk Benefit Assessment

1.2.1 Assessment of efficacy (control of serum phosphorus levels)
The primary support for efficacy comes from two phase 3 trials--KRX-0502-304 (hereafter referred to as 304) and KRX-0502-305 (hereafter referred to as 305)--in dialysis subjects with hyperphosphatemia (baseline mean level about 7.5 mg/dL). Zenerex (KRX-0502 formulation of ferric citrate) demonstrated clinically and statistically significant reductions (-2.15 mg/dL, 95% CI -2.55 to -1.74[1]) in mean serum phosphorus levels at therapeutic doses compared to placebo in the 4-week efficacy period of pivotal trial 304. KRX-0502 also demonstrated similar efficacy compared to the non-iron containing approved phosphate binders (calcium acetate and sevelamer) of the active control arm in the 52-week safety period of trial 304. In trial 305, KRX-0502 was also effective in lowering phosphorus levels when administered at 6 g/day (-1.86 mg/dL) and 8 g/day (-2.13 mg/dL), but had minimal effect at 1 g/day (-0.10 mg/dL).

Collectively, these trials--304 and 305-- provide evidence that KRX-0502 is effective in lowering serum phosphorus levels and that efficacy is maintained during chronic administration.

1.2.2 Assessment of safety
The submission provides information on a total of 233 subjects who received KRX-0502 for at least 6 months (>24 weeks) and 201 subjects for at least approximately 1 year (>48 weeks). These trials were conducted largely (92%) in the U.S. population.

The incidence of treatment emergent serious adverse events was lower in the KRX-0502 arm than the active control (KRX-0502 39.4% vs. active controls 49.0%) or

[1] This effect size, from the FDA statistical reviewer, is slightly different from that of the applicant, but is still statistically significant. For discussion, see section 6.2.4.

placebo (KRX-0502 26% vs. placebo 43%) arms. The incidence of adverse events as a whole was similar between the KRX-0502 (90.3%) and the active control (89.3%) arms.

As with the approved iron and non-iron containing phosphate binders, adverse events were primarily limited to the GI tract. Diarrhea (KRX-0502 25.6% vs. active control 14.1%), feces discoloration (KRX-0502 17.0% vs. active control 0.0%), and constipation (KRX-0502 8.0% vs. active control 5.4%) were the most common adverse events in the KRX-0502 treatment arm, and occurred at a higher incidence than in the non-iron containing active control arm. GI adverse events including diarrhea (KRX-0502 8.3% vs. active controls 0.7%), feces discoloration (KRX-0502 3.5% vs. active controls 0%), and abdominal pain (KRX-0502 2.8% vs. active controls 0.7%) led to a higher incidence of discontinuation of KRX-0502 than the active controls. However, the majority of diarrhea AEs occurred early after starting treatment, were mild in severity, and resolved with continued treatment without dose reduction, modification, or discontinuation. Other GI adverse events including nausea, and vomiting appeared similar or lower on KRX-0502 than on the active controls.

The potential for iron overload is a submission-specific primary safety concern because of the likely chronic use of KRX-0502 along with concomitant IV iron in clinical practice. In the clinical development program, one case of hemochromatosis was diagnosed by a liver biopsy; the high quantity of iron on the biopsy was suggestive of hereditary hemochromatosis. A persistent rise in serum ferritin, from his pre-KRX-0502 baseline of 799 ng/mL (while on monthly IV sucrose) to a peak of 1285 ng/mL, occurred during the 25 weeks of the KRX-0502 treatment, despite discontinuing IV sucrose at week 4. There was no clear evidence of an inflammatory process that coincided with the rise of serum ferritin level. Serum ferritin levels gradually came down to baseline after discontinuing KRX-0502.

In the one-year trial 304, a greater mean increase from baseline in serum ferritin (a marker of iron storage and inflammation) and transferrin saturation occurred in the KRX-0502 arm as compared to the active control arm. Furthermore, the frequency of marked elevations in ferritin (e.g., >1500 ng/mL) was higher on the KRX-0502 than the active control arm. Nonetheless, in the clinical development program, no evidence of increased incidence of iron overload syndrome was detected on KRX-0502 as compared with the approved phosphate binders.

The body content of iron in the normal individual is regulated primarily by absorptive processes that would normally protect an individual against iron overload when iron products are administered by an oral route. However, this regulation of iron absorption is faulty in individuals with hereditary hemochromatosis.

Although hemochromatosis has been traditionally considered a rare, genetically transmitted disorder, newer literature suggests that a latent form of hemochromatosis may be much more common. A current clinical guideline from the American Association for the Study of Liver Diseases recommends screening for hereditary hemochromatosis

in patients with a ferritin >1000 ng/mL in order to prevent the development of cirrhosis and other complications.

However, this recommendation has not been universally adapted by clinical societies, perhaps because of the clinical equipoise on adapting the genetic screening in special populations (such as the dialysis population). Furthermore, there is currently uncertainty on whether or not to administer iron to dialysis patients with higher serum ferritin levels (e.g., >800 ng/mL).

Therefore, while on balance, KRX-0502 will provide clinicians with an additional medication to treat hyperphosphatemia, I believe (b) (4)

(b) (4)

I believe for subjects with a persistent rise in serum ferritin levels after starting KRX-0502, in the absence of other causes, screening for hereditary hemochromatosis should be considered. For subjects with hereditary hemochromatosis or other iron overload syndrome, KRX-0502 should be stopped.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

Pediatric trials should be required under PREA for the phosphate binding indication. The subjects with hemochromatosis or iron overload syndrome should be excluded. Iron parameters should be regularly monitored.

2 Introduction and Regulatory Background

2.1 Product Information

Ferric citrate, KRX-0502, is an iron-based phosphate binder. The applicant has proposed the following two indications in patients with chronic kidney disease on dialysis:

1) the control of serum phosphorus levels (indication studied under IND)

(b) (4)

The proposed dose of KRX-0502 is (b) (4) 6 grams per day administered as (b) (4) 2 tablets (1 gram per tablet) 3 times daily with meals. The dose is to be titrated based on phosphorus levels to a maximal dose of 12 g/day (12 tablets /day).

2.2 Tables of Currently Available Treatments for Proposed Indications

Serum phosphorus is an accepted surrogate endpoint for drug approval in the dialysis population (ESRD). As shown in table 1 below, five types of phosphate binders have been approved in the US, including a recently approved iron-based agent, ferric oxyhydroxide sucrostamix. Use of approved phosphate binders is generally limited by GI tolerability and compliance.

Table 1 Approved phosphate binders in chronic dialysis patients

Drug category	Drug names	Comments
Non-iron based phosphate binders		
Calcium salts	Calcium acetate (Phoslo, Phoslyra, Eliphos, etc)	Hypercalcemia, exacerbate calcification of vasculature and other soft tissues.
Lanthanum salt	Lanthanum carbonate (Fosrenol)	GI adverse events; potential accumulation in the bone and other tissues.
Sevelamer	Sevelamer Hydrochloride (Renagel)	Anion-exchange resin; GI adverse events;
	Sevelamer carbonate (Renvela)	Anion-exchange resin; GI adverse events
Iron-based phosphate binder		
Iron salts	Ferric oxyhydroxide sucrostamix (Velphoro)	GI adverse events; mask GI bleed

In addition, aluminum hydroxide, magnesium hydroxide or carbonate, and calcium carbonate are also occasionally used off-label to lower serum phosphorus. Their use is limited by toxicities such as neurologic, bone, soft tissue, and/or electrolyte abnormalities.

2.3 Availability of Proposed Active Ingredient in the United States

Ferric citrate, currently marketed in this country as a food substance, is generally regarded as safe (GRAS). However, the KRX-0502 formulation of ferric citrate is not yet marketed in the US. See section 4 on CMC for further information on the KRX-0502 formulation.

2.4 Important Safety Issues With Consideration to Related Drugs

Currently marketed phosphate binders adsorb dietary phosphate in the GI tract, thus preventing its uptake into the body. The major safety concern with these products has been complications in the GI tract including diarrhea, constipation and obstruction.

Another concern is that these products may bind other administered drugs. There are also drug-specific safety concerns (see in table 1).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following table summarizes the key regulatory history.

Table 2 Key regulatory history

Source (date of meeting or submission)	Advice from Agency for IND 52868
March 19, 1997	• Submission of an investigator-IND by University of Michigan • The indication under study was control and management of serum phosphorus in ESRD patients on dialysis.
April, 19, 2006	• Transfer of the IND to Panion and BF Biotech Inc
July 14, 2006 EOP2 meeting	• Division agreed that an integrated safety database of approximately 250 to 300 patients treated for one year with KRX-0502 would be sufficient for long-term exposure. • The use of IV iron in the protocol was acceptable from a subject safety perspective, as long as subjects have signs of iron deficiency and anemia, and have been using EPO.
2007	• Transfer of the IND to Keryx
August 14, 2009 Special Protocol No Agreement Letter	• Division recommended a randomized active-controlled 52-week safety study followed by a short-term placebo-controlled withdrawal • Division cautioned that (b) (4) will probably not make it into labeling because (b) (4)
December 30, 2009 SPA Agreement	• SPAs were granted for trials 304 and 305
July 16, 2012 Advice letter on statistical analysis plan for trial 304	• Division advised that (b) (4) • Division indicated that the clinical significance of many of the proposed secondary endpoints was unclear (b) (4) • Division advised that if a significant amount of study data had been amassed, it may be too late to do more than drop not useful endpoints.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

As a whole, the submission was well organized and sufficiently complete to support review of the application within PDUFA time frames. Minor discrepancies were noted in some analysis results, but did not alter the conclusion about efficacy and safety.

3.2 Compliance with Good Clinical Practices

Clinical investigator sites were inspected to assess the quality, integrity, and acceptability of the data submitted in support of the application and the adequacy of the protection of the rights and welfare of human research subjects. Three domestic sites from the two pivotal trials were selected based on a high risk ranking as determined by the GCP Site Selection Tool. The Office of Scientific Investigations recommends that data from these trials may be considered reliable.

3.3 Financial Disclosures

See the attached Clinical Investigator Financial Disclosure form.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry Manufacturing and Controls (CMC) reviewers are recommending a *complete response* because of several issues, including the main quality concern that the drug substance is not well-controlled, leading to significantly variable drug substance batches. Below, I briefly highlight the issues on drug substance and drug product that affect the clinical interpretation of the efficacy or safety data.

Drug Substance:
The applicant claims that KRX-0502 (ferric citrate) exists as an (b) (4) *(a coordination complex)* of (b) (4) (b) (4) The CMC reviewers note that it is unclear if this is (b) (4) is (b) (4) and no data have been provided to demonstrate that these are the active (b) (4) responsible for the proposed (b) (4) Furthermore, the (b) (4) Hence, it appears that it is the total amount of ferric ion that is critical to the mechanism of action (b) (4)

Drug Product:

The applicant has developed an immediate release film-coated tablet for oral administration. Each tablet contains 210 mg of ferric iron equivalent to (b) (4) mg of ferric citrate. (b) (4) . Thus per tablet, (b) (4) . The total amount (b) (4) in the maximum therapeutic dose (12 g/day) of ferric citrate is (b) (4)

Reviewer's comment: (b) (4) *are reported to be* (b) (4) *through the gastrointestinal tract than* (b) (4) *compounds. Thus, to prevent potential* (b) (4)

The KRX-0502 drug product formulation proposed for marketing was used in the 2 pivotal Phase 3 Trials 304 and 305 (and also in trial 307, the long-term follow-up of trial 304).

Trial PBB00101 used a different ferric citrate drug substance (pharmaceutical grade ferric citrate). Trial 201 used a different drug product (a (b) (4) capsule formulation filled with 375 mg KRX-0502). According to the CMC reviewers, relevant information on the different drug substance and drug product information was not submitted with the NDA for review.

4.2 Clinical Microbiology

The submission does not include microbiology data.

4.3 Preclinical Pharmacology/Toxicology

The preclinical pharmacology/toxicology (PT) reviewers are recommending approval of KRX-0502 with some modifications to the proposed label.

Data obtained both from published non-proprietary studies and animal studies sponsored by Keryx have shown the effects of orally administered ferric citrate on liver, GI tract, renal, cardiovascular, and endocrine and immune systems at maximum dosage levels, including lethal hepatotoxicity in the dog, the most sensitive species. The proposed maximum human therapeutic dose (12 g/day, or 200 mg ferric citrate/kg in a 60 kg human, or 42 mg ferric iron/kg) is 8.4 times the maximum iron dosage used in mice (1600 mg for 10 days[3]) and rats (3500 mg/kg/day for 28 days) when calculated on a mg/kg basis. The no-observed adverse event dose in the 42-week dog study was 400 mg/kg, which translated to a 1.08x safety margin to the top human dose of 12 g/day.

(b) (4)

[3] Information from the FDA report on food substance that are generally regarded as safe GRAS.

The projected safety margin was 5-10x based on more overt toxicology and persistent histopathology (e.g., inflammatory liver foci) that occurred in the 42-week dogs study.

4.4 Clinical Pharmacology

The clinical pharmacology review has not been completed. The applicant will submit results of *in vitro* drug-drug interaction studies in May 2014.

4.4.1 Mechanism of Action

In subjects with normal regulatory mechanisms that control the absorption of inorganic iron within the small intestinal mucosal cell, the absorption of ferric iron is limited.

The poor absorption of ferric iron from KRX-0502 allows its binding with phosphate in the gut, thereby preventing phosphate absorption and lowering serum phosphorus levels.

4.4.2 Pharmacodynamics

See section 6.2.9 on effects on serum phosphorus levels. See section 7.3.5 for effects on serum iron parameters.

4.4.3 Pharmacokinetics

Formal pharmacokinetic studies have not been performed with KRX-0502. Examination of serum iron parameters has shown that there is systemic absorption of iron from KRX-0502.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The KRX-0502 clinical development program comprises 18 clinical trials. This submission cites three trials as adequate, well-controlled trials and refers to them as primary support for efficacy of the two proposed indications. These 3 trials are: two pivotal phase 3 trials (304 and 305) and a phase 2 trial, PBB00101. Trials 304 and 305 were conducted mainly in U.S dialysis subjects using the ferric citrate drug product to be marketed; PBB00101 was conducted mainly in Taiwanese dialysis subjects using “pharmaceutical grade ferric citrate”. The three trials have similar primary endpoints: change in serum phosphorus (mg/dL) from baseline (Table 3). The trial specific features that are related to the phosphate control claim are discussed in more detail in sections 5.3 and 9. Trial features related to the maintenance of iron stores claim are described in sections 5, 6 and 9.1.

Four trials--the three controlled trials (304, 305, and PBB00101) and an uncontrolled trial, 201—contribute to the applicant's pooled safety dataset (integrated safety set [ISS]). Trial 201 used a (b) (4) capsule formulation filled with 375 mg KRX-0502 (section 4.1). All four trials enrolled subjects on dialysis. Because ferric citrate is an iron-containing phosphate binder, all four trials in the integrated safety database had eligibility criteria based on biomarkers that could reflect iron stores or inflammation. Iron parameter-based eligibility criteria and monitoring for potential iron overload are described in section 9 (Table 34).

For an overview of these trials, see Table 3 below.

Table 3 Major Trials Cited to Support Efficacy and Safety

Trial ID Phase Country(ies) Company	Trial Design (N randomized, ITT)	Treatment Arms (n exposed)	Duration of Rx	Primary endpoint
Drug substance: KRX-0502, ferric citrate; Drug product: 1 g tablet				
304 (SPA) Phase 3 US, Israel Keryx	*52 -week Safety period:* multicenter, open-label, 2:1 randomization into KRX-0502 [292] vs. active-control* [149]; titrate to a maximum of 12 g/day to target phosphorus level *4-week Efficacy period:* multicenter, randomized withdrawal, placebo-controlled (96 vs. 96), dose-titration (1 g to 12 g)	Start at 6 g/day titrate to a maximum of 12 g/day of KRX-0502 (289) vs. active control (149) Continue KRX-0502 at dose used at the end of Safety period (95) vs. placebo (95)	Up to 56 weeks	Change in phosphorous from baseline/week 52 to Week 56 (ferric citrate vs. placebo)
305 (SPA) Phase 3 US Keryx	multicenter, open-label, uncontrolled, fixed-dose, dose-ranging (total N:154)	1 g/day (51) 6 g/day (52) 8 g/day (48)	28 days	Change in phosphorous from Baseline to Day 28
Drug substance: Ferric citrate (*pharmaceutical grade); Drug product: 500 mg capsule*				
PBB00101 Phase 2 US, Taiwan Keryx	multicenter, double-blind, placebo controlled, fixed-dose, dose-ranging (N: 116)	2 g/day (33) 4 g/day ((34), 6 g/day (33) Placebo (16)	28 days	Change in phosphorous from baseline to Day 14 and Day 28
Drug substance: KRX-0502, ferric citrate*; Drug product: 375 mg capsule*				

Trial ID Phase Country(ies) Company	Trial Design (N randomized, ITT)	Treatment Arms (n exposed)	Duration of Rx	Primary endpoint
201 Phase 2 US Keryx	open-label, uncontrolled, exploratory, dose-ranging, titrate to target phosphorus level. (N=55)	Start at 4.5 g/day (34) or 6 g/day (21), Titrated to a maximum of 11.3 g/day	28 days	Safety

*calcium acetate and/or sevelamer carbonate at investigator discretion. Titration of these approved non-iron based phosphate binders based on the respective US prescription information.

In addition to these trials, as shown in Table 4, another 14 trials are either completed (10) or are ongoing (4). In contrast to the 4 key trials conducted by Keryx with the KRX-0502 formulation in the US, these trials were mostly (8 out of 14) conducted in Japan to support submission in Japan. Importantly, these 8 Japanese trials used a different formulation (JTT-751) of ferric citrate and were conducted by a different sponsor, Japan Tobacco, Inc. (JT)[4], and were not conducted under the U.S. IND.

[4] Keryx sub-licensed Japanese rights for KRX-0502 to and its subsidiary, Torii Pharmaceutical Co., Ltd.

Table 4 Other ongoing and completed trials

Trial ID Phase Country, Company	Trial Design	Subjects randomized	Duration of Therapy
Completed Trials			
Drug substance: KRX-0502, ferric citrate; Drug product: 1 g tablet			
202, Phase 2 Israel, Keryx	uncontrolled, open-label trial	22	28 days
Drug substance: Ferric citrate (*pharmaceutical grade); Drug product: 500 mg capsule*			
Open-Label Extension of PBB00101 Phase 2 Taiwan, Panion	uncontrolled, open-label,	29	Up to 1 year
Drug substance: JTT-751, ferric citrate; Drug product: 250 mg or 500 mg tablets			
GBA 2-1, Phase 2 Japan ,Japan Tobacco	randomized, double-blind, placebo-controlled, parallel-group, dose-response trial	192	28 days
GBA 4-1, Phase 3 Japan ,Japan Tobacco	multicenter, randomized, open-label, active-controlled, parallel-group, non-inferiority trial	229	12 weeks
GBA 4-3, Phase 3 Japan, Japan Tobacco	multicenter, uncontrolled, open-label trial in subjects on peritoneal dialysis	56 (19 in extension trial)	52 weeks (12 weeks, plus up to 40 weeks in extension trial);
GBA 4-4, Phase 3 Japan, Japan Tobacco	randomized, double-blind, placebo-controlled, comparative trial	subjects with CKD not on dialysis (59)	12 weeks (eligible subjects continued into Trial GBA 4-7)

Trial ID Phase Country, Company	Trial Design	Subjects randomized	Duration of Therapy
GBA 4-5, Phase 3 Japan ,Japan Tobacco	multicenter, uncontrolled, open-label, long-term administration trial	234	Up to 28 weeks
GBA 2-2, Phase 2 Japan, Japan Tobacco	uncontrolled, open-label trial	10	14 days
Ferric citrate (commercially available) 500 mg capsule			
Univ. of Michigan Study 1 , Phase 1 Taiwan Investigator	randomized, open-label, active control, crossover study	54	28 days
Univ. of Michigan Study 2, Phase 2a US Investigator	randomized, open-label, active control study	28	28 days
Ongoing Trials			
Drug substance: KRX-0502, ferric citrate; Drug product: 1 g tablet			
KRX-0502-307 Phase 3 US Keryx	multicenter, uncontrolled, open-label, safety extension of Trial KRX-0502-304	71[5]	Up to 48 weeks

[5] This trial is ongoing. The number of subjects enrolled is reported as of the November 1, 2012 cut-off date.

Trial ID Phase Country, Company	**Trial Design**	**Subjects randomized**	**Duration of Therapy**
KRX-0502-204 Phase 2 US Keryx	multicenter, randomized, double-blind, placebo-controlled, 3-period trial	subjects with CKD **not** on dialysis 0[6]	Up to 12 weeks
Drug substance: JTT-751, ferric citrate; Drug product: 250 mg tablet			
GBA 4-6 Phase 3 Japan Japan Tobacco	multicenter, uncontrolled, open-label, long-term administration trial	180	52 weeks
GBA 4-7 Phase 3 Japan Japan Tobacco	multicenter, uncontrolled, open-label extension trial to GBA 4-4	subjects with CKD not on dialysis 29	40 weeks (52 weeks total including time in Trial GBA 4-4)

[6] Planned: 140, randomized 1:1 No subjects enrolled as of 01 Nov 2012 cut-off date

5.2 Review Strategy

In the clinical review of efficacy, I focused on the design and conduct of the two phase 3 pivotal trials conducted in the dialysis population, using the KRX-0502 formulation and the resulting data for both proposed indications. For the control of serum phosphate level claim, I also reviewed the clinical study report for trial PBB00101 to determine if the findings were supportive of the effect on serum phosphorus. Of note, PBB00101 did not have an adequate plan to control the type 1 error rate. For the serum phosphorus efficacy analyses, the phase 3 trials were not pooled because of their different trial design (e.g., placebo controlled vs. active controlled). In addition to the pivotal trials conducted under the SPA, I also reviewed the clinical study report of the other 10 completed trials conducted in the dialysis population to determine if the findings on serum phosphorus were supportive. The trials that are ongoing, were not conducted in the dialysis population, or are exploratory in nature are not reviewed for efficacy.

The applicant believes that these trials, designed to assess effects of KRX-0502 on serum phosphate level, (b) (4) I refer and summarize the Division of Hematology Product's decision for the denial of (b) (4) which is within their jurisdiction, in sections 6 and 9.2.

For the clinical review of safety, I focused on adverse reactions commonly associated with members of this pharmacologic class (e.g., GI adverse effects). I also evaluated iron parameters and possible iron overload.

5.3 Discussion of Individual Clinical Trials

A brief description of trials 304 and 305 is shown below. For additional details, see section 9.

Trial 304
Title: A three-period, 58-week safety and efficacy trial of KRX-0502 (ferric citrate) in subjects with end-stage renal disease on dialysis.

Trial Design
Trial 304 was a 58-week, multicenter, randomized, open-label trial safety and efficacy trial that consisted of a 2-week Washout Period, a 52-week active-controlled safety period followed by a 4-week placebo-controlled randomized withdrawal efficacy assessment period (hereafter referred to as efficacy period) in dialysis patients with hyperphosphatemia. After the 2-week washout period during which phosphate binders were held, subjects with a serum phosphorus between 6.0 mg/d and 10.0 mg/dL during washout were randomized 2:1 to the KRX-0502 group or the active-control group [calcium acetate and/or sevelamer carbonate]) into the safety period. To avoid prolonged exposure to very high serum phosphorus levels, the duration of the Washout

Period for individual subjects depended on the extent of the increase in serum phosphorus. Subjects whose serum phosphorus was ≥9.0 mg/dL during the Washout Period were to start study drug within 48 hours, if possible. Following completion of the safety period, subjects who were randomized to the KRX-0502 group were eligible to be re-randomized 1:1 into the efficacy period where they either continued on the KRX-0502 (at the doses they were on at the end of the efficacy assessment visit) or switched from KRX-0502 to placebo. In the safety and efficacy periods, KRX-0502 dose was titrated per serum phosphate response.

Endpoints also as specified in the final statistical analysis plan (dated January 5, 2013)

Primary endpoint in the placebo-control (efficacy period)

Primary endpoint: change in serum phosphorus from baseline (Visit 21, Week 52) to end of the 4-week Efficacy period, comparing KRX-0502 with Placebo.

The statistical analysis of the primary endpoint used a Last Observation Carried Forward (LOCF) analysis of covariance (ANCOVA) model, with treatment (fixed effect) and baseline covariate. A sensitivity analysis using mixed model repeated measure (MMRM) was also performed on the primary endpoint using a model with terms for treatment group, baseline value, weeks post-baseline, and treatment by weeks post-baseline interaction. Between-treatment differences were also estimated for both ANCOVA and MMRM analyses with corresponding 2-sided 95% CIs around the differences.

Reviewer's comment: Even though the statistical analysis plan was finalized after the trial finished, no major changes that would affect the interpretation of the efficacy finding on serum phosphorus. Please see the statistical review for detail.

Secondary end points tested in the active-control safety period

1. change from baseline in ferritin at week 52 (of the safety period).
2. change from baseline in TSAT at week 52.
3. cumulative use of IV iron over 52 weeks.
4. cumulative use of ESA over 52 weeks.

Reviewer's comment:
The (b) (4) *claim was proposed at the pre-NDA meeting.*

(b) (4)

In terms of the secondary endpoints, the original SAP (dated October 2009) aim to evaluate changes in ferritin and TSAT at all visits of the safety assessment period (hereafter referred to as safety period), and treated these analyses as exploratory endpoints. The secondary endpoints-- change from baseline in ferritin and TSAT at week 52—and controlling for type I error, were specified on the SAP dated July 4, 2012. Please see the statistical review for detail.

Analysis Populations
Efficacy analysis were performed for the full analysis population, which consisted of all subjects who took at least 1 dose of study medication, had baseline assessments, and had at least 1 post-baseline efficacy assessment.

Trial 305:
Title: A 4-week dose-ranging and efficacy trial of KRX-0502 (ferric citrate) in patients with end-stage renal disease (ESRD) following a two-week washout period

Trial Design
This 4-week fixed-dose, dose ranging trial randomized dialysis subjects with hyperphosphatemia (serum phosphorus ≥ 3.5 mg/dL but ≤ 8.0 mg/dL during screening on phosphate binders and ≥ 6.0 mg/dL but <10.0 mg/dL following a 2 week washout) to 1 g/day, 6 g/day and 8 g/day of KRX-0502.

Endpoints
Primary endpoint (final statistical analysis plan dated April 13, 2011)
The primary endpoint was a change in serum phosphorus from baseline to end of the treatment period (Day 28).

The primary endpoint was pre-specified as linear regression model with dose effect. Positive dose response would be confirmed if the null hypothesis of slope=0 was rejected at a significance level of 0.05. Each of the 3 dose groups (1, 6, and 8 g/day) was included in the regression analysis. Missing efficacy data were imputed using LOCF method.

As a sensitivity analysis, change in serum phosphorus from baseline to the end of treatment (Day 28) was also analyzed using an MMRM model that included treatment, visit, and treatment-by-visit as fixed effects and baseline as the covariate. Within-subject variation was modeled using compound symmetry. Missing values were not imputed.

The efficacy analyses were to be based on what the applicant referred to as the Intent-to-treat (ITT) population, which consisted of all subjects who took at least one dose of study medication and provided baseline and at least one on-treatment post baseline phosphorus assessments. Because this population did not include all subjects randomized, it may be better named as modified ITT population.

Reviewer's comment: The statistical analysis plan was finalized after trial completion. However, with respect to the primary endpoint, the analysis plan was not changed from the first version dated October 2, 2009.

Secondary endpoints (final statistical analysis plan dated April 13, 2011)
The first secondary endpoint was a sensitivity analysis of the primary endpoint.

1) The change in serum phosphorus from baseline to endpoint was analyzed via an ANCOVA model with treatment as the fixed class effect and baseline as the covariate as a secondary outcome. The three pairwise comparisons was tested in the following order at a 5% significance level:
    - 8 g vs. 1 g
    - 6 g vs. 1 g
    - 8 g vs. 6 g

To control overall Type I error rate at 5%, a pairwise comparison was significant only if all previous pairwise comparisons, if any, were significant.
The two-sided 95% confidence intervals of treatment differences for all pairwise comparisons were presented.

In contrast, testing for the following secondary endpoints did control for type I error rate.

2) Changes from baseline in serum phosphorus, serum calcium, and calcium times phosphorus product, ferritin, TSAT, and bicarbonate at all post-baseline assessment time points, where the baseline is the last respective assessment prior to receiving the first dose of the study drug. These variables were similarly analyzed using the same methods for some of the primary efficacy variable analyses.
3) The proportion of treatment failures (defined as serum phosphorus ≥ 9.0 mg/dL) at the end of treatment. Between-treatment differences in the percentage and the 95% confidence interval of the differences were calculated using normal approximation without continuity correction.
4) The proportion of patients with serum phosphorus < 5.5 mg/dL at Visit 8 (Day 28).

Reviewer's comment: The trial did not intend to analyze IV iron dosing because of the limited treatment duration (see Section 7.2.2 on the potential limitation on the assessment of dose related AEs in trial 305).

6 Review of Efficacy

Efficacy Summary

In support of the proposed indications, the applicant conducted 2 phase 3 trials in the ESRD population. These trials showed a consistent treatment effect on serum phosphorus.

6.1 Indications

The applicant is proposing the following indications:
1) control of serum phosphorus levels

(b) (4)

6.1.1 Methods

See section 5.2.

6.2.1 Trial 304

6.2.2 Subject Disposition

During the safety period, 441 subjects with CKD on dialysis with hyperphosphatemia were randomized in a 2:1 ratio to receive open label KRX-0502 (N=292) or active control (sevelamer carbonate and/or calcium acetate; N=149) for 52 weeks. The disposition of these subjects is shown below (Table 5).

As shown in the table below, subjects treated with the KRX-0502 formulation tolerated the drugs similarly to the active control in the 52 week safety period. Nonetheless, the percentage of subjects who discontinued study medication prematurely was slightly higher in the KRX-0502 arm as compared to the active control arm. Furthermore, the slightly higher percentage of discontinuations was because of the discontinuation from adverse events. Section 7.3.3 discusses the GI adverse events that lead to premature discontinuation.

Table 5 Disposition of subjects in the open-label active-controlled safety period of trial 304 (ITT population)

	KRX-0502 (Ferric Citrate) Safety period (N=292)	**Active Control Safety period (N=149)**
Subjects Who Received Study Drug (**safety population**)	289 (99.0%)	149 (100.0%)
Subjects Who Completed Safety period on Drug	193 (66.1%)	111 (74.5%)
Subjects Who Discontinued Medication Prematurely	96 (32.9%)	38 (25.5%)
Reasons for Early Termination		
Adverse event	60 (20.5%)	21 (14.1%)
Investigator judgment	5 (1.7%)	2 (1.3%)
Lack of efficacy	0	0
Lost to follow-up	4 (1.4%)	1 (0.7%)
Not recorded	3 (1.0%)	2 (1.3%)
Other	14 (4.8%)	6 (4.0%)
Withdrew consent	10 (3.4%)	6 (4.0%)

Source: reviewer's table, confirmed with the applicant.

To be eligible for re-randomization into the efficacy period, subjects needed to have completed the final visit of the safety period on the study drug. According to the

applicant, subjects who were initially randomized to active-control during the safety period but switched to the KRX-0502 treatment because of hypercalcaemia were eligible to be randomized into the efficacy period, if they completed the final visit of the safety period on study drug (although the protocol stated the subjects randomized to KRX-0502 who completed the final visit of the safety period were eligible).

The number of subjects who completed the safety period on KRX-0502 was not the same as the number of subjects randomized into the efficacy period. This difference was largely because seven KRX-0502 treated subjects were eligible to be randomized into the efficacy period, but were not randomized for the following reasons (see table below). In addition, two subjects were randomized to active control and switched to KRX-0502 during the safety period because of hypercalcemia while on calcium acetate, in accordance with the protocol. Both subjects completed the safety period on KRX-0502 and were randomized into the efficacy period. Finally, two subjects were randomized to KRX-0502 but discontinued KRX-0502 during the safety period and were therefore ineligible to be randomized into the efficacy period, but were nonetheless randomized.

The subjects who were not eligible but were re-randomized to the efficacy period had similar demographic and key characteristics (including ferritin, TSAT, phosphorus, calcium, hemoglobin) at baseline and end of the safety period to the subjects who were eligible and re-randomized (applicant submission dated 12.12.13 in response to IR.) Lastly, no unexpected AEs found in the 7 subjects who were eligible but not re-randomized. Therefore, the exclusion of these 7 subjects is unlikely to have biased the efficacy findings based.

Table 6 Re-randomization of subjects into the efficacy period

	KRX-0502 Ferric Citrate Safety period (Safety: n=289)	**Active Control (N=149)**
Subjects completed the final visit/Week 52 of the Safety period	193	111
Subjects eligible to be randomized to the Efficacy Period	193	2[(1)]
Subjects eligible to be randomized to the Efficacy Assessment Period **but not** randomized	7[(2)]	0
Subjects eligible to be randomized to the Efficacy Period and randomized	186	2[(1)]
Subjects **in**eligible to be randomized to the Efficacy Assessment Period **but** randomized	2[(3)]	2[(4)]
Total subjects randomized to the Efficacy period	188	4

Source: reviewer's table, confirmed with the applicant.
[(1)] Represents two subjects were randomized to Active Control and switched to KRX-0502 during the safety period because of hypercalcemia while on calcium acetate, in accordance with

the protocol. Both subjects completed the safety period on KRX-0502 and, per the protocol, were eligible to be randomized into the efficacy period.
(2) Seven KRX-0502 subjects were eligible to be randomized into the efficacy period, but were not randomized for the following reasons: non-compliant per investigator judgment (n=1), not able to collect labs because of traveling (n=1), moving away (n=1), adverse event (n=1), or "not continuing into efficacy" (n=2), not recorded (n=1).
(3) Represents two subjects randomized to KRX-0502 but discontinued KRX-0502 during the safety period and were therefore ineligible to be randomized into the efficacy assessment period, but were nonetheless randomized.
(4) Represents two subjects randomized to Active Control and switched to KRX-0502 during the Safety period because of hypercalcemia while on calcium acetate, in accordance with the protocol, but discontinued KRX-0502 during the safety period and were therefore ineligible to be randomized into the efficacy period.

Lastly, as shown in Table 7, for the subjects randomized into the efficacy period, the percentage of subjects who discontinued study drug premature was not higher in the KRX-0502 than the placebo arm. In the placebo arm, the majority of the "other" events leading to discontinuation of study drug were because of a serum phosphorus level ≥9.0 mg/dL.

Table 7 Disposition of subjects re-randomized into the placebo-controlled efficacy period of trial 304

	KRX-0502 in efficacy period (N=96)	**Placebo in efficacy period (N=96)**
Subjects Who Received Study Drug	95 (99%)	95 (99%)
Subjects in the Full Analysis Population	91 (95%)	91 (95%)
Subject Who Completed Efficacy period on Study Drug	90 (94%)	70 (73%)
Subject Who Discontinued Study Drug	5 (5%)	25 (26%)
Reason for Early Termination		
Adverse event	2 (2%)	3 (3%)
Investigator judgment	0	2 (2%)
Lack of efficacy	1 (1%)	0
Lost to follow-up	0	0
Not recorded	2 (2%)	4 (4%)
Other	0	15 (16%)
Withdrew consent	0	1 (1%)

Source: reviewer's table, confirmed with the applicant.

6.2.3 Demographics

The baseline demographics, including age, sex, race, and co-morbid conditions, were similar across treatment arms.

Approximately 41% of the randomized subjects were white, 54% were black or African American; the remaining 5% consisted of American Indian or Alaska Native, Native Hawaiian or Pacific Islander, and less than 1% East Asian. About 40% percent were female, and approximately half of subjects were ≥65 years of age. The majority (>96%) of subjects were hemodialysis-dependent and had an average serum phosphorus level of 7.5 mg/dL during washout. The subjects, on average, had no evidence of absolute (and perhaps functional) iron deficiency anemia (Table 8). Lastly, they were on IV iron and ESA.

Table 8: Baseline Characteristics in Trial 304 (full analysis population)

	KRX-0502 Ferric Citrate	**Active Control**
Hemodialysis n (%)	281 (96.1)	146 (97.9)
Peritoneal Dialysis n (%)	11 (3.9)	3 (2.1)
Serum phosphorus Mean (SD)	7.4 (1.6)	7.6 (1.7)
Ferritin (ng/mL) Mean (SD)	592 (293)	610 (308)
TSAT (%) Mean (SD)	31 (11)	31 (12)
Hemoglobin (g/dL) Mean (SD)	11.6 (1.2)	11.7 (1.3)
Median IV iron (mg/day)	2.3	3.0
Median ESA (units/day)	802	720

Source: Extracted from the applicant's tables, ISS Table 2.2.1

Reviewer's comments on iron deficiency in ESRD patients:
To give some perspective, according to the US guidelines[1], absolute iron deficiency is defined as follows:

1. *The percent transferrin saturation (TSAT) (plasma iron divided by total iron binding capacity x 100) less than 20 percent, and*
2. *Serum ferritin concentration <100 ng/mL.*

Patients with absolute iron deficiency respond to IV iron with increasing hemoglobin (an erythropoietic response).

In addition, according to the US guidelines, ESRD patients with anemia (hematocrit <33%) and/or requiring greater than expected ESA and also have TSAT and ferritin levels above those required for absolute iron deficiency can also be classified as having "functional iron deficiency". The confirmation of functional iron deficiency is obtained by having an erythropoietic response and/or reduction in ESA dose with supplemental IV iron[7]. Functional deficiency is associated with a TSAT ≤20 percent and elevated ferritin

[7] National Kidney Foundation and Kidney Disease Outcome Quality Initiative's 2000 guideline of Anemia in Chronic Kidney Disease. Besarab et al, American Journal of Kidney Diseases, Vol 34, No 1 (July), 1999: pp 21-28

levels (typically between 100 to 800 ng/mL or even higher). There is a wide window for serum ferritin levels that can be associated with functional iron deficiency; ferritin is both a marker of iron store and a marker of inflammation, a condition that is commonly seen in chronic kidney disease/ESRD patients.

The 2012 Kidney Disease Improving Global Outcome guidelines suggest a lower ferritin upper limit for functional iron deficiency[8]. It suggests oral or intravenous iron therapy for patients with anemia and a TSAT ≤30 percent and ferritin ≤500 ng/mL.

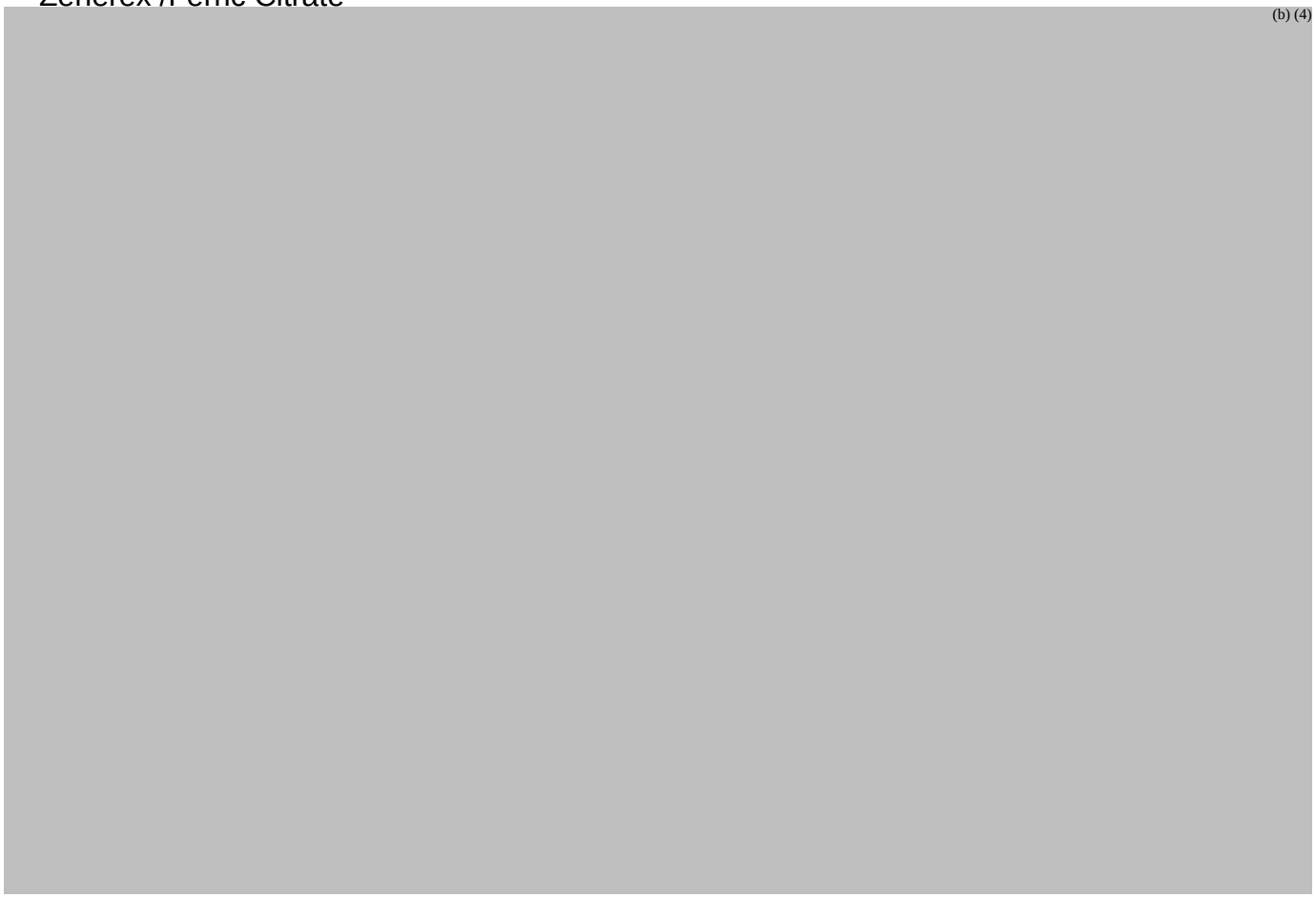
Therefore, the entry ferritin and TSAT criteria did not require subjects have absolute or perhaps functional iron deficiency. The eligibility criteria: ferritin <1000 ng/mL (a normal ferritin is <200 ng/mL) and TSAT <50% (TSAT is generally considered elevated if ≥60 percent in men and ≥50 percent in women) was meant to exclude parameters that could be consistent with iron overload.

6.2.4 Analysis of Primary Endpoint

According to the applicant's analysis of the primary endpoint using ANCOVA, KRX-0502-treated subjects had a clinically and statistically significantly reduction (-2.18, $p<0.0001$) in mean serum phosphorus level compared with placebo following 4 weeks of treatment in the efficacy period. The FDA statistician could not replicate the exact treatment size reported by the applicant, but found similar results (-2.15, 95% CI -2.55 to -1.74). The MMRM sensitivity analysis showed similar results with the ANOCA analysis.

[8] Kidney Disease Improving Global Outcome (KDIGO) clinical practice guidelines for anemia in chronic kidney disease. Kidney lnt Suppl 2012;
2:288.

(b) (4)



Source: the applicant's proposed labeling

Reviewer's comment: While this is an open-label trial, because the primary efficacy endpoint and most of the secondary efficacy endpoints are based on objective laboratory measurements conducted by central laboratory staff blinded to treatment and dose, the open-label design was not considered to have the potential to bias the efficacy conclusions of the trials.

6.2.5 Analysis of Secondary Endpoints

Also see section 4.4.2.

As shown in Table 9, the mean change from baseline in ferritin and TSAT was statistically significantly greater in the KRX-0502 than in the active control arm. The average daily use (median daily cumulative) of IV iron and ESAs decreased significantly using KRX-0502 as a phosphate binder compared with active control over 52 weeks.

Table 9: Secondary endpoint in order of testing (Trial 304)

Secondary Endpoint (Week 52)	BRAND	Active Control	Treatment Difference (95% CI)	p-value
Ferritin (ng/mL)				
Mean baseline (Week 0)	592.80	609.50		
Mean change from baseline (Week 52)	302.07	22.37	273.92 (190.22, 357.61)	<0.0001[a]
TSAT (%)				
Mean baseline (Week 0)	31.3	30.8		
Mean change from baseline (Week 52)	7.9	−1.0	9.33 (6.22, 12.44)	<0.0001[a]
Median cumulative IV iron administered (mg/day)	1.87	3.83	NA[b]	<0.0001[b]
Median cumulative ESA administered (units/day)	755.80	993.46	NA[b]	<0.05[b]

Source: applicant's CSR for trial 304, Tables 15 and 16.
a. Average daily IV iron administration based on the cumulative IV iron administration up to Week 52 was calculated as the total cumulative IV iron administration divided by the total number of days on study drug.
b Overlapping doses were prorated based on days to only include dose for the period of time on study drug during the Safety period.
c Basic assumptions for using ANCOVA were not met; therefore, the 2-sided Wilcoxon Rank Sum Test with normal approximation was used to calculate the P-value for the difference between the treatment groups

6.2.6 Other Endpoints

None.

6.2.7 Subpopulations

In the efficacy period of trial 304, there were no significant differences in treatment effects on the change from baseline in serum phosphorus levels across sub-groups. However, because of the small sample sizes, interpretation is limited.
No notable difference in the primary endpoint (changes from baseline in serum phosphorus) by subgroups of sex (<65, ≥65 to <75, and ≥75 years), race (white, black), diabetes status (diabetes and no diabetes). Because of the small sample sizes for Asian race and peritoneal dialysis, the interpretation is limited.

In the safety period of trial 304, the treatment effects in the KRX-0502 and the active control arms were similar across the wide range of serum phosphorus baselines. In both arms, a greater reduction in serum phosphorus occurred for subjects with a higher baseline serum phosphorus level.

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Given the findings from the dose-response studies and the known mechanism of action, a fixed dose of KRX-0502 for long-term use in patients with CKD on dialysis is not feasible. Because of factors such as differences in dietary phosphate intake between and within individuals, phosphorus management with phosphate binders requires regular assessment of serum phosphorus levels and titration of the dose of KRX-0502 to maintain serum phosphorus levels at target levels (currently suggested to be in the 3.5 to 5.5 mg/dL range by KDOQI clinical guidelines).

In trial 304, subjects received a starting dose of 6 g/day that was titrated to maintain serum phosphorus at target levels, up to a maximum dose of 12 g/day (and down titration to a minimum of 1 g/day). Titration was started as early as 1 week after washout, and then every 2 weeks thereafter during the safety period as needed for serum phosphorus levels.

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In the efficacy period, from Week-52-baseline to Week 56, KRX-0502 continued to maintain serum phosphorus levels, serum phosphorus levels decrease significantly within 1 to 2 weeks of starting treatment with KRX-0502.

In the safety period where KRX-0502 and the active controls were titrated to target a serum phosphorus range, the change in serum phosphorus levels over time indicate that KRX-0502 was, on average, equally efficacious in reducing serum phosphorus

using the studied titration algorithm as compared to the active controls titrated according to the prescribing information. The maximum treatment effect on serum phosphorus was achieved by 12 weeks. In addition, KRX-0502 was persistently effective in lowering serum phosphorus levels throughout the 1-year trial.

6.2.10 Additional Efficacy Issues/Analyses

None.

6.3.1 Trial 305

6.3.2 Subject Disposition

Subject disposition of trial 305 is shown in the table below.

Table 10 Subject Disposition in trial 305

ITT (all randomized)	KRX-0502 1 g/day (N=52)	KRX-0502 6 g/day (N=52)	KRX-0502 8 g/day (N=50)
Safety population[1] (exposed to drug)	51 (98%)	52 (100%)	48 (96%)
Modified ITT population*	50 (96%)	51 (98%)	45 (90%)
Subject Completed	39 (76%)	47 (90%)	36 (72%)
Subject Discontinued Treatment	12 (23%)	5 (10%)	12 (24%)
Reason for Early Termination			
Investigator judgment	1 (2%)	0 (0%)	0 (0%)
Withdrew consent	0 (0%)	0 (0%)	1 (2%)
Adverse event	2 (4%)	3 (6%)	8 (16%)
Other[2]	9 (17%)	2 (4%)	3 (6%)

[1] The reasons for the three subjects who were randomized but not exposed to the drug were not meeting inclusion criteria on the second attempt, was not dispensed study medication, and having received a cadeveric renal transplant.
[2] Discontinued KRX-0502 for "treatment failure" (serum phosphorus >9 mg/dL or <2.5 mg/dL).
Source: extracted from the applicant's CSR for trial 305: table 3 and Figure 3.

The incidence of adverse events that led to KRX-0502 discontinuation was at the 8 g/day arm, as compared to the 1 g/day and 6 g/day arms. The adverse events driving the dose-related differential discontinuation was diarrhea (Table 33), which occurred early (within 4 weeks) during treatment.

6.3.3 Demographics

The baseline subject characteristics (including age, sex, race, and co-morbid conditions) and baseline serum phosphorous levels were generally well balanced

among the dose groups and were representative of a population of hemodialysis-dependent patients with ESRD. The key baseline characteristics are shown below.

Table 11 Baseline characteristics in trial 305 (ITT population)

	KRX-0502 1 g/day (n=52)	**KRX-0502 6 g/day (n=52)**	**KRX-0502 8 g/day (n=50)**
Hemodialysis n (%)	52 (100%)	52 (100%)	50 (100%)
Serum phosphorus Mean (SD)	7.3 (1.71)	7.6 (1.71)	7.4 (1.60)
Ferritin (ng/mL) Mean (SD)	552.5 (287.7)	517.5 (265.3)	544.7 (246.2)
TSAT (%) Mean (SD)	31.8 (11.1)	33.5 (13.6)	29.7 (9.3)
Hemoglobin (g/dL) Mean (SD)	11.6 (1.1)	11.6 (1.0)	11.7 (1.2)

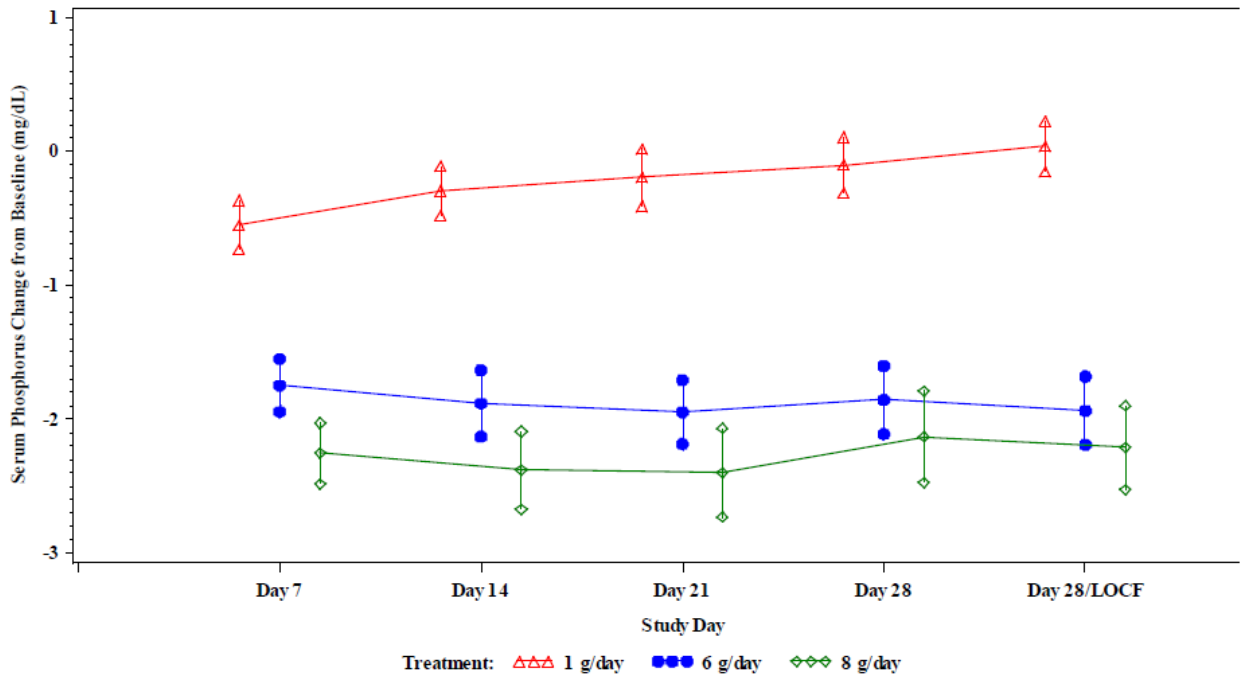
Source: applicant's table submitted on April 22, 2014 per request. The baseline median IV iron and the median ESA doses were not captured in this trial.

6.3.4 Analysis of Primary endpoint

The primary endpoint analysis (linear regression model with dose effect) showed that the changes in serum phosphorous concentrations were related to KRX-0502 dose. Among the subjects evaluated for efficacy (mITT population), mean serum phosphorous concentrations were approximately 5.5 mg/dL at the screening visit and increased to approximately 7.5 mg/dL at the end of the Washout Period (baseline). Following the initiation of treatment, mean serum phosphorous levels declined in the 6 g/day and 8 g/day groups and had returned to near screening levels by Day 7. In the 1 g/day group, mean phosphorous levels had declined only slightly by Day 7 and remained well above screening levels throughout the treatment period. Mean phosphorous values in all groups remained relatively stable between Day 7 and the remainder of the 28-day treatment period.

The mean (+/- SE) of the change from baseline in serum phosphorus by study day (trial 305, mITT population) shows that the mean reduction in serum phosphorous at the end of the treatment period (Day 28) was 0.10 mg/dL in the 1 g/day group, 1.86 mg/dL in the 6 g/day group, and 2.13 mg/dL in the 8 g/day group.

Figure 2 Change from baseline in serum phosphorus by study day (trial 305, mITT population)

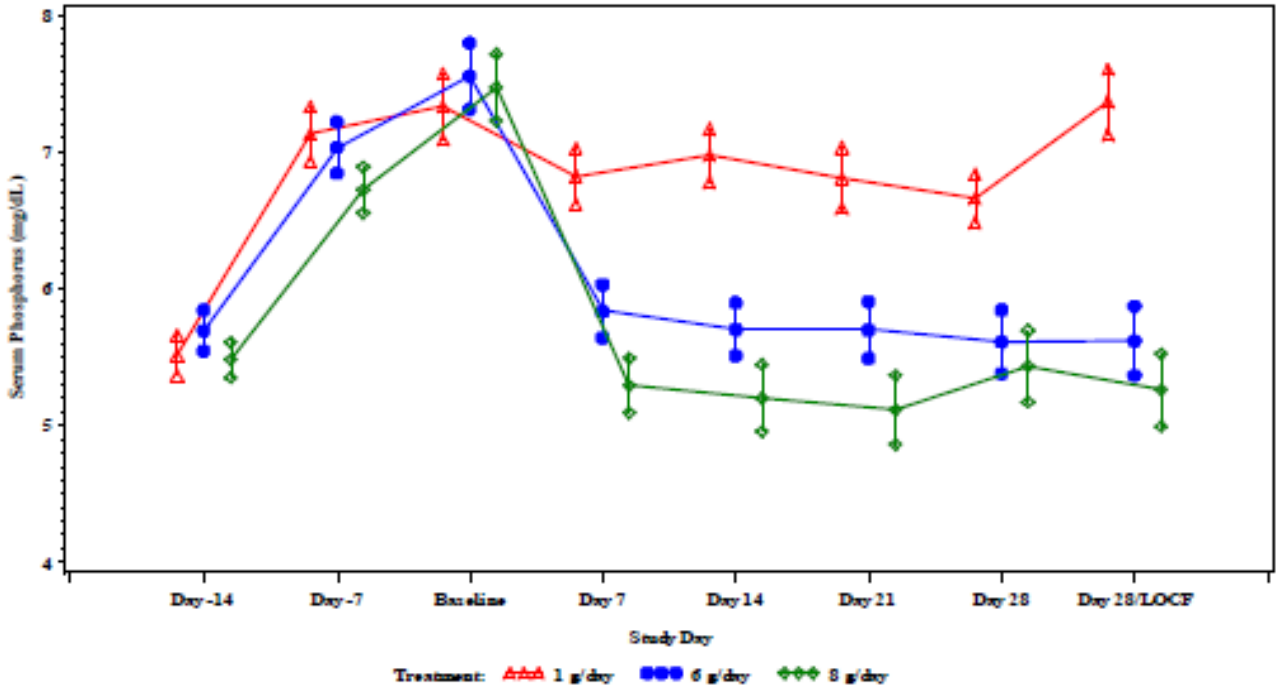


Source: Applicant's CSR figure 3. Results replicated by the FDA statistician.
The change in serum phosphorous from baseline to the end of the 28-day treatment period was analyzed using a regression model with dose effect.

6.3.5 Analysis of Secondary Endpoint

Mean serum phosphorus levels peaked at baseline (Study Drug Initiation Visit), after completion of the Washout Period and were similar in the 1, 6, and 8 g/day groups at the initiation of treatment (Figure 3). Following treatment, mean serum phosphorous levels declined rapidly in the 6 g/day and 8 g/day groups and had returned to near screening levels by Day 7. In the 1 g/day group, mean phosphorous levels declined only slightly by Day 7 and remained well above screening levels throughout the treatment period.

Figure 3 Mean (+/- SE) of serum phosphorus by study time (mITT population, trial 305)



Source: Applicant's CSR figure 2. Results replicated by the FDA statistician.

6.3.6 Other Endpoints

On Day 28, 51% of patients in the 6 g/day group and 58% of patients in the 8 g/day group had achieved clinically meaningful reductions in serum phosphorus (defined as achievement of serum phosphorous of ≤5.5 mg/dL). Conversely, only 12% of the patients in the 1 g/day group achieved a serum phosphorous concentration of ≤5.5 mg/dL. This result is supportive of primary efficacy endpoint on serum phosphorus.

The results of other exploratory endpoints are shown below. Dose related increases in the mean ferritin and TSAT levels appeared. With the increased dose of this non-calcium based phosphate binder, mean serum calcium level was not reduced from baseline. The clinical significance of the modest changes of these parameters with dose is not clear.

Table 12 Exploratory endpoints in trial 305

Change from baseline to Day 28, n,mean (SD) (mITT population)	**KRX-0502 1 g/day (N=50)**	**KRX-0502 6 g/day (N=51)**	**KRX-0502 8 g/day (N=45)**
serum calcium	n=50 0.0 (0.6)	n=51 0.2 (0.6)	n=45 0.3 (0.6)
serum calcium phosphorus product	n=50 1.0 (13.2)	n=51 -16.0 (16.9)	n=45 -18.6 (18.2)

Change from baseline to Day 28, n,mean (SD) (mITT population)	**KRX-0502 1 g/day (N=50)**	**KRX-0502 6 g/day (N=51)**	**KRX-0502 8 g/day (N=45)**
ferritin	n=39 12.7 (153.4)	n=44 90.1 (198.6)	n=34 90.2 (279.0)
TSAT (%)	n=38 -0.8 (10.7)	n=44 1.5 (17.0)	n=34 4.4 (12.9)
bicarbonate	n=38 0.1 (2.4)	n=44 1.6 (3.1)	n=33 1.5 (3.9)

Source: applicant's tables 13; 15; 17; 12.5.2.1; 21. Results replicated by the FDA statistician.

6.3.7 Subpopulations

The applicant performed the subgroup analyses of efficacy data from trial 304, the larger trial, rather than trial 305. See section 6.2.7.

6.3.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Also see section 6.2.8. Trial 305 shows that 6 g/day and 8 g/day are better than 1 g/day over a 28-day period for lowering serum phosphorus levels. Six g/day is one of the proposed starting doses.

6.3.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This is a 4-week trial. See section 6.2.9 for information on the long-term pivotal trial.

6.3.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

A total of 557 dialysis dependent subjects were exposed to KRX-0502 in the one-year trial (304) and the 3 4-week trials (305, PBB00101, 201). The submission provides information on a total of 233 subjects who received KRX-0502 for at least 6 months (>24 weeks) and 201 subjects for at least approximately 1 year (>48 weeks).

The main concern for this submission was iron overload syndrome in subject with likely genetic predisposition, which will be described in sections 7.3.4, 7.3.5, and 7.4.2.

Adverse events were largely consistent with the pharmacologic class. See section 1 for summary.

7.1 Methods

The applicant identified two pivotal, randomized, double-blind, placebo-controlled trials, 304 and 305, and two phase 2 trials to form Integrated Summary of Safety (Table 3). The data sources were adequate, and the applicant's methods were reasonable.

I assessed the incidence, frequency of adverse events, and the number of subjects with adverse events in the pivotal trials and reviewed the incidence of AEs reported in ISS.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

My safety evaluation focused on datasets, case report forms (CRF), narratives and the clinical study report for the pivotal trials 304 and 305. Because the pivotal trial 304 had the longest follow-up (one year), largest number of subjects exposed, and one of the highest dose of KRX-0502 for titration (see section 7.2.1), I primarily focused on trial 304 for my safety analysis. I analyzed separately the placebo-control safety period and the active-control efficacy period of trial 304. Because the highest fixed-dose (8 gram per day) was studied in the trial 305, I focused on trial 305 for my analysis of dose-related response. I also evaluated the CSR from other fixed dose supportive trials. Because of the differences in design (e.g., trial 304 was the only trial that had an active control arm) and in duration of therapy (e.g., 4 week for trial 305 vs. 56 weeks total for trial 304), I did not pool these two pivotal trials for my safety analysis.

In addition, I reviewed the safety findings in the applicant's ISS (Table 3 in Section 5.1), that pooled the shorter trials 305, PBB00101, and 201 with the long-term pivotal trial 304. These 4 clinical trials were conducted in patients with ESRD, using the KRX-0502 formulation.

Of the fourteen other trials referred to as supportive trials (see Table 4), I reviewed clinical study reports that provide limited analyses on deaths and dropouts for adverse events for the completed trials.

The applicant's rationale for distinguishing the key and supportive trials is reasonable. The supportive trials were largely conducted in Japan and using a different formulation, JTT-751 formulation. The key trials in the United States and used the KRX-0502 formulation. In addition, the use of IV iron was more permissive in the key trials than the supportive trials, conducted mainly in Japan, reflecting the difference in standard practice between the two countries. Please see appendix for more details on the differences in the entry criteria, stopping rules for using IV iron between the key and supportive trial in designs.

Lastly, the pivotal trials were not blinded. The laboratory parameters for safety (e.g., iron parameters) are relatively objective. The labs were systematically collected and there were not much missing data. Therefore, the lack of blinding is unlikely to influence the laboratory findings. Nonetheless, I can't rule out if the lack of investigator blinding could have influenced an Investigator's assessments of AEs.

7.1.2 Categorization of Adverse Events

For the datasets in ISS, adverse events (AE) were coded to MedDRA versions 13. I reviewed the verbatim and dictionary-derived terms and confirmed the appropriateness of the mapping from verbatim to dictionary-derived terms. To explore safety issues, I grouped terms that are part of a clinical syndrome (e.g., iron overload syndrome), in addition to using the MedDRA body system categorization.

In trial 305, the applicant defined on-treatment AE as AEs that started from the date of study drug initiation to the date of discontinuation plus 1. To define treatment emergence in trial 304 and in the ISS, the applicant used a different follow-up period to these AEs by non-fatal/non-serious AEs versus fatal/serious AEs. For non-fatal and non-serious AEs considered treatment emergent, the AE had to have a start date between the date of initiation of study drug and the date of discontinuation of study drug, inclusive of the dates of initiation and discontinuation, for the given treatment period (that is safety period or efficacy period for trial 304). For fatal and serious AEs considered treatment emergent, the AE had to have a start date on or after the date of initiation of study drug and up to 30 days after the date of discontinuation of study drug. In addition, if the date of AE onset was completely missing, applicant set the date of AE onset to the date of the first dose of study drug during the given treatment period. These rules appear to be a conservative and reasonable assessment of AE.

Because subjects who completed the safety period on KRX-0502 were re-randomized into the placebo-controlled efficacy period in trial 304, the applicant used the following rule to define treatment emergent AEs in the efficacy period of this trial: Fatal and serious AEs with a start date up to 30 days after discontinuation of study drug in the safety period but after date of initiation of study drug in the efficacy period. This rule seems reasonable.

I identified adverse events regardless of the treatment emergence classification.

I performed a sensitivity analysis with the following adverse events that could be consistent with hemochromatosis: hemochromatosis, cirrhosis, ascites, encephalopathy, hepatomegaly, splenomegaly, abdominal pain, arthralgia, arthritis, chondrocalcinosis, joint effusion, joint injury, joint swelling, impotence, decreased libido, hyperglycaemia, testicular atrophy, cardiac failure congestive, heart failure, cardiac failure acute, cardiomyopathy, skin pigmentation, weakness, lethargy, fatigue, loss of body hair, gynecomastia, diabetes, hypothyroidism.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In general, adverse event data were not pooled across studies for reasons stated in Section 7.1.

7.2 Adequacy of Safety Assessments

In general, the safety monitoring for trials in the ISS appears adequate. Please see section 5.3 for monitoring.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The submission provides safety information on a total of 1458 unique subjects who had received at least one dose of a form of ferric citrate (KRX-0502 or JTT-751) in the development program, including 1388 ESRD subjects on dialysis (of whom 67 were on peritoneal dialysis: 56 from trial GBA4-3 and 19 from trial 304), and 70 CKD subjects not on dialysis. See section 5.1 for a listing of trials and the formulations used.

The submission provides information on a total of 233 subjects who received KRX-0502 for at least 6 months (>24 weeks) and 201 subjects for at least 1 year (>48 weeks) based on the trials conducted largely (92%) in the U.S. population.

In the ISS dataset (Table 13), slightly over half of the subjects with ESRD were exposed to KRX-0502 doses 6 g to <9 g daily. Over one-third of the subjects who were treated for over 48 weeks and were enrolled the long-term pivotal trial 304; Subjects enrolled the other trials in the pooled datasets were exposed for a maximum of 28 days. The pivotal trial 304 studied the highest KRX-0502 dose. In this trial, where dose were titrated per individual serum phosphorus response, 80 subjects (27.6%) required ≥9 g/day for phosphorus control.

Table 13 Ferric citrate exposure by mean dose and duration categories (ISS population)

	<6 gram/day n=192 (34.8%)	**≥ 6 to <9 gram/day n=285 (51.2%)**	**≥ 9 gram/day n=80 (14.4%)**	**Overall N=557**
≤ 4 weeks	63 (32.8%)	73 (25.6%)	1 (1.3%)	137 (24.6%)
>4 to 24 weeks	81 (42.2%)	103 (36.1%)	3 (3.8%)	187 (33.6%)
>24 to 48 weeks	11 (5.7%)	9 (3.2%)	12 (15.0%)	32 (5.7%)
>48 weeks	37 (19.3)	100 (35.1%)	64 (80.0%)	201 (36.1%)

Source of table 13: Extracted from the applicant's submission dated January 24, 2014, in response to FDA request. According to the applicant, the selection of dose cut-offs was based largely on the doses selected for the pivotal KRX-0502 studies. The starting dose was 6 g/day, and 9 g/day was simply the intermediate between the 6 g/day and the maximum dose (12 g/day).

Reviewer's comment: With the collective experience for ferric citrate (KRX-0502 and JTT-751), the extent of exposure in the target dialysis population seems adequate for a chronically administered drug. However, most of the exposure experience came from trials with titrated doses. Also, there appears to be limited exposure data at the higher doses (≥ 9 g/day). I defer to my clinical pharmacology colleagues on whether the labeling should information on the commonly prescribed KRX-0502 doses for adequate phosphorus control, while noting the maximum dose (12 g/day) evaluated. I defer to clinical pharmacology colleagues on the appropriateness of a proposed starting dose of (b) (4) *which is not directly studied with KRX-0502.*

7.2.2 Explorations for Dose Response

See section 7.1.1.
In addition, the applicant evaluated the associated of the dose (mean / median/ modal/ maximum daily dose, and total median dose) and profile of adverse events that are suggestive of hemochromatosis (section 7.3.5).

7.2.3 Special Animal and/or In Vitro Testing

No special animal studies were conducted.
In vitro studies were conducted to look at DDI (see section 7.5.5).

7.2.4 Routine Clinical Testing

Routine clinical testing of subjects in the KRX-0502 clinical development program, including the long term pivotal trial 304 was adequate. They included biochemistry and hematology panels every 12 weeks, serum phosphorus levels every 1 to 4 weeks, and iron stores every 4 weeks.

7.2.5 Metabolic, Clearance, and Interaction Workup

Drug metabolism and excretion are discussed in Section 4.4. Drug-drug interactions are discussed in Section 4.4 and Section 7.5.5.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Based on the safety profiles of other phosphate binders that have been being used in the ESRD population, the main concerns with this class of agents are GI tolerability and

the potential to bind other agents. In addition, the potential for iron overload is a submission specific concern (see section 7.3.5).

7.3 Major Safety Results

7.3.1 Deaths

As of November 1st, 2012, across studies in the Pooled Safety Set, there were 14 subjects in the KRX-0502 group (2.5% overall, 4.8% in trial 304) and 8 subjects (5.4%) in the active control group who died less than 30 days after study drug discontinuation/completion (Table 15). No deaths occurred in the Placebo group. All 14 deaths on KRX-0502 treatment occurred in Trial 304: 13 deaths in the safety period and, 1 death in the subsequent efficacy period.

Table 14 Deaths that occurred less than 30 days after study drug discontinuation/completion (ISS)

	KRX-0502 (Ferric Citrate) (n=557)		*Active Control (n=149)*		*Placebo Control (n=111)*	
	Number of subjects	*Proportion (%)*	*Number of subjects*	*Proportion (%)*	*Number of subjects*	*Proportion (%)*
Total Deaths	14	2.5%	8	5.4%	0	0
304	14	4.8%	8	5.4%	0	0
305	0	0.0%				
201	0	0.0%				
PBB00101	0	0.0%			0	0

Source: Extracted from applicant's clarification submitted on January28, 2014.

When considering deaths regardless of study drug discontinuation, 7 additional deaths (a total of 29 deaths) occurred as of the November 1st, 2012 cutoff (Table 15). The proportion of subjects who died was similar between the KRX-0502 (6.9%) and the active control (6%) arm because of the 2:1 randomization.

Table 15 Total Number of Deaths in Trial 304 (Regardless of Study Drug Discontinuation)

	KRX-0502 (Ferric Citrate) (n=289)		*Active Control (n=149)*		*Placebo Control (n=95)*	
	Number of subjects	*Proportion (%)*	*Number of subjects*	*Proportion (%)*	*Number of subjects*	*Proportion (%)*
Deaths in 304	20	6.9%	9	6.0%	0	0

Source: Reviewer's analysis based on the applicant's adae dataset, verified with the applicant. According to the applicant's submission dated January 28th, 2014 in response to FDA's request for clarification, one subject was incorrectly marked as having died by the applicant in their original submission.

Collectively, Table 16, Table 17, and Table 18 present the causes of the 29 deaths in Trial 304.

The Table 16 shows the causes of death occurring less than 30 days after study drug discontinuation/completion in the safety period of the study.

Table 16: Listings of the 19 deaths that occurred less than 30 days after study drug discontinuation/completion in Trial 304

Age/Sex	Relevant co-morbid conditions in addition to ESRD on HD, unless other specified	Reason(s) for death	Days from starting study drug to death
KRX-0502			
Active Control Safety period			
45/M	type 1 diabetes, hypertension	Sudden Death	(b) (6)
51/M	type 2 diabetes, CHF, CVA	CVA Sepsis	
76/M	uremia, altered mental status, hypertension, anemia, metabolic acidosis	Asthenia Cerebral Haemorrhage Myocardial Infarction	
86/F*	hypertension, COPD, CHF, appendicitis, colorectal cancer diagnosed 7 years prior to randomization	Cholecystitis Gallbladder Cancer Hepatic Cancer Metastatic Neoplasm*	
71/M	diabetes with retinopathy and nephropathy morbid obesity, CHF, PVD, hypertension, gout, amputation (left below knee), hyperlipidemia, COPD, sleep apnea	Cardiac Arrest	
61 /F	diabetic with retinopathy, hypertension, dyslipidemia	Arteriovenous Graft Atrial Thrombosis Pulmonary Embolism Respiratory Failure	
77/M	hypertension, diabetes	Sudden Death	
43 /F	hypertension and uncontrolled diabetes mellitus type 1.	Hypoglycaemia	
59 /M	bacteremia, amyloidosis, illicit drug use	Cardiac Arrest Sepsis	
65 /M	type 2 diabetes, hypertension, CHF, PVD and bilateral below knee amputations	Mental Disorder Pneumonia Staphylococcal Infection	
90/M	type 2 diabetes, CHF, TIA	Arteriosclerosis	

Placebo Control Efficacy period			
43		Cardiac arrest, "Chest pain	(b) (6)
Active control			
67/F	hypertension, type II diabetes, CHF, restrictive cardiomyopathy, non-alcoholic cirrhosis of the liver, hepatic encephalopathy, and esophageal varices	Cellulitis	
50 /M	CAD, ischemic cardiomyopathy, COPD, IV drug use, right leg amputation, infection of skin of left knee and left forearm, tobacco use, CHF, hepatitis B and C, type II diabetes	Cardiac Arrest	
61 /M	type 2 diabetes, CAD with previous history of MI, hypertension, PVD, amputations: right below knee amputation and left transmetatarsal, fem-pop bypass,	Cardiac Arrest	
56 /M	hypertension, peritonitis, metabolic bone disease, anemia	Septic Shock	
56/F	hypertension, arthritis, epilepsy, systemic lupus erythematosis	Sudden Death	
73 /F	type 2 diabetes, hypertension, CHF, CAD, pulmonary hypertension	Diastolic Dysfunction Endocarditis	
49/F	COPD, asthma, hyperkalemia, diabetes, depression, renal cell cancer, GERD, hiatal hernia and CHF.	Worsening dyspnoea, refused evaluation for ER	

Source: applicant's submission dated March, 24, 2014 in response to IR request; applicant's narratives and case report forms on deaths; applicant's medical history dataset
PVD=peripheral vascular disease; CHF=congestive heart failure; CVA=cerebral vascular accident; COPD=chronic obstructive pulmonary disease; Coronary artery disease=CAD; MI=myocardial infarction

Additional narrative for Table 16:
**A 86 female was admitted to the hospital for shortness of breath and hypoxia, subsequently diagnosed as pneumonia, (b) (6) weeks after starting KRX-0502. A MRI for back pain during this hospitalization revealed an acute/subacute L-1 compression fracture as well as a 5 cm liver mass and other smaller hepatic lesions. She refused surgery and died within*

apparently (b) (6) *weeks of the cancer diagnosis. Given the advanced nature of the cancer relative to the recent commencement of KRX-050 and her history of colorectal cancer, an occult cancer at the time of her entry into the trial was considered likely*.

In addition to the subjects listed in the table above, there were three other subjects who died >30 days after discontinuation/completion (Table 17), as they had AEs that started within 30 days after discontinuation/completion.

Table 17 Listings of 3 deaths that occurred 30 days or greater after study drug discontinuation/completion in Trial 304's Safety period

Age/Sex	Co-morbid conditions	Reason(s)	Days from starting study drug to death
KRX-0502			
47/F	HIV, hypertension, hepatitis C, asthma, hypertension, endometriosis, cervical dysplasia, smoking, history of alcohol and drug abuse	Lobar Pneumonia Mental Disorder	(b) (6)
76/F	atrial flutter, diabetes mellitus, mild aortic stenosis, mild CHF	Atrial Fibrillation Pneumonia, Hypoxia, Hypotension	
Active control			
59/F	hypertension, CAD, valvular heart disease, atrial fibrillation, and supraventricular tachycardia	Sepsis	

Source: applicant's submission dated March, 24, 2014
CHF=congestive heart failure; CVA=cerebral vascular accident

In addition, no notable difference occurred in time to death or cause of death between the two treatment arms. The types of AEs resulting in death were similar in the two treatment groups and were consistent with the most common causes of death in patients with CKD on dialysis (events related to cardiovascular disease and events related to infections). In most of the cases, the causes of death were expected from the underlying co-morbidities in the population.

Finally, there were 7 subjects whose deaths occurred greater 30 days after study drug discontinuation in Trial 304 (Table 18), but were not included in the applicant's table dated March 24, 2014. Overall, the narratives do not suggest a causal role of KRX-050 in these deaths.

Table 18 Listings of the 7 deaths that occurred greater 30 days after study drug discontinuation in Trial 304's safety period

Age/Sex	Co-morbid conditions	Reason(s) for Discontinuation Study Drug/ Reason(s) for Death	Days from starting study drug to death	Days from stopping KRX-0502 to death
KRX-0502				
132-012, 84/M	gastroesophageal reflux disease, congestive heart failure, orthostatic hypotension, atrial fibrillation, and type-2 diabetes	KRX-0502 for 4 weeks, discontinued because diarrhea. Started on sevelemer carbonate. Orthostatic hypotension, worsening congestive heart failure, worsening cardiomyopathy with (EF 10-15%), pneumonia.	(b) (6)	
202-001 49/M	type 2 diabetes, with diabetic foot infection hypertension, hypercholesterolemia	KRX-0502 discontinued because dyspepsia, constipation, dark stool. Osteomyelitis of right foot and ankle		
103-017 21/F	CHF, hypertension, clotted access, arthritis, lupus, urinary tract infection, seizure, neuropathy, hypocalcemia, parathyroidectomy, asthma, restrictive lung disease	KRX-0502 discontinued because diarrhea. Sudden Death, after missing her last two scheduled dialysis sessions because of a clotted access.		
122-006 61/M	type 2 diabetes, morbid obesity, hypertension, GERD, CHF and PVD, afib on coumadin	KRX-0502 discontinued after about 7 months because of worsening anemia (elevated INR), progressive fatigue, weakness, SOB, abdominal		

Age/Sex	Co-morbid conditions	Reason(s) for Discontinuation Study Drug/ Reason(s) for Death	Days from starting study drug to death	Days from stopping KRX-0502 to death
		pain, black stool. Started on calcium *carbonate.* Small bowel perforation*		
151-005 71/M	ESRD on PD, diabetes, hypertension, past C.difficile infection	AE for discontinuing KRX-0502 was reported as fatal c. difficile. However, the date of KRX-0502 on CRF was about 8 weeks prior to c. difficile infection/death. Fulminant C.difficile infection developed after antibiotic use for cellulitis		
75/M 147-001	diabetes, obesity, hypertension, CHF, MI, CAD with recurrent chest pain, PVD, arthritis and bilateral BKAs	KRX-0502 was interrupted for weakness, severe angina (treatment emergent hypogonadism was not attributed to KRX-0502). However, CRF states that study drug was discontinued (not just interrupted). Hydropneumothorax leading to respiratory failure		
Active control				
157-005, 81/M	type 2 diabetes, hypertension, hyperlipidemia, prior stroke	Reason for interrupting active control: cerebral vascular accident Reason for death: cardiac arrest		

(b) (6)

Source: extracted from applicant's submission dated March, 24, 2014 in response to IR request, applicant's narratives and case report forms on deaths, and the applicant's adsl dataset's variables: discontinued in period 1 flag (disc01FL), completing safety period 1 flag (comp01FL), and days from treatment discontinuation to death date (daydsdth), Reason For Withdrawal in Period 1 (disrea01), AE discontinued reason category period 1 (dsacat1),
Afib=atrial fibrillation; PVD=peripheral vascular disease; CHF=congestive heart failure; CVA=cerebral vascular accident; COPD=chronic obstructive pulmonary disease; Coronary artery disease=CAD; MI=myocardial infarction; GERD=gastroesophageal reflux disease, BKA=below the knee amputations

Additional narrative for Table 18:

** The small bowel perforation occurred one month stopping KRX-0502. For the small bowel perforation, he was readmitted for 6-week history of abdominal pain, dark tarry stool, and anemia. He underwent emergent laparotomy that revealed extensive necrotic and perforated small bowel necessitating a resection of all but 70 cm of the small bowel. He developed multi-organ failure and died. The autopsy revealed extensive generalized arterial vascular disease with microscopic evidence of clot in the superior mesenteric artery and concluded the cause of death as "multi-organ failure following bowel perforation because of bowel necrosis because of bowel ischemia because of atherosclerosis". Based on the time course of the events relative to KRX-0502 administration and his underlying co-morbidities, the small bowel perforation does not appear to be from a local effect from KRX-0502.*

As of the October 15, 2013 cutoff for the 120-day safety update, there were 4 additional deaths (2.4%) in trial 307, the long-term safety extension of trial 304. The causes of death (cardiac arrest; could not be determined; sepsis/ventricular fibrillation/lactic acidosis; sudden death) from this preliminary report are not unexpected in the ESRD population.

7.3.2 Serious Adverse Events

The incidence of serious AEs as a whole was similar or lower in the KRX-0502 arm than the active control or the placebo arm. Comparing the safety population (subjects exposed to study drugs) of the efficacy period (Trial 304), no consistent increase in serious adverse events of one body system category or one PT was detected in the KRX-0502 arm than the controls.

The AE profiles for all SAE and treatment emergent SAEs were generally similar in trial 304.

Serious Adverse Events in the Safety period of Trial 304

As a whole, the incidence of treatment emergent serious AEs was lower on KRX-0502 arm than the active control arm.
Table 19 also shows (in order of frequency) the serious AE body system categories of special interest, either because they contain terms associated with iron overload syndrome, or because they were noted to be higher than control arm in the efficacy period of trials 304 or 305. The incidence of all these AE categories was lower in the KRX-0502 than the active control arm.

Table 19: Treatment Emergent Serious Adverse Events of Special Interest (Trial 304 Safety period)

	KRX-0502 (FERRIC CITRATE) (N = 289)			*ACTIVE CONTROL (N = 149)*		
	Events	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Total Number of SAEs	**305**	**114**	**39.4**	**233**	**73**	**49.0**
SAEs of Special Interest by SOC classification						
Infections and infestations	47	37	12.8	42	30	20.1
Gastrointestinal disorders	33	20	6.9	34	18	12.1
Cardiac disorders	23	20	6.9	22	17	11.4
Respiratory, thoracic and mediastinal Disorders	29	20	6.9	22	15	10.1
Nervous system disorders	16	14	4.8	8	6	4.0
Hepatobiliary disorders	2	2	0.7	3	2	1.3

Source: reviewer's table using the applicant's algorithm.

For example, even though an apparent dose related increase in infections was noted with KRX-0502 in trial 305 (Table 32), the rate of treatment emergent serious infections was lower in the KRX-0502 than the active control arm in the safety period of trial 304. Of note, in trial 304, the cumulative dose IV iron, which is known to be associated with infections, was also lower in the KRX-0502 than in the active control arm. Therefore, the lack of consistent association between infection risk and KRX-0502 across trials casts doubts on causality.

While treatment emergent gastrointestinal AEs were the most common AEs (see section 7.4.1), the incidence of serious treatment emergent gastrointestinal AEs was not greater in the KRX-0502 arm than in the active control arm.

Serious Adverse Events during the Efficacy Period of Trial 304

Treatment emergent AEs that were considered serious or led to withdrawal or interruption of study drug were numerical lower in the KRX-0502 than the placebo arm. Treatment emergent AEs that were considered severe were comparable between the two treatment arms.

No new/consistent adverse events were more common in the KRX-0502 than the placebo arm in the efficacy period were also found in the safety period being more common on the KRX-0502 arm than active control. Most serious treatment emergent AEs that grouped into any SOC categories were lower in KRX-0502 arm than in the placebo arm. Only the treatment emergent AEs that were grouped into cardiac disorders and *injury, poisoning and procedural complication* categories were numerically higher on KRX-0502 arm as compared to the placebo arm (Table 20).

Table 20: Treated Emergent Serious Adverse Events that were more Frequent in KRX-0502- than Placebo- Treated Subjects (Efficacy Period of Trial 304)

	KRX-0502 (FERRIC CITRATE) (N = 95)			*PLACEBO (N = 95)*		
	Events	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
All TE serious AEs	**71**	**25**	**26%**	**113**	**41**	**43%**
Cardiac disorders TE serious AEs shown below	5	4	4	0	0	0
Acute coronary syndrome	1	1	1	0	0	0
Atrial flutter	1	1	1	0	0	0
Cardiac arrest	1	1	1	0	0	0
Coronary artery disease	1	1	1	0	0	0
Mitral valve incompetence	1	1	1	0	0	0
Injury, poisoning and procedural	5	4	4	1	1	1

	KRX-0502 (FERRIC CITRATE) (N = 95)			*PLACEBO (N = 95)*		
	Events	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
complications						
Ankle fracture	1	1	1	0	0	0
Fall	1	1	1	0	0	0
Fibula fracture	1	1	1	0	0	0
Postoperative wound complication	1	1	1	0	0	0
Rib fracture	0	0	0	1	1	1
Vascular access complication	1	1	1	0	0	0

Source: reviewer's analysis, using the following variable in adae datasets: *SAF02FL=Y, TRTEMFL=Y, AESER= Y, and APERIODC= Efficacy Treatment Period*

Because cardiac disorders are relatively common in the dialysis population, and the efficacy period enrolled a smaller number of subjects than the safety period, the increase in cardiac AEs than placebo may be because of a play of chance. Similarly, without a biologic basis, the numerically higher adverse events on the KRX-0502 than the placebo arm that fall into the *injury, poisoning and procedural complication* is also likely to be because of the play of chance.

Note, there were no GI AEs that were classified as serious reported in either treatment arm during the 4-week efficacy period.

7.3.3 Dropouts and/or Discontinuations

During the 52-week safety period of trial 304, 60 subjects (20.8%) on KRX-0502 discontinued study drug because of an adverse event, as compared to 21 subjects (14.1%) in the active control arm. [9]

GI adverse events were the most common reasons for discontinuing KRX-0502. As shown in **Table 21**, treatment emergent gastrointestinal disorders led to more discontinuation in the KRX-0502 than the active control arm, and were responsible for the higher incidence on discontinuations on KRX-0502. Of these gastrointestinal AEs, diarrhea was most frequent.

[9] My results based on the applicant's adae dataset yielded somewhat different findings from the applicant. The applicant re-examined their results, and agreed in their response dated January 2, 2014, to amend their results and proposed language in the labeling.

Table 21: TEAEs that led to more discontinuation of ferric citrate than active control (Trial 304, safety period)

	KRX-0502 (FERRIC CITRATE) (N = 289)			*ACTIVE CONTROL (N = 149)*		
	Events	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Subjects Discontinued for AEs		*60*	*20.8%*		*21*	*14.1%*
Gastrointestinal disorders	96	40	13.8	10	6	4.0
Diarrhoea	29	24	8.3	1	1	0.7
Faeces discoloured	11	10	3.5	0	0	0.0
Abdominal pain	9	8	2.8	1	1	0.7

Source: Reviewer's analysis.

However, as shown in Table 22, in the majority of subjects with the treatment emergent feces discoloration and diarrhea, these adverse events recovered and resolved without dose reduction, modification, or discontinuation of ferric citrate.

Table 22: Gastrointestinal TEAEs that recovered or resolved without dose reduction, modification, or discontinuation (trial 304 safety period)

	KRX-0502 (FERRIC CITRATE) (N = 289)			ACTIVE CONTROL (N = 149)		
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Feces discolored	46	43	55.8	0	0	0.0
Diarrhea	57	45	58.4	13	11	52.4

Source: reviewer analysis.

In the efficacy period that followed the safety period, GI disorders did not lead to increased discontinuation of KRX-0502 as compared to placebo. The incidence suggests that in subjects who were able to tolerate ferric citrate previously (as in the 52-week safety period), ferric citrate continued to be well-tolerated in the subsequent placebo controlled 4-week efficacy period.

Table 23 Treatment emergent adverse events that led to withdrawal or interruption of study drug in the efficacy period of trial 304

	KRX-0502 (FERRIC CITRATE) (N = 95)			*PLACEBO (N = 95)*		
	Events	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
TEAEs that led to withdrawal or interruption of study drug	25	14	15%	41	21	22%

Therefore, the evaluation of the TEAE in the two periods of the trial 304 suggests these AEs were generally tolerated (recovered, resolved without dose reduction or discontinuation).

7.3.4 Significant Adverse Events

The incidence and frequency of treatment emergent adverse events and proportional of subjects with treatment emergent severe AEs were similar between the KRX-0502 and the placebo arm.

Also see Sections 7.3.2 and 7.2.2.

7.3.5 Submission Specific Primary Safety Concerns

The potential for iron overload was a submission specific primary safety concern because the potential for chronic use of KRX-0502 concomitant with IV iron in clinical practice. In the KRX-0502 pivotal trials, concomitant use of IV iron was allowed, in some cases, despite a ferritin level >1000 ng/mL that could be indicative of inflammatory process or high iron storage. Moreover, as shown in section 6, elevations in serum ferritin and TSAT occurred with KRX-0502 treatment when compared with active control treatment (Table 9) or with increasing KRX-0502 dose (Table 12).

In addition, marked increases in mean change from baseline over the 52 weeks in serum ferritin, TSAT, and iron levels in the KRX-0502 arm as compared with little or no change using active control arm (Table 24). The increases in the mean serum iron and TSAT levels of the KRX-0502 arm leveled off by week 12. The rate of increase for the mean ferritin level was most rapid within the first 12 weeks.

Table 24 Iron parameters in trial 304's safety period

	Treatment	Mean (SD)						Change from Baseline at EOT[a] Mean (%)
		Baseline	Week 12	Week 24	Week 36	Week 48	Week 52	
Serum iron (µg/dL)	KRX-0502	72.7[c] (29.41)	89.5[c] (39.2)	90.8[c] (42.66)	90.0[c] (38.96)	91.0[c] (41.78)	88.2[c] (42.58)	15.5 (21.3%)
	Active control[b]	68.9 (25.30)	72.9 (29.52)	73.2 (28.90)	71.8 (27.15)	68.7 (26.59)	69.4 (29.28)	0.5 (0.73%)
Ferritin (ng/mL)	KRX-0502	592.80[c] (292.863)	750.39[c] (381.423)	847.34[c] (412.543)	863.83[c] (442.931)	886.20 (461.146)	894.88[c] (481.788)	302.08 (51.0%)
	Active control[b]	607.31 (309.015)	649.05 (326.295)	650.37 (304.252)	633.02 (330.187)	621.24 (355.971)	633.68 (373.197)	26.37 (4.3%)
TIBC (µg/dL)	KRX-0502	232.90 (40.058)	224.95 (40.901)	227.08 (43.695)	227.07 (41.862)	224.69 (42.439)	224.45 (43.928)	-8.45 (-3.63%)
	Active control[b]	226.81 (38.493)	233.57 (38.327)	236.02 (37.073)	238.39 (39.433)	236.78 (38.389)	234.48 (38.743)	7.67 (3.38%)
TSAT (%)	KRX-0502	31.0[c] (10.99)	40.2[c] (16.00)	39.9[c] (15.52)	39.8[c] (15.66)	40.6[c] (16.94)	39.4[c] (16.81)	8.4 (27.1%)
	Control[b]	31.0 (11.75)	31.4 (12.13)	31.6 (11.96)	30.4 (10.88)	29.4 (10.71)	29.7 (11.49)	-1.3 (-4.19%)

Source: applicant's table 10 in the summary of clinical pharmacology
Baseline values were values recorded pre-administration on the starting day of administration.
a Change from baseline was drawn from tables unless otherwise indicated. Percentage change was calculated as follows: [(last mean value − baseline mean value) / baseline mean value] × 100.
b Calcium acetate or sevelamer carbonate or any combination of calcium acetate and sevelamer carbonate at the discretion of the Principal Investigator.
c KRX-0502 vs. active control was significantly different ($p<0.0001$); analyzed using an ANCOVA.
Note: Only subjects with both baseline and post-baseline observations for the parameter of interest were included.
EOT=end of treatment; SD=standard deviation; TIBC=total iron binding capacity; TSAT=transferrin iron saturation.
ANCOVA analysis that includes subjects with both baseline and post-baseline values.

Therefore, I evaluated the adverse events that may represent or suggest hemochromatosis/iron overload.

<u>A case of confirmed iron overload/hemochromatosis on liver biopsy (trial 304)</u>
A 36 year old subject with a history of type 2 diabetes, hypertension, congestive heart failure, chest pain, cardiomegaly, and ESRD on hemodialysis, but without a known

history hemochromatosis, was treated with KRX-0502. Prior to initiating KRX-0502 (on baseline IV iron therapy), his ferritin was 799 ng/mL and TSAT 29%; he did not undergo genetic testing for hereditary hemochromatosis. He received KRX-0502 for 25 weeks (started at 6 g/day and titrated to 10 g/ day) before discontinuing treatment because of a diagnosis of hemochromatosis.

His work up for hemochromatosis was triggered by an incidental finding of an "abnormal liver" on CT scan, obtained to evaluate hematemesis, which ultimately was determined to be a result of reflux esophagitis. A subsequent liver biopsy at week 18 showed increased iron accumulation, with hepatic iron quantitated as 5857 micrograms/g liver tissue (normal range 200-2000 microgram/g tissue; >3964 microgram/g tissue is highly suggestive of homozygous hereditary hemochromatosis[10]). Macrovescicular steatosis (1%) was reported, but not fibrosis or cirrhosis. Reportedly, the subject elected not to undergo the genetic testing for HFE mutations to diagnose hereditary hemochromatosis, a major cause of iron overload syndrome.

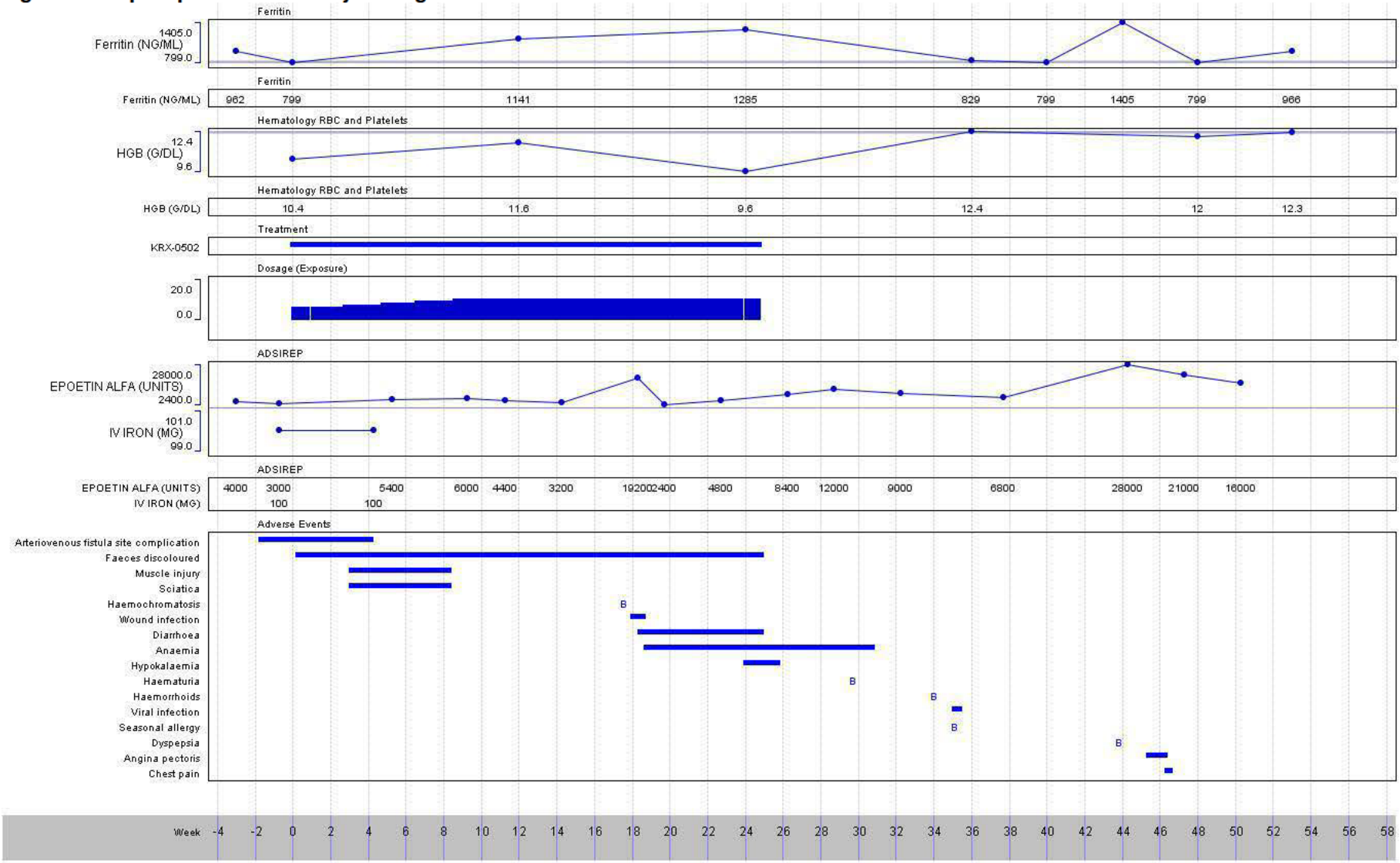
Figure 4 shows the key concomitant medication, laboratory parameters, and adverse event profile for this subject. He received intravenously administered iron sucrose for two months at 100 mg per month, last dose on week 4. (His dialysis unit protocol was apparently to administer an IV iron product until a ferritin >1200 ng/mL or a TSAT >50%). A persistent rise in serum ferritin from his pre-KRX-0502 baseline of 799 ng/mL (while on monthly IV sucrose), peaking at 1285 ng/mL at week 25, appeared to coincide with the initiation and up-titration of KRX-0502. While an occult inflammatory process can't be excluded, his adverse event profile did not document an infection that coincided with the initial rise in ferritin over the 25 weeks. Lastly, after discontinuing KRX-0502, his serum ferritin returned to his pre-KRX-0502 baseline.

Of note, his maximum serum ferritin (second peak in the figure) was 1405 ng/mL (normal in non-CKD subjects <200 ng/mL, which quickly dropped back to his baseline. The cause of the second peak in ferritin appears unrelated to iron administration but possibly related to a self-limited infection.

Aside from the increase in serum ferritin, no new/worsening signs or symptoms associated with hemochromatosis were reported in this subject. His serum iron, TSAT, AST, ALT, and bilirubin were within normal limits throughout the observation period. His alkaline phosphatase was mildly elevated in the 135-217 range from 2 months after starting KRX-0502 onward. His angina and precardial chest pain that occurred 5 months after discontinuing KRX-0502 were not attributed to KRX-0502 or iron overload of the heart, but to his underlying comorbidities.

[10] Kowdley KV and colleagues. Utility of hepatic iron index in American patients with hereditary hemochromatosis. Gastroenterology. 1997;113(4):1270.

Figure 4: Graphic profile of the subject diagnosed with hemochromatosis on KRX-0502 treatment



Source: reviewer's graph

Reviewer's comments:
Without a liver biopsy prior to initiating KRX-0502, it is not known if this subject had underlying iron deposition before KRX-0502 use. Thus, it is not clear how much KRX-0502 or iron sources contributed to the iron deposition.

Nonetheless, it is well accepted that patients carrying mutations in the HFE gene which is responsible for hereditary hemochromatosis, have increase in intestinal iron absorption, and thus are at increased risk of iron overload[11].

Diagnosis of hereditary hemochromatosis is usually based on a combination of various genetic or phenotypic criteria. The current (2005) American College Physician clinical guideline does not recommend for or against screening for hereditary hemochromatosis. The 2011 American Association for the Study of Liver Diseases (AASLD) guideline, recommends screening for HFE in asymptomatic patients with a ferritin >1000 ng/mL (normal 40 to 200 ng/mL), because patients with hereditary hemochromatosis and serum ferritin levels >1000 ng/mL were found to be at increased risk for the development of cirrhosis.

The application of the AASLD guideline to the dialysis population is currently not clear (as screening for hemochromatosis has not been addressed in guidelines in the kidney area). The dialysis population can have high serum ferritin from inflammatory processes that are not uncommon.

While this case illustrates the unspecific nature of an isolated serum ferritin level for diagnosing iron-overload in dialysis population, it also suggests that for a patient with a persistent and marked rise in serum ferritin level with initiating KRX-0502, after stopping IV iron and ruling out inflammatory processes, work-up for hereditary hemochromatosis and/or discontinuing KRX-0502 dose should be considered.

Profile of adverse events that can potentially represent iron overload/hemochromatosis
According to the American Association for the Study of Liver Disease (AASLD) practice guideline, while hemochromatosis is increasingly being recognized by clinicians, it is still underdiagnosed. The classic symptoms consist of cirrhosis, diabetes, and skin pigmentation, and also include other symptoms that are nonspecific and may be seen in ESRD patients: weakness, lethargy, abdominal pain, arthralgia, loss of libido, impotence, cardiac failure.

The applicant identified the adverse events potentially associated with iron overload are shown in Table 25.

Table 25: Applicant Identified Preferred Terms for Adverse Events Potentially Associated With Iron Overload

[11] Genetics of hereditary hemochromatosis, Uptodate accessed April 4, 2014

Hepatobiliary Disorders	Heart Failure Events	Arrhythmia Events	Endocrine Dysfunction	Thrombotic Events (Non-venous)
Liver toxicity events	Cardiac failure	Arrhythmia	Diabetic ketoacidosis	Acute coronary syndrome
Acute hepatic failure	Cardiac failure acute	Atrial fibrillation	Hypogonadism	Acute myocardial infarction
Cirrhosis	Cardiac failure chronic	Atrial flutter	Hyperglycaemia	Arteriovenous fistula thrombosis
Haemochromatosis	Cardiac failure congestive	Atrioventricular block complete	Hypoglycaemia	Arteriovenous graft thrombosis
Hepatic function abnormal	Cardiac failure (any other)	Bradycardia	Metabolic syndrome	Atrial thrombosis
Hepatic cirrhosis	Fluid overload	Electrocardiogram QT prolonged		Cerebral infarction
(add any mention of cirrhosis or hepatic failure)	Generalized oedema (from general disorders)	Extrasystoles		Cerebrovascular accident
AST elevated	Localised oedema	Heart rate irregular		Graft thrombosis
ALT elevated	Oedema peripheral	Palpitations		Intracardiac thrombus
Bilirubin elevated		Sinus bradycardia		Ischaemic cerebral infarction
		Sinus tachycardia		Myocardial infarction
		Supraventricular extrasystoles		Transient ischemic attack
		Tachycardia		Troponin increased/ troponin I increased
		Tachycardia paroxysmal		Vascular graft thrombosis
		Ventricular extrasystoles		
		Ventricular fibrillation		

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

Source: ISS appendix, table 8.

Reviewer's comment: The above listed events seem largely reasonable. However, some events are not associated with hemochromatosis (specifically, thrombotic events, endocrine events other than worsening of diabetes mellitus) or may be common in ESRD patients (arrhythmic events) to contribute to noise. Therefore, I performed a sensitivity analysis with the following adverse events associated with hemochromatosis (see section 7.1.2). For results, see Reviewer's evaluation TEAEs suggestive of hemochromatosis.

Applicant's evaluation of dose and the profile of adverse events potentially associated with iron overload/hemochromatosis

The applicant's analyses of the types of AEs listed in Table 25, with the exception of heart failure events, did not reveal any pattern of increased dose/exposure to KRX-0502 among subjects reporting these events than the entire study population.

Table 26 shows higher mean/median daily dose and higher total median dose of KRX-0502 received by the two subjects who developed heart failure in the efficacy period as compared to all KRX-0502 treated subjects in the efficacy and safety period of trial 305. These two subjects were in fact re-randomized to the 4-week placebo arm after receiving KRX-0502 in the safety period. However, overall, there was a lack of consistent association with higher KRX-0502 dose and heart failure in the two periods of trial 304.

Table 26: KRX-0502 exposure in subjects with AEs Potentially Associated with Iron Overload (Trial Safety Population)

		KRX-0502 (FERRIC CITRATE)	
	Prescribed Doses (g/day)	*Safety period (N = 289)*	*Efficacy period (N = 95)*
Subjects taking KRX-0502			
	Mode	6.0	12
	Mean (SD)	7.9 (2.4)	8.7
	Median	7.5	9
	Maximum	12.0	12
	Total (median g)	2505.8	261
Subjects with any AE potentially associated with iron overload	n	64	4
	Mode	6.0	
	Mean (SD)	7.9 (2.4)	9.2 (2.4)
	Median	7.2	8.9
	Maximum	11.8	12.0
	Total (median g)	2411.0	282.2
Heart Failure Events	n	22	2
	Mode	6.0	
	Mean (SD)	7.7 (2.6)	11.2 (1.1)
	Median	7.1	11.2
	Maximum	11.8	12.0
	Total (median g)	2503.7	324.8

Source: extracted from the applicant's Ad Hoc Table 22

Reviewer's comment: Heart failure is known to occur in ESRD patients, who often have ischemic heart disease. According to the applicant's dataset and submission, the two subjects developed congestive heart failure either on the placebo withdrawal efficacy period (after treatment with KRX-0502 on the safety period), or before even starting KRX-0502. Their ferritin values were less than 1000 ng/mL throughout the trial. They did not develop other adverse events suggestive of hemochromatosis. Thus as a whole, data suggest that these two cases of congestive heart failure are unlikely to represent iron overload of the heart attributed by KRX-0502 use.

Applicant's evaluation of KRX-0502 dose and the profile of liver function abnormalities potentially associated with iron overload/hemochromatosis

No consistent or significant of elevation in daily doses or total median dose was detected in subjects who met the LFT criteria than all subjects receiving KRX-0502 (the applicant's Ad hoc Table 22). However, very few subjects had elevations in LFTs that meet established criteria for clinical concern (CTCAE grade 2). For example, there was only 1 subject with >1.5X elevation in total bilirubin, who did not receive particularly high doses of KRX-0502 (mean daily dose 7.6 g/day vs. 7.5 g/day), and this subject had liver dysfunction at baseline which may confound the finding of total bilirubin elevation. Subjects with an increases in LFTs from baseline (>100% increase but less than 3x ULN) had a modestly higher mean/median daily dose of KRX-0502 (approximately 10% higher mean daily dose, and up to 20% higher in total median dose) than all subjects taking KRX-0502.

Reviewer's comment: Hemochromatosis is typically associated with mild elevations in LFTs. Thus the applicant's cutoffs are not sensitive to detect hemochromatosis related liver injury.

Applicant's evaluation of KRX-0502 dose and iron profiles abnormalities potentially associated with iron overload/hemochromatosis

The applicant chose ferritin >1500 ng/mL and TSAT >50% on two consecutive visits as iron profile abnormalities potentially associated with iron overload/hemochromatosis.

According to the applicant, 70 subjects had a serum ferritin >1500 ng/mL[12] at least once during either the safety period or efficacy period. Subjects who had these levels in iron parameters only had modestly higher mean/median daily dose of KRX-0502 (approximately 10% higher mean daily dose, 20% higher in total median dose).

In the DSMC assessment, most of the elevations in serum ferritin to levels >1500 ng/mL were because of the direct or delayed effect of IV iron, underlying medical conditions, and/or TEAEs. Based on the analysis using an absolute value of ferritin, the applicant concluded that "increased ferritin was not associated with an increase in the incidence of AEs suggesting iron overload and/or laboratory findings suggesting liver dysfunction."

[12] 1500 ng/mL was a rather arbitrary cutoff selected by the Study Chair of the protocol and the Data Safety Monitoring Committee (DSMC) for assessing safety and pharmacovigilance.

Table 27: Adjudication committee: subjects with ferritin >1500 ng/mL

Category	KRX-0502[a]	Active Control[a]	Post-treatment/ Observational Period (Not on Study Drug)[b]	Adjudicated Subjects[b]
Ferritin >1500 or <1500	**N (%)**	**N (%)**	**N**	**N (%)**
Number of subjects with ferritin >1500 ng/mL	55 (19%)	13 (8.7%)	2	70 (16.3%)
Number of subjects with ferritin ≤1500 ng/mL[d]	234 (81%)	136 (91.3%)	0	1 (0.2%)
Baseline Ferritin	**N (%)**	**N (%)**	**N**	**N (%)**
Number of subjects with baseline ferritin at randomization >1000 ng/mL	8 (2.8%)	6 (4.0%)	1	15 (3.4%)
Ferritin Values	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Baseline ferritin (ng/mL)	804 (288)	908 (390)	950 (187)	827 (307)
Post-baseline ferritin (ng/mL)[e]	1977 (474)	1830 (667)	2309 (959)	1959 (523)
Number of Times >1500 ng/mL	**N (%)**	**N (%)**	**N**	**N (%)**
One occurrence with ferritin >1500 ng/mL	25 (8.6%)	11 (7.4%)	1	37 (8.4%)
More than 1 occurrence with ferritin >1500 ng/mL	30 (10.4%)	2 (1.3%)	1	33 (7.5%)
Final Adjudication[f]	**N (%)[g]**	**N (%)[g]**	**N**	**N**
Number of subjects with ferritin >1500 ng/mL	55 (19.0%)	13 (8.7%)	2	70
Direct effect of IV iron	22 (40.0%)	10 (76.9%)	2[f]	34
Delayed effect of IV iron	18 (32.7%)	4 (30.7%)	0	22
Adverse event/Serious adverse event	25 (45.5%)	5 (38.4%)	1	31
Study drug	3 (5.5%)	0	0	3
Other	2 (3.6%)	1 (7.6%)	0	3

Source: 120-day safety update, table 6
[a] The incidence rate was calculated using the Safety Population
[b] All values in this column represent results for only the 71 subjects adjudicated for ferritin.
[d] One subject had a liver biopsy showing iron overload/hemochromatosis and study drug was stopped. The increase in ferritin was due to the administration of IV iron.
[e] For subjects with more than 1 occurrence with an elevation in ferritin >1500 ng/mL, the highest ferritin value reported was used.
[f] Subjects could have multiple reasons adjudicated by the DSMC and Study Chair to account for the elevation in ferritin >1500 ng/mL. In addition, for 11 KRX-0502 treated subjects, the reason for having an elevation of ferritin > 1500 ng/mL was categorized as unknown.
[g] Incidence rate was based on the total number of subjects with that specific adjudication.
IV=intravenous; N=number of subjects in the treatment group; SD=standard deviation.

DMSC attributed the rise of serum ferritin levels (from pre-KRX-0502 baseline levels of below 1000 ng/mL to above 1500 ng/mL with continued KRX-0502 treatment over the 52 weeks) in three subjects to KRX-0502 use. These three subjects had post-treatment ferritin elevations above 1500 ng/mL on multiple visits. In terms of the adverse events that could be consistent iron overload, one of the subjects developed left olecranon bursitis after week 48 of KRX-0502 treatment. The bursitis was deemed mild, but did not resolve.

Reviewer's evaluation TEAEs suggestive of hemochromatosis

I found no difference in the incidence of this group of adverse events in the KRX-0502 arm compared with the active control arm, or in the subset with a ferritin > 1000 ng/mL (trial 304, safety period, safety population). Furthermore, in the efficacy period (trial 304), I found a lower proportion of subjects developed AEs suggestive of hemochromatosis in the KRX-0502 than the placebo arm.

Table 28 Treatment Emergent Adverse Events Suggestive of Hemochromatosis in subjects with a ferritin >1000 ng/mL (Trial 304, Safety period)

	KRX-0502 (FERRIC CITRATE) (N = 289)			*ACTIVE CONTROL (N = 149)*		
	Events	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
number of subjects with a ferritin >1000		154	53.3%		57	38.3%
Total for AEs shown below	29	21	13.6%	14	12	21.1%
Abdominal pain	10	10	6.5%	4	4	7.0%
Arthralgia	9	6	3.9%	3	3	5.3%
Arthritis	1	1	0.6%	0	0	0.0%
Ascites	1	1	0.6%	2	1	1.8%
Encephalopathy	0	0	0.0%	1	1	1.8%
Fatigue	1	1	0.6%	2	1	1.8%
Joint effusion	1	1	0.6%	1	1	1.8%
Joint injury	2	2	1.3%	0	0	0.0%
Joint swelling	1	1	0.6%	0	0	0.0%
Lethargy	3	1	0.6%	1	1	1.8%

Table 29 Treatment Emergent Adverse Events Suggestive of Hemochromatosis in subjects with a ferritin >1000 ng/mL (Trial 304, Efficacy period)

	KRX-0502 (FERRIC CITRATE) (N = 95)			*PLACEBO (N = 95)*		
	Events	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
number of subjects with a ferritin >1000		54	57%		66	69%
Total for AEs shown below	6	3	6%	18	13	20%
Abdominal pain	1	1	2%	6	6	9%

	KRX-0502 (FERRIC CITRATE) (N = 95)			*PLACEBO (N = 95)*		
	Events	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Arthralgia	5	2	4%	3	3	5%
Arthritis	0	0	0%	1	1	2%
Ascites	0	0	0%	1	1	2%
Fatigue	0	0	0%	1	1	2%
Joint injury	0	0	0%	2	2	3%
Joint swelling	0	0	0%	1	1	2%
Lethargy	0	0	0%	3	1	2%

Thus, in the overall trial population, the observed AE profile detects no association between KRX-0502 use and hemochromatosis. Nonetheless, hemochromatosis is often underdiagnosed because of the vague or lack of specific symptoms early in the disease manifestation, as illustrated by the case of confirmed iron overload/hemochromatosis.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events in trial 305 are discussed in section 7.2.2.

Common Adverse Events in the Long-Term Controlled Trial 304

Among the TEAEs in trial 304 that were categorized into the 23 MedDRA body system categories, TEAEs that commonly occurred in the KRX-0502 arm include AEs that fell into 1) gastrointestinal disorders, 2) infections and infections, 3) general disorders and administration site conditions, 4) injury, poisoning and procedural complications, 5) respiratory, thoracic and mediastinal disorders, 6) musculoskeletal and connective tissue disorders, and 7) nervous system disorders. Of these 7 body systems, only adverse events classified into the gastrointestinal disorder body system category had a >2% higher incidence in subjects treated with KRX-0502 as compared to active control (see Table 30).

In addition, treatment emergent falls, procedural pain, limb discomfort occurred in > 2% higher proportions in KRX-0502 than active control treated subjects (see Table 30).

Table 30: Treatment emergent common adverse events that occurred > 2% higher proportion in KRX-0502 than active control treated subjects (trial 304 safety period).

	KRX-0502 (FERRIC CITRATE) (N = 289)			*ACTIVE CONTROL (N = 149)*		
	Events	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Gastrointestinal disorders	383	164	56.8	168	70	47.0
Diarrhea	97	74	25.6	28	21	14.1
Feces discolored	52	49	17.0	0	0	0.0
Constipation	29	23	8.0	10	8	5.4
Injury, poisoning and procedural complications	168	92	31.8	139	56	37.6
Fall	15	12	4.2	4	3	2.0
Procedural pain	8	8	2.8	0	0	0
Musculoskeletal and connective tissue disorders	95	61	21.1	61	40	26.9
Limb discomfort	9	8	2.8	1	1	0.7

Source: reviewer's analysis, using the following variables in the adae dataset: *SAF01FL=Y, TRTEMFL=Y, APERIODC = Safety period*

As shown above, treatment emergent fecal discoloration, constipation, diarrhea occurred more frequently in the KRX-0502 than the active control arm. In addition, the following GI adverse events (regardless of treatment emergence) were also slightly higher on KRX-0502 arm than the active control arm: abdominal discomfort/distension/pain /dyspepsia/dysphagia.

Similar to the profile for the serious adverse event in the gastrointestinal disorders or infections and infestations categories (section 7.3.2), the common adverse events that were grouped into these categories were no more frequent in the KRX-0502 arm than placebo arm in the efficacy periods of Trial 304. In fact, the only adverse event categories have higher incidence of aggregate AEs in the KRX-0502 than placebo arm by > 2% were *Injury, poisoning and procedural complications* and *cardiac disorders categories (*Table 31*).* Within these two categories, the dictionary derived adverse event terms that were more common in the KRX-0502 than the placebo arm are shown in the table below.

Table 31: Treatment Emergent Common Adverse Events (Trial 304 Efficacy period, Safety Population)

SOC/PT	*KRX-0502 (FERRIC CITRATE) (N = 95)*			*PLACEBO (N = 95)*		
	Events	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Total TEAEs	567	85	89%	728	93	98%
Gastrointestinal disorders	6	5	5	11	8	8
Infections and infestations	4	4	4	16	12	13
Injury, poisoning and procedural complications	11	9	9	3	3	3
Vascular access complication	5	5	5	0	0	0
Arteriovenous fistula site complication	1	1	1	0	0	0
Graft complication	1	1	1	0	0	0
Cardiac disorders	5	4	4	1	1	1
Cardiac arrest	1	1	1	0	0	0

Source: reviewer's analysis, using the following variables in adae datasets: *SAF02FL=Y, TRTEMFL=Y, and APERIODC= Efficacy Treatment Period.*

In addition, few adverse events were reported with at least 2% higher incidence in subjects on KRX-0502 than on placebo. These dictionary coded AEs (PT terms) were vascular access complications (see table above), catheter site hemorrhage (2% vs. 0%), hypotension (2% vs. 0%), peripheral edema (2% vs. 0%), rash (2% vs. 0%). It is difficult to tell if the increased incidence of vascular access complication was because of a play of chance.

7.4.2 Laboratory Findings

Hematology:
There was no clinically significant use in hemoglobin over time in trial 304 or between the KRX-0502 and the active control arm.

Iron status:
This topic was discussed in Section 6. Please see section 6, section 7.3.5 for changes in ferritin and TSAT.
Mean serum iron: The increase in serum iron from baseline in the KRX-0502 than the active control arm was consistent with GI absorption. However, it is difficult to tease apart the increase in serum iron from KRX-0502 versus from IV iron.

Clinical chemistry:

My evaluation of clinical chemistry was focused on the trial 304, the longer trial. I also evaluated for any dose-related changes in serum calcium, bicarbonate, and Vitamin D levels (available in the CSR for trial 305). I found no evidence of hypophosphatemia, hypocalcemia or hypercalcaemia.

Trial 304:
Calcium: Throughout the 52 weeks of trial 304's safety period, there was a modest trend toward a slightly lower mean serum calcium on the KRX-0502 than the active control arm, which included calcium based phosphate binders. (There were no notable changes from baseline in serum calcium. The resulting mean calcium-phosphorus products were similar between KRX-0502 and the active control arm.

Serum Bicarbonate:
No clinically and statistically significant difference occurred in the mean serum bicarbonate level between KRX-0502 versus the active control, throughout the 52 weeks of trial 304. In both treatment arms, serum bicarbonate did not decrease from baseline.

Intact parathyroid hormone (iPTH): The mean iPTH was not significantly different in the KRX-0502 group compared with the active control group at any time point in trial 304.. Mean iPTH values were elevated in both treatment groups at baseline after discontinuing the phosphate binder during the Wash-out Period and showed appropriate decline with treatment of hyperphosphatemia.

Fat soluble Vitamins
No clinically or statistically significant decrease in mean levels from baseline with KRX-0502 treatment. No clinically and statistically significant difference between the KRX-0502 and the active control arms over the 52 week treatment period (trial 304).

- 25-Dihydroxy-Vitamin D3: No difference in the mean vitamin D3 level between the KRX-0502 and the active control arms. No clinically significant decrease from baseline in vitamin D3.

- Vitamin A: No clinically significant decrease in the mean vitamin A levels in both treatment arms. Similar changes from baseline between the treatment arms.

- Vitamin B12: Some variability in the mean vitamin B12 levels (particularly in the KRX-0502 arm), but no clinically significant decrease with treatment were detected over the 52 weeks. No statistical significance difference between the KRX-0502 and the active control arms.

- Vitamin E: No consistent decrease from baseline. No clinically or statistically significant difference between KRX-0502 and active control arms.

- Vitamin K: No decrease in vitamin K level or significant between group difference.

Folic acid: Slight decrease in the mean folic acid levels from baseline appeared in both treatment arms, without any detectable difference between the treatment arms throughout the 52 weeks.

Liver Enzymes:
According to the applicant's clinical overview, no subject met criteria for DILI.
See 7.3.5 for discussion of liver enzyme abnormalities and KRX-0502 dose. The incidence of hepatobiliary disorders was lower in KRX-0502 than the active control arm (adverse events sections above).

7.4.3 Vital Signs

Trial 304: During the Safety period, the mean vital sign measurements were similar to the Study-baseline measurements within treatment groups and were similar between the groups at all time points (CSR Table 14.3.3.1.1). The proportion of subjects with hypertension, hypotension (KRX-0502 7.3% versus active control 10.7%) and tachycardia (KRX-0502: 2.8% versus Active control: 3.4%) was similar between the KRX-0502 and the active control arms. However, the proportion of subjects with hypotension was higher in the KRX-0502 than placebo arm (2% vs. 0%).

The proportion of subjects who discontinued for blood pressure increased, hypertension or malignant hypertension was similar between the KRX-0502 and the active control arm.

Trial 305: No dose-related changes occurred from baseline in blood pressure and heart rate.

7.4.3 Electrocardiograms (ECGs)

Electrocardiogram measurements were performed at screening and at the end-of-trial in trial PBB00101. No clinically significant trends when compared with placebo in mean change from Baseline were noted for PR, QRS, QT, QTc, or HR in the KRX-0502 treatment groups (2 g/day, 4 g/day, and 6 g/day).

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

KRX-0502 is a small molecule and is not expected to have immunogenic potential. Neither the nonclinical studies nor the clinical studies suggest an increase in adverse events of potential immunogenic etiology.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the pivotal trial 305 (up to a maximum dose of 8 gram per day of KRX-0502), dose-related increases in the overall incidence of AEs, severity or seriousness of AEs appeared (Table 32).

There was a dose-related relationship regarding the incidence of adverse events that fell into the gastrointestinal disorders category (Table 32). The incidence of GI TEAEs, with the exception of discolored feces, was highest in the 8 g/day group and similar in the 1 g/day and 6 g/day groups (CSR Table 27). Severe GI adverse events, specifically diarrhea and upper abdominal pain, were more observed at the 8 g/day, but not 1 g/day or 6 g/day (Table 32).

In addition, higher dose appears to lead to higher incidence of infections and infestations AEs (representing both systemic and local infections) regardless of seriousness or severity. This dose-relationship was observed for all AEs regardless of occurrence on-treatment (data not shown) and on-treatment AEs (Table 32). However, there was not an apparent dose-relationship with the infectious adverse events that were considered serious or severe, regardless of the on-treatment status. In addition, dose of IV iron was not collected during trial 305. Therefore, it is not known if the increase in infection rate associated with an increasing KRX-0502 dose in trial 305 was associated with concomitant increase in IV iron use.

Lastly, higher dose appears to lead to higher frequency of on-treatment AEs that fell into the nervous system disorders body system (Table 32). This dose-relationship hold for both serious and severe AEs that fell into the nervous system disorders category. A dose-relationship for nervous system disorders was also observed in all AEs analysis. There is no known biologic basis for KRX-0502 attributing to this observation to my knowledge. No increased nervous system disorders occurred in the KRX-0502 than the active control arm in trial 304. Thus this finding may represent a play of chance or to confounder factors in this trial.

Table 32: On-treatment adverse events (Trial 305, Safety Population)

	1 g/day (N = 51)			*6 g/day (N = 52)*			*8 g/day (N = 48)*		
	Events	*subjects (n)*	*%*	*Events*	*subjects (n)*	*%*	*Events*	*subjects (n)*	*%*
On-treatment AEs	**60**	**28**	**55**	**78**	**39**	**75**	**114**	**33**	**69**
Gastrointestinal disorders	28	17	33	29	20	38	44	22	46
Infections and infestations	3	3	6	6	5	10	8	6	13
Nervous system disorders	4	3	6	5	5	10	10	6	13
On-treatment serious AEs	**1**	**1**	**2**	**7**	**3**	**6**	**4**	**4**	**8**
Gastrointestinal disorders	0	0	0	1	1	2%	0	0	0%
Cholelithiasis	0	0	0	1	1	2	0	0	0
Infections and infestations	1	1	2	1	1	2%	0	0	0%
Device related sepsis	0	0	0	1	1	2	0	0	0
Pneumonia	1	1	2	0	0	0	0	0	0
Nervous system disorders	0	0	0	1	1	2	2	2	4
Cerebral haemorrhage	0	0	0	0	0	0	1	1	2
Haemorrhage intracranial	0	0	0	0	0	0	1	1	2
Syncope	0	0	0	1	1	2	0	0	0
On-treatment severe AEs	**3**	**3**	**6**	**5**	**3**	**6**	**14**	**10**	**21**
Gastrointestinal disorders	2	2	4	0	0	0	4	3	6
Diarrhea	0	0	0	0	0	0	3	2	4
Abdominal pain upper	0	0	0	0	0	0	1	1	2
Infections and infestations	1	1	2	0	0	0	0	0	0
Pneumonia	1	1	2	0	0	0	0	0	0
Nervous system disorders	0	0	0	0	0	0	3	3	6
Cerebral haemorrhage	*0*	*0*	*0*	0	0	0	1	1	2
Haemorrhage intracranial	*0*	*0*	*0*	0	0	0	1	1	2
Headache	*0*	*0*	*0*	0	0	0	1	1	2

Source: reviewer's analysis. An on-treatment AE was defined an AE that started during the on-treatment period: from the date of study drug initiation to the date of discontinuation of study drug plus 1.

In addition, examination of the AE profile suggested a higher frequency of AEs leading to KRX-0502 withdrawal in the 8 g/day fixed-dose group compared to the 6 g/day or 1 g/day group (Table 33). Diarrhea, abdominal pain, nausea, vomiting can be moderate to severe in intensity to led to drug withdrawal or interruption (Table 33). Furthermore, the incidence of moderate and severe gastrointestinal adverse events that led to drug withdrawal or interruption is highest in the 8 gram/day group, compared to the 1 gram/day or 6 gram/day group. Of these GI adverse events, diarrhea was the only severe AE that led to drug withdrawal.

Table 33: Moderate and Severe on-Treatment AEs that led to drug discontinuation or interruptions (Trial 305, Safety Population)

	1 g/day (N = 51)			*6 g/day (N = 52)*			*8 g/day (N = 48)*		
	Events	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Total	**2**	**2**	**4**	**2**	**2**	**4**	**11**	**6**	**13**
Gastrointestinal disorders	1	1	2	1	1	2	9	5	10
Abdominal pain	0	0	0	0	0	0	2	1	2
Diarrhea	1	1	2	1	1	2	5	4	8
Nausea	0	0	0	0	0	0	1	1	2
Vomiting	0	0	0	0	0	0	1	1	2
Infections and infestations	1	1	2	0	0	0	0	0	0
Pneumonia	1	1	2	0	0	0	0	0	0

Source: reviewer's analysis

7.5.2 Time Dependency for Adverse Events

In trial 304, for subjects who continued study drug, treatment-emergent diarrhea occurred throughout the course of treatment with KRX-0502, similar to that of active control (KRX-0502 [n=71], days from starting study drug: mean 122 days [SD 121 day], median 85 days, maximum 382 days; active control [n=27]: mean 179 days [SD 103 day], median 176 days, maximum 353 days). Compared to diarrhea that did not lead to discontinuation of KRX-0502, diarrhea that led to KRX-0502 discontinuation (days from starting KRX-0502 (n=29): mean 50 days [SD 80 day]; median 26 days) on average occurred earlier in the course of treatment.

No other obvious time dependent adverse event was observed with this product either in short-term or the one-year trial, 304. Long term safety follow-up trial of 304 is ongoing, and based on the 120-day preliminary safety report no new safety finding was identified.

7.5.3 Drug-Demographic Interactions

The potential for drug-demographic interactions with KRX-0502 treatment was evaluated through subgroup analyses of the Pooled Safety Set for gender, age, and race. No potential interactions were identified in these analyses, with a similar safety profile (assessed by AEs) seen across all gender, age, and race categories.

7.5.4 Drug-Disease Interactions

The limited number of PD patients makes it difficult to compare AEs on HD versus on PD. No substantive differences between the 2 types of dialysis were reported in the Japanese trials that studied lower doses of KRX-0502 and used less IV iron. It is still possible that KRX-0502 may have different effects on iron parameters in PD than HD patients, because PD patients typically have less iron loss and exogenous IV iron use than HD patients. Nonetheless, excluding patients with hemochromatosis/iron overload syndrome from receiving KRX-0502 and following iron parameters and adjust KRX-0502 and IV iron doses as needed will likely address the risk of iron overload syndrome (b) (4)

For most AE categories, the percentage of subjects with AEs was higher among subjects with diabetes than subjects without diabetes (ISS appendix, Table 76). When examining the various categories of AEs, by SOC and individual PTs, there were no consistent trends in the occurrence of AEs or the pattern of reporting of AEs between subjects with and without diabetes treated with KRX-0502 or active control. Hence, data do not suggest an increased risk in patients with diabetes.

7.5.5 Drug-Drug Interactions

The *in vitro* drug-drug interaction results are pending at this time.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

In the ISS database, the number and proportion of subjects with neoplasms benign, malignant, and unspecified (including cysts and polyps) was not higher in KRX-0502 as compared to the active control arm.

7.6.2 Human Reproduction and Pregnancy Data

In the Safety period of trial 304, a 39-year-old black female reported an unintended pregnancy on Day 174 of KRX-0502 treatment. The gestational age of the fetus was not reported. The administration of KRX-0502 was reported interrupted until she experienced a spontaneous abortion on Day 199 of the study. After the abortion, she resumed KRX-0502.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric studies have been conducted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose: There were no reports of acute overdose with KRX-0502 in the clinical development program. Because accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age, this product must be kept out of the reach of children. In case of accidental overdose, a doctor or poison control center should be contacted immediately. As absorption of the ferric iron is thought to be low, and thus the risk of systemic acute iron toxicity is expected to be low, at least for adults.

Abuse potential and withdrawal symptoms: In subjects evaluated in clinical studies, there has been no pattern of AEs or overuse reported that suggest KRX-0502 may have potential for abuse. No withdrawal or rebound effects were seen for subjects in the Placebo-controlled, 4-week withdrawal period in trial 304, with the exception of the expected rise in serum phosphorus in the placebo group.

7.7 Additional Submissions / Safety Issues

No new safety concerns were identified in the supportive trials.

8 Postmarket Experience

The NDA for JTT-751 (ferric citrate) in subjects with CKD (on dialysis and not on dialysis) was submitted to the Japan health authorities for review in January 2013, and approved on January 2014 for improvement of hyperphosphatemia in chronic kidney disease patients.

9 Appendices

9.1 Labeling Recommendations

1 INDICATIONS AND USAGE:
Division of Hematology Products recommends the wording "… (b) (4) …" should be removed from the indication statement. DHP believes that the submitted application is inadequate to support a claim and that there is no evidence to support a (b) (4) Instead, DHP believes clinical evidence for (b) (4) Furthermore, DHP finds (b) (4) not acceptable and notes no rationale is provided for the Zenerex (b) (4)

4 CONTRAINDICATIONS
Zenerex is contraindicated in patients with (b) (4) iron overload syndromes (e.g., hemochromatosis).

Reviewer's recommendation: I agree with the contraindication.

5 WARNINGS AND PRECAUTIONS
5.1 (b) (4)
Elevation of serum ferritin and transferrin saturation (TSAT) levels has been observed. All patients receiving Zenerex require (b) (4) monitoring of iron parameters (serum ferritin and TSAT). Patients on Zenerex may (b) (4) reduction in, or discontinuation of, IV iron therapy. (b) (4)

Reviewer's recommended phrasing:
5.1 (b) (4)
Elevation of serum ferritin and transferrin saturation (TSAT) levels has been observed. All patients receiving Zenerex *require* (b) (4) *monitoring of iron parameters (serum ferritin and TSAT) and hemoglobin. Patients on* Zenerex *may need reduction in, or discontinuation of, IV iron therapy.* (b) (4)

Rationale: To provide more specific instructions on iron parameter monitoring. I recommend deleting following sentence: (b) (4)

(b) (4)

ecause

6 Applicant's Proposed Label:

(b) (4)

Reviewer's recommendation: Delete above. Replace with (b) (4)

9.2 Advisory Committee Meeting

There was no advisory committee meeting. A number of phosphate binders have been approved, including an iron containing phosphorus binder. KRX-0502 is not a new molecular entity. There is no novel issue.

9.3 Iron parameters for enrollment and ferric citrate and IV iron dosing

Below, I summarize the similarities and differences between the pivotal and supportive trials in the iron parameters for trial enrollment and for IV iron dosing.

Iron based enrollment criteria for all 4 key trials in the integrated safety database
Because ferric citrate is an iron-containing phosphate binder, all four trials (304, 305, 201 and PBB00101) in the integrated safety database had eligibility criteria based on levels of ferritin and TSAT (Table 34). In addition, none of the trials had eligibility criteria based on the level of IV iron use at baseline.

The more permissive use of IV iron in the key trials than the supportive trials
For the key trials and the majority of the supportive trials, IV iron was allowed with dosing per the PI's discretion (with the exceptions were the early trials PBB00101, GBA2-1 and GBA2-2, in which IV iron use was not permitted). However, the key and supportive trials differed in the ferritin and TSAT threshold for allowing IV iron use (Table 34 and Table 35).

For subjects with ferritin and TSAT levels that were above the threshold for allowing IV iron use in all 4 key trials, intravenous (IV) iron therapy was not encouraged but permitted at discretion of investigator or if approved by the Clinical Coordinating Center.

However, the criteria regarding when to withhold IV iron treatment differed between the key trials (conducted in US) and other trials (largely conducted in Japan). According to the applicant, these criteria reflected different patterns of use in the US and in Japan.

Stopping rules for ferric citrate based on iron parameters

For all the 4 key trials, no iron parameter was specified for stopping ferric citrate. In contrast, the supportive trials conducted in Japan had stopping criteria for ferric citrate based on iron parameters that are suggestive of iron overload.

Table 34 Iron Parameters Based Entry Criteria and Stopping Rule for IV iron Use (Four Key Trials and Two Extension trials)

Phase	Trial	Eligible if	IV Iron Use Permitted If*
Phase 3	304	ferritin <1000 and TSAT <50%	ferritin ≤1000 and TSAT ≤30%*
Phase 3 extension of 304	307	No criteria based on TSAT or ferritin	ferritin ≤500 and TSAT ≤30%[$]
Phase 3	305	ferritin <1000 and TSAT <50%	ferritin ≤1000 and TSAT ≤50%.
Phase 2	PBB00101	ferritin ≤ 800	prohibited
Phase 2 Extension PBB00101	OLE-PBB00101	No criteria based on TSAT or ferritin	ferritin ≤600 and TSAT ≤50%
Phase 2	201	ferritin <1000 and TSAT <50%	ferritin <500 and TSAT <30%*

According to the final protocol amendments of the above trials. Confirmed with the sponsor (submission November 11, 2013).
* IV iron can be given to subjects with ferritin and/or TSAT above these thresholds, if investigator deemed necessary.
**dosing at PI discretion but withheld if hematocrit >36%

As shown in the table above, there was variability in the exclusion criteria based on iron parameters. The long-term extension trials (307, OLE- PBB00101) had more restrictive IV iron use criteria (based on iron indices) than the parent trials.

Note, the Japanese trials used more conservative ferritin criteria for enrolling subjects and for with-holding IV iron than the US pivotal trials.

Table 35 Iron Parameters Based Entry Criteria and Stopping Rules for IV iron Use (Supportive Trials)

[1] Unit of ferritin is ng/mL

*IV iron could be administered outside these parameters if the principal investigator or the sub-investigator considered it is necessary to provide iron supplement therapy.

Phase	Trials	Eligible if	Stop ferric citrate if	IV iron permitted if
Phase 2 HD	GBA2-1	Ferritin[1] ≤300**	Ferritin ≥800 or TSAT ≥50%	Prohibited
Phase 2 HD	GBA2-2	Ferritin ≤300 or TSAT ≤ 50%**	Ferritin ≥800	Prohibited
Phase 3 HD	GBA4-1	Ferritin ≤500 and TSAT ≤50%	Ferritin ≥800	Ferritin ≤100 and TSAT ≤20%*
Phase 3 PD	GBA4-3 (ongoing)	Ferritin ≤500 and TSAT ≤50%**	Ferritin ≥800	Ferritin ≤100 and TSAT ≤20%*
Phase 3	GBA4-5	Ferritin ≤500 and TSAT ≤50%**	Ferritin ≥800	Ferritin ≤100 and TSAT ≤20%*
Phase 3	GBA4-6 (ongoing)	Ferritin ≤500 and TSAT ≤50%**	Ferritin ≥800	Ferritin ≤100 and TSAT ≤20%*
Phase 2	202 HD	Ferritin <1000 and TSAT <50%**	No criteria based on iron parameters	Ferritin ≤500 and TSAT ≤25%
Phase 3 (non-dialysis)	GBA4-4	Ferritin ≤500 and TSAT ≤50%**	Ferritin ≥800	Ferritin ≤100 and TSAT ≤20%
Phase 3 (non-dialysis) (ongoing)	GBA4-7 (extension of GBA4-4)	Not specified**	Ferritin ≥800	Ferritin ≤100 and TSAT ≤20%*

**Excluded subjects with hemochromatosis, those receiving treatment for iron overload, or suspected iron overload (in trial GBA4-6 only), or thalassemia, with iron absorption because of ineffective erythropoiesis (in trial 202 only)

Source: Extracted from the applicant's submissions dated November 11, 2013 in response to the FDA information request.

The IV iron usage criteria in the trials generally mirrored the practice patterns of the respective regions. The applicant reported substantially more use of IV iron in the US than Japan. According to Dialysis Outcomes Practice Patterns Study [DOPPS 2013],[13]

[13] The applicant cited the lower baseline serum ferritin in the Japanese trials (mean ranging between 70 and 100 ng/mL) compared to US studies (mean >500 ng/mL) as indirect evidence for IV iron usage. In addition, the applicant cited DOPP: confirm that a substantial percentage of all dialysis patients in the US

83% of US patients receive IV iron compared with 38% in Japan. The applicant believes that the practice of greater IV iron use in the US is likely attributable to concerns that using higher doses of ESAs to achieve higher serum hemoglobin levels in patients on dialysis or with chronic kidney disease is associated with an increased incidence of AEs, and results from the DRIVE Study that suggested that giving IV iron to achieve serum ferritin levels of 1200 ng/mL and serum TSAT levels of 50% reduces the need for ESAs and maintains hemoglobin levels [Coyne et al 2007].

9.4 Trial 304:

Important Trial Dates
First subject randomized: December 22, 2010
Last subject completed last visit: November 07, 2012

Geographic Distribution
Fifty-eight sites in the United States and 2 sites in Israel.

Trial Administrative Structure
There was a 2 member Data Safety Monitoring Committee. There was also a one-member Clinical Coordinating Center (CCC) at Vanderbilt University that monitored compliance with the protocol.

Trial Population
ESRD subjects on thrice-weekly hemodialysis or on peritoneal dialysis for at least three months prior to the screening visit who were currently taking ≥3 and ≤18 pills/day of calcium acetate, calcium carbonate, lanthanum carbonate, and/or sevelamer (carbonate or hydrochloride or sevelamer powder equivalent to sevelamer tablets), or any other agent serving as a phosphate binder, or any combination of these agents were eligible for enrollment. Subjects who had serum phosphorus levels <10.0 mg/dL during the 3 month prior to screening and serum phosphorus levels ≥ 6.0 mg/d within 2 weeks after discontinuing phosphate-binding therapy during washout were eligible to be randomized into the trial.

The eligibility criteria did not require subjects to have absolute iron deficiency. For a summary of ferritin and TSAT eligibility criteria, see Table 34 in section 9.
Lastly, this trial did not screen for or exclude subjects with a history of hemochromatosis or other iron storage disorders.

Trial Procedures (based on the final amendment dated June 30, 2011)
Titration of KRX-0502 per serum phosphorus level

have serum ferritin levels of >800 and >1200 ng/mL (43% and 16%, respectively), compared with only 6.2% of patients in Japan having ferritin levels of >800 ng/mL, and

KRX-0502 was started at 6 g per day (2 g three times daily with meals). Throughout the trial, KRX-0502 was titrated according to serum phosphorus levels, targeting levels between 3.5 and 5.5 mg/dL.

In the 52-week Safety period, serum phosphorus and calcium were checked once week for 2 weeks, then once every 2 to 4 weeks thereafter. In the 4-week Efficacy period, serum phosphorus and calcium were checked once weekly.

Doses were up-titrated by 1 g/day for serum phosphorus levels between 5.6 and 6.9 mg/dL and by 3 g/day for serum phosphorus levels > 6.9 mL/dL. Doses were down titrated by 1 g/day (for serum phosphorus levels between 2.5 mg/dL and 3.4 mg/dL). For a serum phosphorus level <2.5 mg/dL, study drug dose was held and restarted at a lower dose after the serum phosphorus level rise above 3.5 mg/dL.

Assessment of iron storages and hemoglobin
An iron panel (which consisted of TSAT, ferritin, serum iron, and total iron binding capacity) was checked every 4 weeks throughout the trial. Complete blood count was checked at every 4-week (efficacy period) to every 3-month (safety period) intervals.

Treatment failure criteria for stopping therapy for individual subjects during safety period
If a subject was > 80% compliant with 12 tablets/day of KRX-0502 or 12 pills/day of calcium acetate and/or sevelamer carbonate for at least 2 visits in a row, and had a serum phosphorus > 8.0 mg/dL, the subject was considered a treatment failure. The study drug was to be stopped, but the subject was to complete all trial visits.

Subjects were also considered treatment failures if they had an adjusted serum calcium >10.5 mg/dL, were in the active-control group receiving calcium acetate, and the PI elected to stop calcium acetate, after consultation with the Clinical Coordinating Center (CCC).

Medications and diet that can also influence serum phosphorus levels
The use of Vitamin D (and its analogues) and Sensipar (cinacalcet) were at the discretion of the PI. The doses of Vitamin D (and its analogues) were recorded at all visits.

Prior to starting the study drug in the safety period, dieticians instructed the subjects to keep their diet consistent in Vitamin D-rich food throughout the trial as much as possible. Within 30 days before the start of the efficacy period, the Dietician, blinded to assignment to KRX-0502 or placebo during the efficacy period, provided dietary instruction to the subjects again.

Concomitant IV iron and erythropoietin use
Over the course of the trial, the rules for withholding IV iron evolved. The protocol loosened the restriction while the trial was ongoing. IV iron was generally not permitted

if a serum ferritin was >1000 mcg/L or a TSAT was >30% in central lab results. However, administration of IV can be allowed and not considered a protocol violation, if the investigator deemed it in a subject's best interest, and if CCC was consulted and documented its approval.

Erythropoietin use was permitted, with dose adjustments at the discretion of the Investigator or site.

Other prohibited or restricted medications
The trial excluded subjects with an absolute requirement for vitamin C (which can increase the GI absorption of ferrous iron). Oral iron was also prohibited.

Subjects may take daily water soluble vitamins that include a small amount (e.g. 60 to 100 mg4) of Vitamin C (e.g., Centrum, Nephrocaps, Renaphro), but the subjects were to be instructed to take these vitamin C containing multivitamin two hours or more prior to or following food ingestion or at bedtime.

9.5 Trial 305:

Date of trial conduct:
First subject randomized: June 01, 2010
Last subject completed: November 19, 2010

Geographic Distribution: Fifteen sites in the US

Trial Population: Similar to trial 304, trial 305 did not require subjects to be iron deficient and did not pre-specifying hemoglobin as an endpoint. In addition, trial 305 had similar entry criteria (e.g., ferritin- and TSAT-based criteria), prohibited or restricted medications.

Study Procedure (per the final protocol amendment dated August 19, 2010)
Medications and diet that can also influence serum phosphorus levels
The use of Vitamin D (or its analogs) and/or Sensipar (cinacalcet) were to ideally remain constant throughout the trial and any changes must be documented on the CRFs.

Concomitant IV iron use: The criteria of when IV iron was to be administered changed several times during the trial, likely reflecting the equipoise on when to administer IV iron for subjects with functional iron deficiency. Before first subject randomized, (the second protocol amendment dated January 27, 2010), the IV iron was not allowed for a ferritin >500 ng/mL "to ensure that subjects are not being overloaded with iron". In the final protocol amendment 3 dated August 19, 201, two months after first subject randomized, IV iron was allowed for subjects with ferritin ≤1000 ng/mL and TSAT ≤50%. Nonetheless, IV iron therapy could be continued in the subjects with ferritin >1000 or TSAT >50%, if the investigator considered it in the subject's best interest.

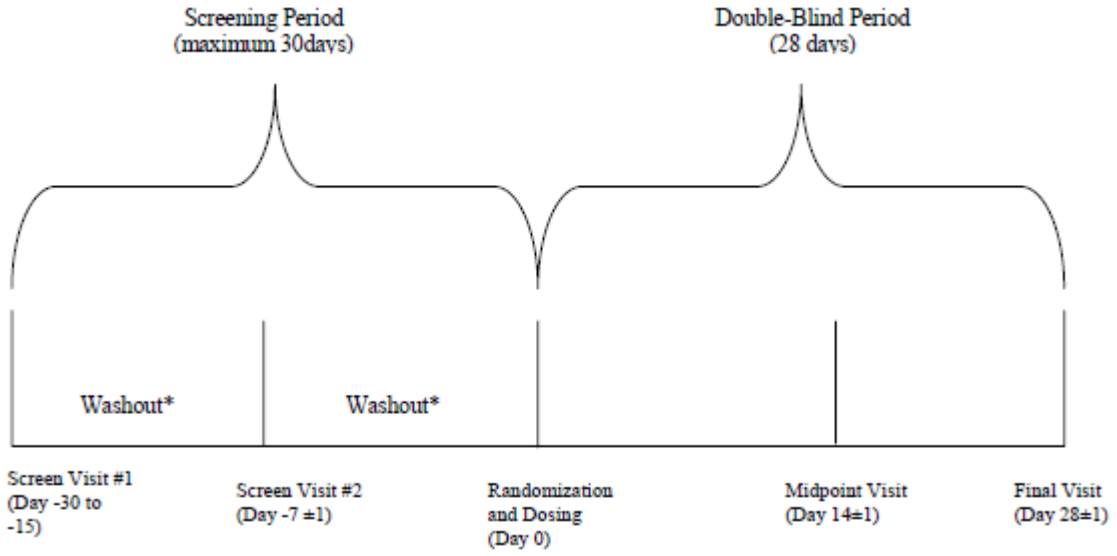
9.6 Trial PBB00101:

Title of the study: A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of the Effects of Ferric Citrate on Serum Phosphate in Subjects with End Stage Renal Disease (ESRD)

Study period:
First Subject Randomized Date**:** April 30, 2004
Study Termination Date**:** August 31, 2005

Geographic Distribution: USA and Taiwan

Trial Design



Source: Applicant's CSR

Study Procedure (per the protocol version 4, dated July 26, 2004)
For trial PBB00101, conducted by the prior sponsor, Panion, the serum phosphorus level was ≥ 5.5 mg/dL and ≤10 mg/dL during Washout.
Eligibility criteria for the Period 1, Washout Period were discussed in section.

Endpoints
The primary efficacy variable was the change in serum phosphorus from baseline (Day 0) to Day 14 and end of treatment (Day 28).

Clinical Investigator Financial Disclosure

Application Number: 205874

Submission Date(s): 8/7/13

Applicant: Keryx Biopharmaceuticals

Product: Zenerex, Ferric citrate

Reviewer: Nancy N. Xu

Date of Review: 4/22/14

Covered Clinical Study (Name and/or Number): PBB00101, KRX-0502-201, KRX-0502-202, KRX-0502-304, and KRX-0502-305

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 140		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None.		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None, according to the applicant.		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes N/A	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes N/A	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from applicant)

According to the certification of financial interest and arrangements of clinical investigators (form 3454), the applicant has disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1]

[1] See [web address].

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NANCY XU
04/28/2014

ALIZA M THOMPSON
04/28/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205874 **Applicant:** KERYX Biopharmaceuticals, Inc. **Stamp Date:** 8/8/13

Drug Name: Ferric Citrate **NDA/BLA Type:** Standard

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	Y			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	Y			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	Y			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	Y			
5.	Are all documents submitted in English or are English translations provided when necessary?	Y			
6.	Is the clinical section legible so that substantive review can begin?	Y			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	Y			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	Y			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	Y			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	Y			
11.	Has the applicant submitted a benefit-risk analysis for the product?	Y			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	Y			505(b)(2) referencing ferric citrate nonclinical studies in the published literature
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? *Study Number: KRX-0502-305* Study Title: A 4-Week Dose-Ranging and Efficacy Study of KRX-0502 (Ferric Citrate) in Patients with End-Stage Renal Disease (ESRD) Following a Two-Week Washout Period Sample Size: 151 exposed. Arms: 1, 4, 6 gram per day Location in submission: module 5.3.5.1	Y			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study Number: PBB00101 Study Title: A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of the Effects of Ferric Citrate on Serum Phosphate in Patients with End Stage Renal Disease Sample Size: 100 exposed. Arms: 2, 4, 6 gram per day Location in submission: CSR in module 5.3.5.1 *Study Number: GBA2-1* Study Title: A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of the Effects of Ferric Citrate on Serum Phosphate in Patients with End Stage Renal Disease Sample Size: 144 exposed. Arms: 1.5, 3, 6 gram per day Location in submission: CSR in module 5.3.5.1				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Two phase 3 trials have been conducted under SPA. Pivotal Study #1: KRX-0502-304 Pivotal Study #2: KRX-0502-305 The proposed indication is for the "control of serum phosphorus levels (b) (4) in patients with chronic kidney disease (CKD) on dialysis."	Y			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	Y			Yes, for the proposed indication for the control of serum phosphorus level
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	Y			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		N		This information has been requested.
SAFETY					
18	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	Y			
19	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			NA	
20	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	Y			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	Y			Satisfies previous agreements reached with the Division
22	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			NA	
23	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	Y			
24	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	Y			
25	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	Y			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Y			According to the clinical pharmacology reviewer, 3 in-vitro drug-drug interaction studies were submitted.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			NA	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	Y			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			NA	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		N		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	Y			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	Y			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	Y			
34.	Are all datasets to support the critical safety analyses	Y			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	Y			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	Y			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	Y			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	Y			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	Y			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____Yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Ferric citrate was developed as a phosphate binder and your pivotal clinical trials were designed to demonstrate the drug's effectiveness in lowering serum phosphorus levels. We note that you are also proposing (b) (4) This claim will be a review issue.

If not received within 74 days, these requests should be indicated in the 74 day letter.

1) Where in the submission do you provide a rationale for assuming the applicability of foreign data to the U.S. population? If you have not provided this information, please submit.
2) Please submit the protocol for trial KRX-0502-307.
3) Please provide the sas analysis code as sas files rather than PDF documents. If there will be a delay in getting the sas files to us, we would like the following analysis files first: (b) (4)
4) You have submitted an abbreviated CSR dated May 7, 2013 for the open label long-term safety trial, OLE-PBB00101. Please also submit the original CSR dated November 26, 2007.
5) As previously requested (see minutes dated September 19, 2012 and March 5, 2013), please submit the meeting minutes for the safety committee(s) for studies KRX-0502-304

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

and KRX-0502-305, as well as any correspondence between the safety committee(s) and Keryx and/or the clinical coordinating center. Please ensure that these materials come with a table of contents and are bookmarked by date. Agendas and copies of any presentations should be included. For a meeting that was cancelled or where no minutes were taken, please provide a place holder for that meeting noting such and signed by a member of the clinical team.

Reviewing Medical Officer	Date
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NANCY XU
10/02/2013

ALIZA M THOMPSON
10/02/2013